

Corneel Heymans and his work on respiratory reflexes

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For many years it was universally believed that the effects of hypoxia and/or hypercapnia were exerted directly on the ponto-medullary respiratory centres. This belief persisted until 1926, when Jan-Frans and Corneel Heymans published their discovery of peripheral chemoreceptor reflexogenic zones [1].

Jan-Frans Heymans (1859-1932) was the founder of the Department of Experimental Pharmacology at the University of Ghent, the first of its kind in Belgium. Heymans's early interest was in tuberculosis. He was the first to use on a large scale, in 1905, in laboratory animals and cattle, a vaccine prepared from attenuated tubercle bacilli. Famous son following famous father, Corneel Heymans (1892-1968), his medical studies interrupted by voluntary military service in the trench artillery during World War I, completed his medical training at his home town University in 1921.

The corner stone of the classical experiments of father and son was the development of the isolated head technique [2] in which dog A served as the donor and dog B as the recipient (fig. 1). The two carotid arteries and the two external jugular veins were isolated in the neck of dog A and were anastomosed to their counterparts in dog B. In dog B, the vago-sympathetic nerves were preserved after careful isolation, a tracheal cannula was inserted and artificial ventilation provided. The skin and muscles of the neck were separated by ligatures and a modified *écraseur* of Chassaignac used to crush all tissues in the neck except the vascular anastomoses with dog A and the two cervical vagi. The method allowed maintenance of the cerebral circulation of recipient dog B for many hours and was a masterpiece of experimental technique.

It should be remembered that there were no systemic anticoagulants in those days. Heparin had not been marketed and sodium citrate caused, by forming feebly ionized complexes with Ca^{++} , such a profound fall in calcium ionic concentration as to provoke cardiovascular collapse. Previous workers had used defibrinated blood for such experiments but as is well known nowadays, such blood contained masses of 5-OH tryptamine, vasodilator polypeptides and other noxious substances that caused rapid deterioration of the perfused preparation. Heymans circumvented the problem by the ingenious, if

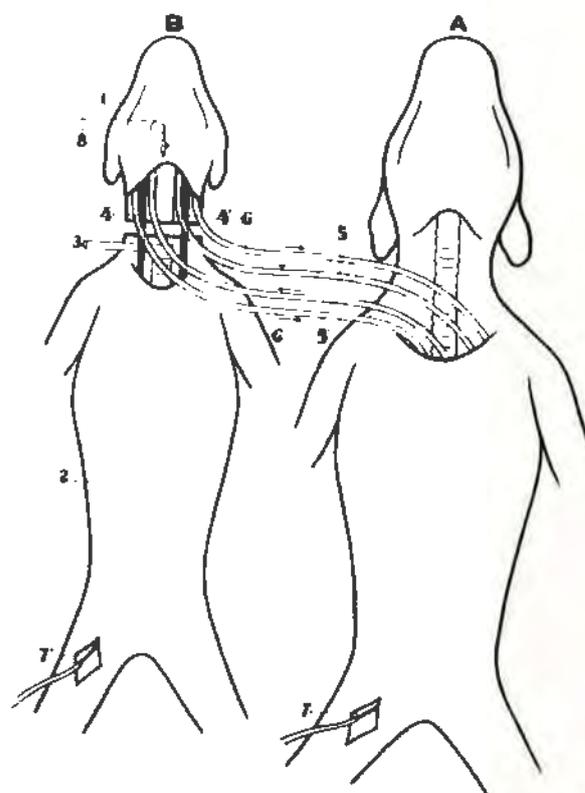


Fig. 1. Donor dog A perfuses the isolated head of recipient dog B. The head of dog B is completely separated from its trunk except for the vagi.

laborious method of using modified Payr cannulae for his anastomotic connections. According to this method the vessel to be anastomosed was threaded through a glass cannula used for the anastomotic connection (fig. 2). The vessel was turned back on the outside of the glass, so that the intima of the vessel was outermost, and secured by a ligature. The other blood vessel used for the anastomosis was then drawn over the intima of the first vessel and also secured by a ligature. Thus the blood was nowhere in contact with glass, but only with the intima, both at the connection site and within the cannula itself.

J.F. and C. Heymans used this preparation to show that chemical changes in the peripheral blood induced reflex alterations in the central respiratory rhythm of the head as monitored by graphic registration of movements of the larynx and of the alae nasi.

