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Noeud Vital and the Respiratory Centers

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Abstract

We now recognize that the main breathing generator resides principally in the medulla oblongata. Vivisectionists—specifically, Julien Legallois—discovered "the respiratory center." Cutting through the brainstem stops respiration but not if the medulla remains intact and the brain is sliced in successive portions. Pierre Flourens localized surgical ablation experiments further identified a 1-mm area in the medulla, which he called vital knot or node (*noeud vital*). Detailed characterization had to wait until the 1920s, when Lumsden carried out more specific transection experiments to improve morphological differentiation of the respiratory center into inspiratory and expiratory divisions.

Keywords: Noeud vital, Respiratory centers, Brainstem, Animal research

The respiratory center in the brainstem and its three classes of neural mechanisms (the chemoreflexes, the central drive, and neuronal feedback from the muscles of respiration) were identified and characterized in fits and starts in the late 1800s and early 1900s. The regulation of $PaCO_2$ at a physiologic set point maintains vigilance, which changes with large increases in $PaCO_2$. Neurologic injury affects respiratory drive and is a daily concern for neurointensivists. Testing (or observing) the function of the respiratory center is a common task for the neurointensivist. Adjusting blood gas for responsiveness testing is helpful in weaning patients from the ventilator following major brain injuries. Apnea or irregular breathing patterns can be expected with primary brainstem injury. Performing the apnea test is an essential skill for neurointensivists. The history of the discovery of the respiratory centers (through vivisection experiments) is of interest and has an unusual start with dramatic cutting experiments.

Finding Its Anatomy

The discovery of respiratory centers has been attributed to Julien (Jean Cesar) Legallois. His discovery (explained in detail in *Expériences sur le principe de la vie*) was a result of vivisection experiments undertaken to discover the structures (and organs) needed to sustain life [1]. His decapitation experiments involved a heart–lung preparation ligating the inferior vena cava, aorta, carotid arteries, and jugular vein while ventilating the lungs through a syringe inserted in a decapitated rabbit (Fig. 1) [1]. Legallois's cutting experiments (halted decades later by antivivisection activists) were designed to illustrate how organ systems interact to maintain the existence of life. Without too much attention to detail, Legallois searched for the minimum requirements a dissected portion needed to maintain life; hence, he amputated and dissected until he thought he had arrived at an answer. He concentrated on the heart, spinal cord, and brain. He observed that decapitated heads still gasped for air while the chest was immobile without a spinal cord. This led to a second experiment in which he sliced the brain caudally to the spinal cord. Respiration stopped when the medulla oblongata met the nuclei of the eighth cranial nerve. (It should be remembered that the brainstem was not yet well defined, and lower parts of the brainstem were often incorporated into the spinal cord.)

Pierre Flourens further localized surgical ablation experiments, and these differences led to a vicious debate. Flourens identified a small area, which he called vital knot or node (*noeud vital*), (Fig. 2) of 1 mm diameter in the medulla in the mid-nineteenth century [2]. He arrived at this discovery by making high cervical transections

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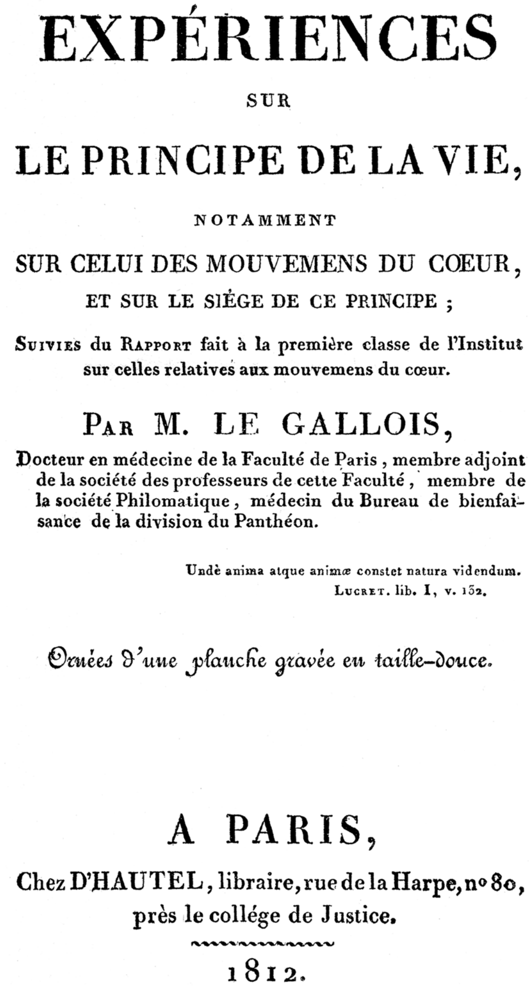