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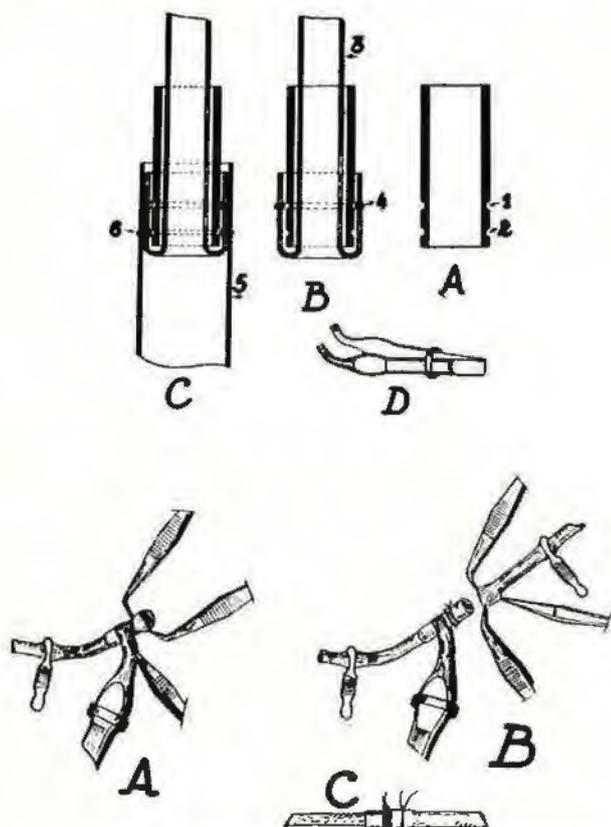


Fig. 2. Technique of vascular anastomosis using modified Payr cannulae. Upper: A: shows the appearance of the cannula in sagittal section and indicates the position of the grooves (1, 2); B: shows the position of the first ligature (4) on the everted vessel (3); C: shows the second vessel (5) drawn over the first and the position of the second ligature (6); D: shows the cannula holder; note the grooved prongs of this holder. Lower: A: shows the method of grasping and everting the first vessel over the cannula with the cannula holder in place; B: shows the method of slipping the second vessel over the first, everted one; C: shows the completed anastomosis from the outside.

Asphyxial changes in the recipient trunk, secured by stopping its artificial ventilation, powerfully increased laryngeal movements of the isolated head as long as the vagi were intact. Conversely, hyperventilation of the trunk induced a cessation of the laryngeal movements. In further elegant experiments they defined the site of the chemosensitive vagal nerve endings by using a third dog C to perfuse the cardio-pulmonary area of dog B (fig. 3). If only the lung circuit of dog B was submitted to perfusion with hypercapnic, anoxic or asphyxiated blood from dog C, no respiratory reflexes were aroused in the isolated head of dog B. If, however, the cardio-aortic area of dog B was perfused with asphyxial or anoxic blood from dog C, the respiratory reflexes shown by the augmentation of laryngeal or nasal movements in the 'isolated' head of B were brisk – provided, of course, that the two vagi of dog B were intact. They concluded that the chemoreceptor zones concerned were situated in the cardio-aortic area and not in the pulmonary vascular circuit [3]. This conclusion has been amply verified by later work.

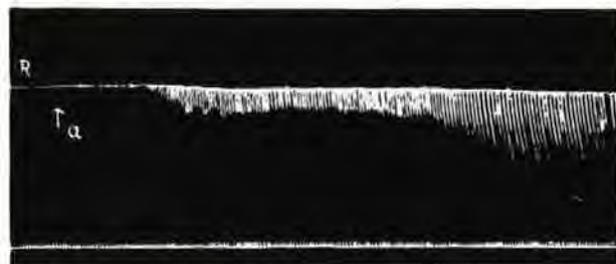
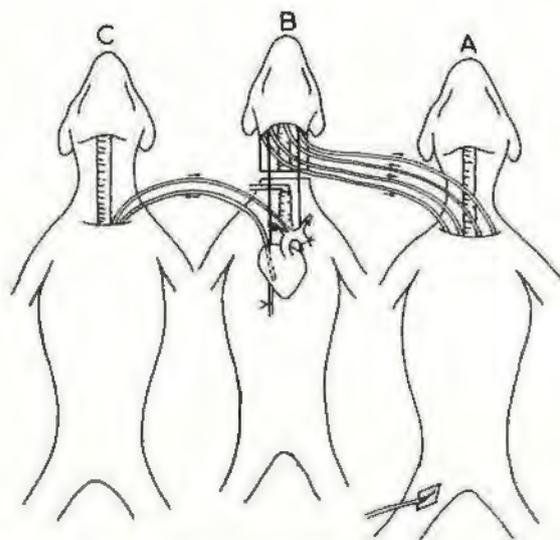


Fig. 3. Upper: The isolated head of dog B is perfused by dog A. Only the vagi-aortic nerves connect the head of B with its trunk. Dog C is used to perfuse the cardio-aortic area of dog B. The carotid artery of dog C supplies blood to the ascending aorta of dog B, and the blood circulating through the coronary system of dog B is returned from the right ventricle via a cannula to the jugular vein of dog C. Lower: Respiratory movements of head B. a: asphyxia of dog C and heart-aortic arch area of dog B. Stimulation of respiratory centre of head B.

Striking though these findings were, they were hardly convincing when it came to attributing a physiological role to the aortic chemoreflexes. The very abnormality of the isolated head preparation, ventilated artificially with central respiratory activity monitored from the larynx, raised the question of whether these reflex effects were called into play in more 'physiological' circumstances.

The story of the discovery of the chemoreceptors of the carotid body has been narrated by C. Heymans himself: 'My father always advised his pupils never to kill an animal at the end of a planned experiment if the animal might still be used for any other experimental purpose, and to take advantage of this animal to perform any experimental trial, even if it looked foolish, and to keep ones' eyes well open in order to catch any unexpected events. One day, also having in mind the advice of Darwin "I like to perform foolish experiments", we finished a planned experiment on the functions of the carotid sinus baroreceptors. One carotid sinus area of the dog was denervated, the other being still innervated. Wondering for what experimental purpose this dog could still

be used, we injected into the circulation of the common carotid artery with normal carotid sinus innervation some potassium cyanide solution. According to expectation, a very marked hyperpnoea occurred. But, when similar amounts of cyanide were next injected into the circulation of the common carotid artery, the carotid sinus of which was denervated, no hyperpnoea occurred (fig. 4). The alternative injections were repeated several times and the same very unexpected respiratory responses were observed. The next day a planned experiment was performed and it gave the same results. The primary unplanned experiment, at first sight a very foolish-looking trial, thus started a series of planned experiments, performed with several methods, which led to the identification of the chemoreceptors of the carotid body and their fundamental functions in the reflex physiological regulation of respiration and the reflex responses of the respiratory centre to many drugs, such as lobeline, acetylcholine, nicotine and many others' [4].

This first demonstration of the carotid chemoreflex aroused by histotoxic anoxia, important though it was, could hardly have led so quickly as actually occurred to the full development of our understanding of a possible physiological role of the carotid chemoreflexes in monitoring and affecting respiration if Heymans had not already been armed with the formidable technique of perfusing the carotid bifurcation, using either a donor dog or a Dale-Schuster pump, and blood of altered chemical composition.

Both Pasteur's dictum 'Le hasard ne favorise que

les esprits préparés' and Ludwig's dictum, 'Die Methode ist alles' have been well exemplified here. However, techniques amount to very little if not guided by the mind, or, as Poincaré said, 'Science is built with facts like a house is built with stones, but an accumulation of facts is no more a science than a pile of stones is a house'.

In a classical series of papers, published between 1930 and 1932, C. HEYMANS and co-workers [4] produced convincing evidence that hypoxia stimulates respiration solely by reflex means, the reflex being aroused by stimulation of the chemoreceptors of the carotid and aortic bodies. After section of the carotid sinus and vagal nerves, hypoxia exerts only a depressant action on breathing. Hypercapnia, on the other hand, stimulates breathing both by chemoreceptor reflex excitation and by a direct action on the medullary respiratory centres. Thus the hyperpnoea induced by breathing carbon dioxide-rich mixtures is scarcely affected by cutting the sinus and vagal nerves. The same was true in the case of acidemia induced by the injection of acids or acid-forming substances into the blood stream.

Heymans's discovery explained the function of an organ, in man no bigger than the head of a match, which had, until then, been unknown or dismissed. It revealed that this little body acts as a gustatory organ tasting oxygen in the blood, signalling every slightest change in its supply to the respiratory centre, which in turn produces increased impulses to the respiratory muscles, resulting in greater pulmonary ventilation