EXPÉRIENCES
SUR
LE PRINCIPE DE LA VIE,
NOTAMMENT
SUR CELUI DES MOUVEMENS DU COEUR,
ET SUR LE SIÉGE DE CE PRINCIPE;
SUIVIES du RAPPORT fait à la première classe de l'Institut sur celles relatives aux mouvemens du cœur.

PAR M. LE GALLOIS,

Docteur en médecine de la Faculté de Paris, membre adjoint de la société des professeurs de cette Faculté, membre de la société Philomatique, médecin du Bureau de bienfaisance de la division du Panthéon.

Undè anima atque animæ constet natura videndum.
LUCRET. lib. I, v. 152.

Ornées d'une planche gravée en taille-douce.

A PARIS,
Chez D'HAUTEL, libraire, rue de la Harpe, no 80, près le collége de Justice.

1812.

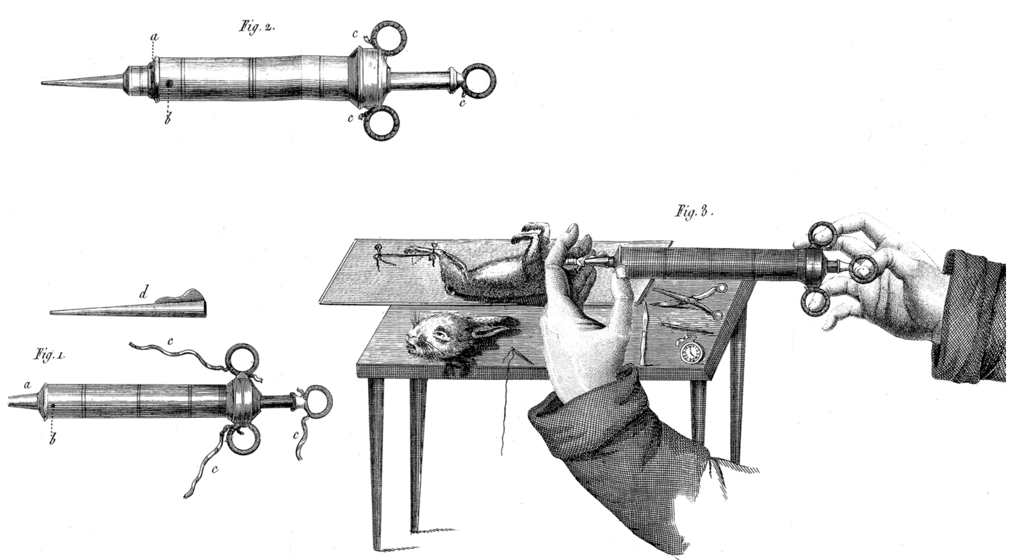

Fig. 1 "Expériences sur le principe de la vie" (1802) and set-up of Legallois's decapitation experiments

in rabbits and discovering the existence of respiratory movements in the mouth without chest movements. A number of physiologists, including Brown–Séquard, did not believe Flourens [2–4]. Brown–Séquard claimed to have seen rhythmic respiratory movements in decapitated animals, implying that the respiratory center might be lower in the spinal cord, but others felt it could simply be agonal and asphyxial [5].