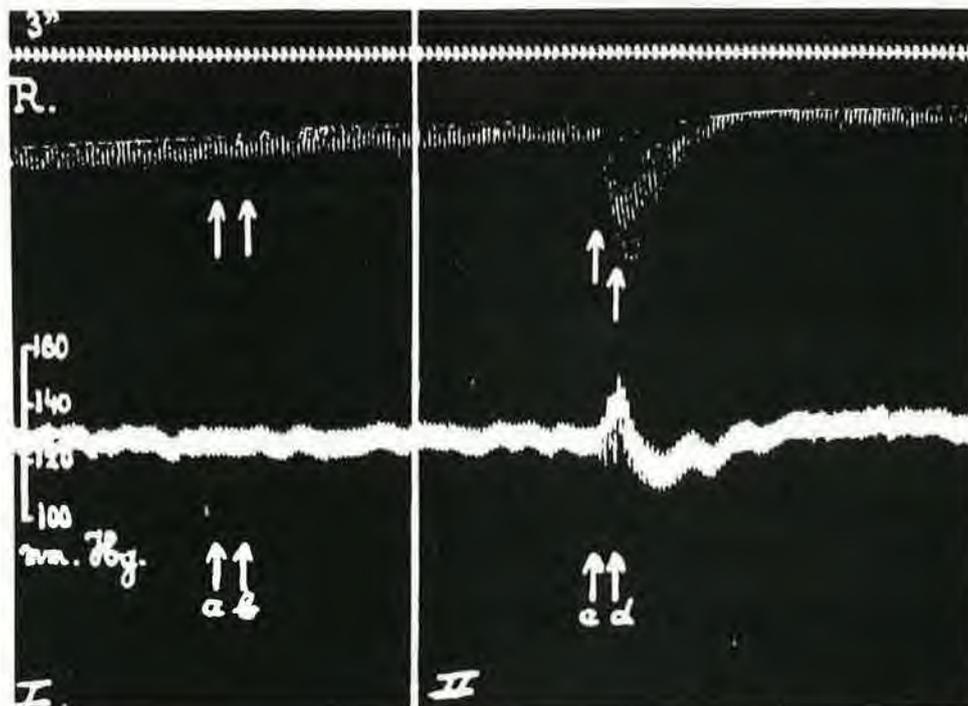


Fig. 4. Observatio princeps of the reflex chemoreceptor stimulatory effect of cyanide. Dog, 16 kg, chloralose anaesthesia. Denervated right common carotid artery. Normally innervated left common carotid artery. 3": time in 3 s, R: pneumogram; mmHg: arterial blood pressure in mmHg; I: between a and b: injection of 0.2 ml KCN 2% into the right common carotid artery: no influence on respiration. II: between c and d: injection of the same dose of KCN into the left common carotid artery: respiratory stimulation and bradycardia.

and increased uptake and transport of oxygen to the tissues. Thus in addition to the respiratory centre in the medulla, the body has another centre for detecting changes in the blood, the carotid body.

The work of Heymans bears the hallmarks of the grand masters of experimental physiology and pharmacology, lucidity of reasoning, multiplicity and irrefutability of the evidence produced, sobriety and specificity of methodology. Attracted by fundamental problems, Heymans possessed the art of discerning the essential from the accessory, of expressing his view in a sober but crystal-clear way, and of intergrating, in a most harmonious synthesis, the experimental results obtained. To achieve what Heymans did, required unusual energy, which he possessed, together with a prodigious memory and reasoning vigour.

The fundamental contributions of Heymans and his school were achieved using simple equipment: two operating tables, a Palmer kymograph with smoked paper, mercury manometers, a Marey respiratory capsule, a pump for artificial respiration, a Haldane chamber, a chloralose solution, Payr cannulae for vascular anastomoses, and a self-designed spinal crusher, not to forget a fowl feather to remove blood clots from the connecting glass cannula used for blood pressure measurement.

Emphasis was placed on simple and straightforward formulation of questions, logical planning of experiments and merciless discussion of results. In Heymans's mind, a clear-cut question ought to lead, through a clear-cut technique, to a clear-cut answer. He believed, as did his fellow-countryman and Nobel prize-predecessor, Jules Bordet, 'that when an experimental fact has been correctly observed under adequate conditions and when all possibilities of error have been removed, thanks to the judicious use of controls, it remains for the research worker to play a rigorous game against himself to try to refute his own

discovery, and to admit it at last, only when it can no longer be denied'.

This way of thinking was eminently served by the type of experimental work performed, which aimed at differentiating between the possible sites of action of a physiological mechanism or a pharmacological effect. As to drugs, they were considered by Heymans, in the line of Claude Bernard's tradition, as tools in the study of physiological phenomena rather than as a goal *per se*.

The pioneer experiments of Heymans on aortic and carotid chemoreceptors which gained him the Nobel Prize in 1938 stimulated and developed interest in these structures and their reflexes. No one was happier than Corneel Heymans to participate in the development and to argue with junior researchers about the results which they had obtained.

Few scientists have contributed as much to our understanding of the basic control mechanisms of the cardiovascular and respiratory systems as Corneel Heymans. In the history of medicine his pioneer experimental work is a landmark. To his friends, his generosity and geniality is their enduring memory. For he was a great man as well as a great scientist.

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