Further characterization had to wait until the 1920s, when Lumsden carried out transection experiments (Fig. 3) [6]. Eupneic breathing required an intact pons and medulla oblongata. Transecting caudally to the rostral pons resulted in apnea with a sustained inspiratory hold (apneusis). Transection at the pontine medullary junction resulted in gasping rather than apnea [6, 7]. Transections to the obex stopped all chest and abdomen movements. Multiple transection and stimulation experiments located the rough outlines of a respiratory center underlying the caudal third of the floor of the 4th ventricle floor. Further morphologic experiments identified inspiratory and expiratory centers and later the pneumotaxic center [8]. Lumsden's sectional experiments demonstrated

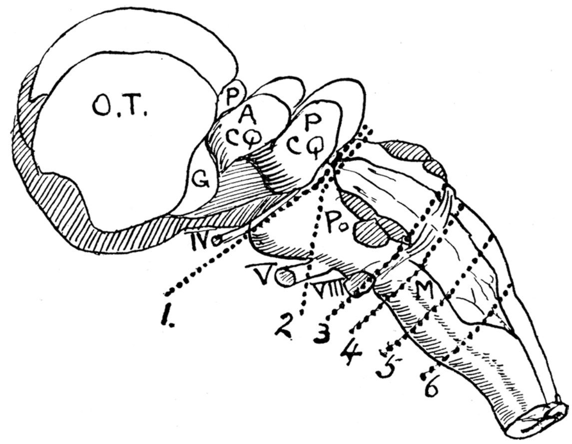

Fig. 3 Sectioning the brainstem to find respiratory centers by Lumsden. (Section 1: behind the quadrigeminal bodies. Section 2: upper part of the pons. Section 3: through the cochlear nucleus. Section 4: below the cochlear nucleus. Section between lines 5 and 6 caused cessation of all respiratory movements and death

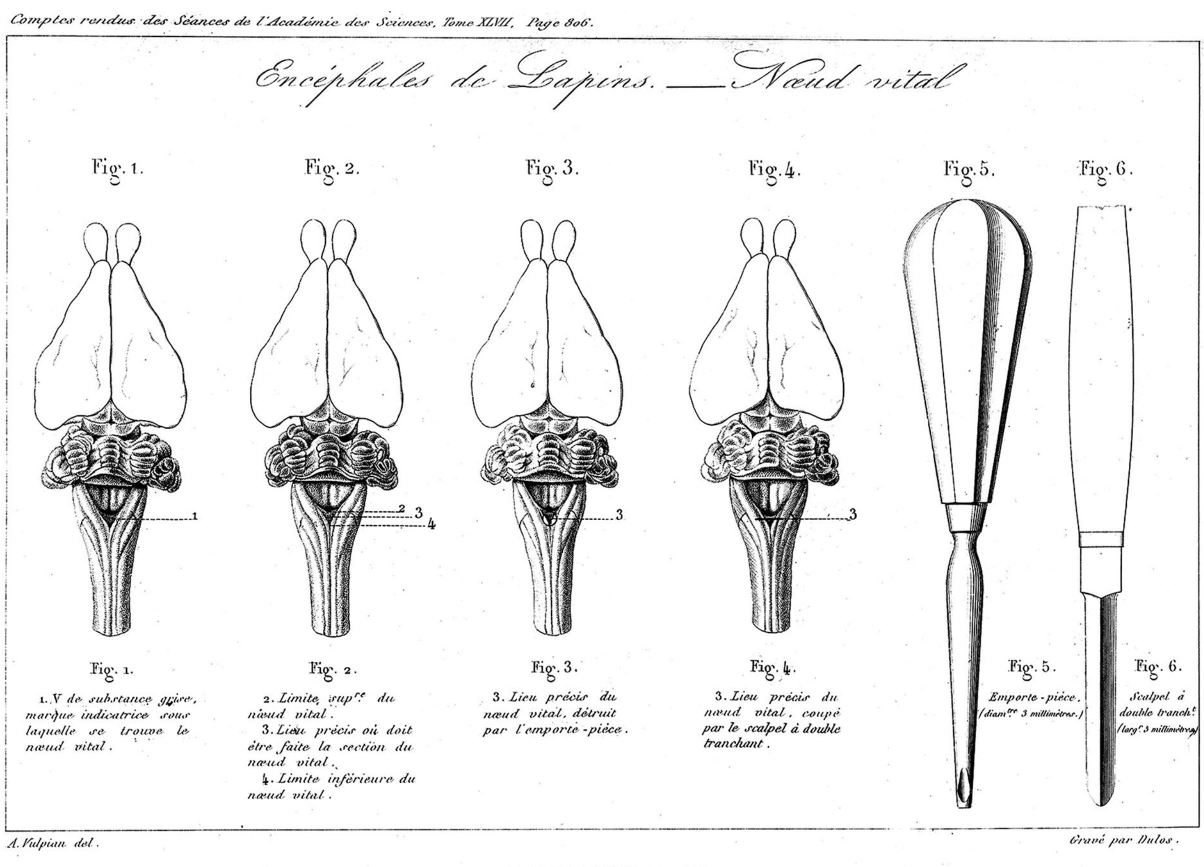

Fig. 2 *Noeud vital* in the medulla of a rabbit as proposed by Flourens. (Figures 2–4 show precise localization (Lieu *précis*)

a prolonged inspiratory type of breathing produced by sectioning dorsal to the posterior quadrigeminal bodies. The "convulsive and incoordinate" apnea in the area he called 'the apneustic center' was distinct from the so-called gasping center in the lower part of the spinal bulb. Lumsden observed that in asphyxia the nervous centers become afunctional caudally—first pneumotaxic center (apnea) followed by gasping as the last movement. However, later experiments demonstrated the rhythm of breathing to be determined by factors outside the centers rather than intrinsic mechanisms [8]. The major afferents to these centers determined their discharge.

Finding Its Physiology

Once the brainstem was isolated, more animal experiments followed. The most celebrated of these were by Gesell, who was able to make microelectric recordings and found a large number of active neurons in the dorsal medulla but very few "respiratory cells" in the suprapontine structures. He was unable to separate inspiratory or expiratory centers. "In many experiments, we were unable to find any respiratory potentials whatever, even with the most searching efforts. Such scarcity of potentials would seem to indicate that relatively few cells are needed in the medulla to activate enough ventral horn cells to carry on eupneic breathing" [9].

Finding Its Chemistry

Heymans found chemoreceptors in carotid and aortic bodies in 1927 and 1930 with afferent fibers in vagus and glossopharyngeal nerves followed by the identification of ventrolateral chemoreceptors of the medulla oblongata [10, 11]. Dejours found carotid chemoreceptors were part of ventilator response to hyperoxia (decrease in drive) and hypoxemia (increase in drive), and none of this occurred with denervation.

Most notable was the finding that PCO_2 could stimulate the carotid chemoreceptor only after the presence of acidosis. However, a major advance came with Leusen's experiments. After denervating the peripheral chemoreceptors, it was found that both PCO_2 and pH of the cerebrospinal fluid (CSF) stimulate drive [12, 13].

The pH of CSF did not exactly correspond with arterial pH as a result of the blood–brain barrier, but increasing PCO_2 results in CO_2 diffusion, quickly altering CSF pH, making ventilatory drive responsive to ion change. A threshold for peripheral ventilatory effect of PCO_2 is between 30 and 40 mm Hg and linear in its effect. (The central ventilator effect for PCO_2 was similar in range.) CSF pH changes with arterial PCO_2 rather than arterial acidosis. The retro trapezius nucleus consists of a cluster of chemoreceptor neurons that detect changes in brain pH. These neurons adjust breathing rate, inspiratory and expiratory muscle activity, and resistance of upper airway [14].

Conclusions

Legallois and Flourens were famous cutters; they tried to understand the vital brain functions by removing parts to see what would happen. Such gross sectioning would, of course, lead to some understanding but would also miss the fine connections within the removed parts. Legallois has traditionally received credit for the discovery of the respiratory center, but evidently this discovery was not acknowledged by Flourens and Lumsden. The dissection and ablation experiments defined a rough ideal of localization of the respiratory centers and the responses to changes in PO_2, PCO_2, and pH. Its localization in the brainstem was quite surprising.

We now recognize that the main breathing generator resides principally in the medulla oblongata. The autonomic rhythm of breathing is located in the bilateral respiratory group ventral to the nucleus ambiguus in the medulla oblongata [15]. Experimental studies with specific lesions strategically placed in specific neuron groups identified a ventral respiratory group with inspiratory and expiratory neurons. Work on central respiratory generators has identified the primacy of the pre-Bötzinger complex. Inhibitory neurons within this complex have a crucial role in the generation of central apneas. Central respiratory chemoreceptors—responding to hypercarbia—are present in the serotonergic raphe neurons in the pons and medulla as well as the retrotrapezoid nucleus. Despite the largely undifferentiated design of these early experiments, their focus on the brainstem and *noeud vital* was revealing. In criticizing unsubstantiated theories, Flourens famously said "each succeeding age has a philosophy of its own [16]," but, in essence, his (literally) pinpointing discovery has stood the test of time.

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EFMW researched and wrote the manuscript.

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Conflict of interest
The author declares that they have no conflict of interest.

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References

1. Legallois JC. Expériences sur le principe de la vie, notamment sure celui des mouvements du cœur, et le siège de ce principe; suivies du Rapport fait à la première classe de l'Institute sur celles relatives aux mouvements du cœur. Paris: Chez D'Hautel; 1802.
2. Flourens P. Note sur le point vital de la moëlle allongée. Compte Rendu des Séances de l'Académie des Sciences. 1851;33:437–9.
3. Flourens P. Recherches expérimentales sur les propriétés et les fonctions du système nerveux dans les animaux vertèbres. Paris: Crevot; 1824.
4. Flourens P. Nouveaux détails sur le nœud vital. Compte Rendu des Séances de l'Académie des Sciences. 1858;47:803–7.
5. Aminoff MJ. Brown–Sequard: an improbable genius who transformed medicine. New York: Oxford University Press; 2011.
6. Lumsden T. Observations on the respiratory centres in the cat. J Physiol. 1923;57:153–60.
7. Lumsden T. The regulation of respiration: part I. J Physiol. 1923;58:81–91.
8. Pitts RF. Organization of the respiratory center. Physiol Rev. 1946;26:609–30.
9. Gesell R, Bricker J, Magee C. Structural and functional organization of the central mechanism controlling breathing. Am J Physiol. 1936;117:423–52.
10. Heymans C, Bouckaert JJ. Sinus caroticus and respiratory reflexes: I. Cerebral blood flow and respiration. Adrenaline apnoea. J Physiol. 1930;69:254–66.
11. Heymans JF, Heymans C. Sur les modifications directes et sur la régulation réflexe de l'activité du centre respiratoire de la tête isolée du chien. Archives Internationales de Pharmacodynamie et Therapie. 1927;33:273.
12. Leusen IR. Chemosensitivity of the respiratory center; influence of CO_2 in the cerebral ventricles on respiration. Am J Physiol. 1954;176:39–44.
13. Leusen IR. Chemosensitivity of the respiratory center influence of changes in the H+ and total buffer concentrations in the cerebral ventricles on respiration. Am J Physiol. 1954;176:45–51.
14. Guyenet PG, Bayliss DA. Neural control of breathing and CO_2 homeostasis. Neuron. 2015;87:946–61.
15. Smith JC, Abdala AP, Borgmann A, Rybak IA, Paton JF. Brainstem respiratory networks: building blocks and microcircuits. Trends Neurosci. 2013;36:152–62.
16. Flourens P. Phrenology examined, University Publications of America edition. Philadelphia: Hogan and Thompson; 1846.