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Nobel Prize in Medicines 1938

Corneille Jean François Heymans

The Nobel Prize in Physiology or Medicine 1938 was awarded to Corneille Heymans "for the discovery of the role played by the sinus and aortic mechanisms in the regulation of respiration".

For over a century now it has been known that respiration in vertebrates including man is regulated from a small area in the medulla, known as the respiratory centre. From this centre nervous impulses of variable strength travel along the spinal cord and motor nerves, and reach the respiratory muscles. These muscles then come into play to produce respiratory movements. It is a well-known fact that respiratory movements can be intentionally modified, particularly during speech or singing, but respiration can also be influenced in different ways by mechanisms without conscious volition. For instance, entering a cold bath stops respiration for a few moments, pain tends to increase respiration. A sudden expansion of the lungs stops inspiration and induces expiration. Similarly, when air is withdrawn from the lungs by suction, expiration is halted and inspiration is induced. These facts were revealed by Hering and Breuer, and demonstrate the way in which reflexes influence respiration. Following the centripetal nervous pathways information is transmitted to the respiratory centre which reacts according to the nature of the information by initiating corresponding modifications of respiration. The chemical composition of the blood also has an effect on respiration. This is the essential factor which controls the degree of ventilation, i.e. the quantity of air which passes through the lungs. If the tension of carbon dioxide in the blood increases, or if the oxygen tension is reduced, the ventilation will increase. In this way respiration will adapt to the great variations in the requirements of the body, which themselves are due to the intensity of metabolic processes in the organism. Prior to Heymans's work, it was thought that the blood acted directly on the respiratory centre.

In 1927, together with the late Professor J. F. Heymans, his father and teacher, Heymans studied the respiratory reflexes which are transmitted by the tenth cranial nerve, i.e. the vagus or pneumogastric nerve. They made use of a technique which had been developed by the elder Heymans in collaboration with De Somer in 1912. This technique made it possible to keep alive the completely isolated head of a dog by perfusion of blood from another dog, while the body also remained alive with the help of artificial respiration. By ensuring that the only communication between the head and the rest of the body was provided by the two vagus nerves (and the depressor or aortic nerves which reach them from the aortic arch) the necessary conditions were produced for studying the links between the head and body dependent upon these nervous pathways. The two Heymans were thus able to demonstrate that expansion of the lungs stopped the respiratory movements of the head in the expiratory position, which was indicated by the recording of laryngeal and alae nasi movements, while collapse of the lungs immediately induced inspiratory-type respiration in the head. These experiments had provided decisive proof that the still controversial respiratory reflexes described by Hering and Breuer did in fact exist. It was also demonstrated that interruption of the artificial respiration applied to the body with resulting accumulation of carbon dioxide and decrease in oxygen contents rapidly led to an increase in respiratory movements of the head. On the other hand, hyperventilation of the body with free air, which produced increased excretion of carbon

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dioxide from the body, and increased the oxygen tension, stopped the respiratory movements of the head. After section of the vagus nerves, none of these effects were produced. Proof had therefore been produced for the first time that the vago-depressor nerves were capable of transmitting chemical stimuli arising peripherally. Consequently, if hyperventilation of the lungs was carried out, using a mixture containing a high proportion of carbon dioxide and a low proportion of oxygen, so that in spite of increased ventilation the tension of carbon dioxide in the lungs continued to increase while the oxygen tension decreased, the respiratory movements of the head, far from being reduced, tended to increase. The effects of hyperventilation with air could not therefore be explained as mechanical phenomena. They must have resulted from the suppression of the chemical stimulus to the nerve terminals of the vago-depressor nerves. By a careful and technically ingenious analysis, it was shown that these reflexes originating from chemical stimuli arise from the heart itself and the portion of the aorta nearest to it. Respiration could also be inhibited by high blood pressure in the body, as Heymans's experiments showed.

This intrinsically important discovery is of all the more interest in view of Hering's discovery (1923-1924) that the area known as the carotid sinus, on the internal carotid at its junction with the common carotid artery, has an analogous function to that of the areas in the aorta from which the depressor nerves arise. Thus an increase in arterial pressure in the internal carotid stimulates a number of nerve terminals in the walls of the sinus and produces a reflex which is transmitted by the ninth pair of cranial nerves, the glossopharyngeal nerves, and reaches the territories of the vagus and vaso-motor nerves. This produces dilatation in certain vascular areas and a slowing up of the cardiac rhythm. The original hypertension is thus counteracted, at least to a certain extent. The area innervated by the depressor nerves and the carotid sinus is therefore part of a common system, sometimes called the bridles of the blood pressure.

Heymans also studied with great precision the reflexes arising from the sinus area. Thus, together with a number of collaborators, he closely examined the mechanism by which the repercussions of these reflexes act on the cardiac rhythm and on the blood pressure. As is the case of reflexes governed by the depressor nerves, he found that the cardiac rhythm was slowed by increasing the tone of the branches of the vagus nerves, which have a delaying effect on the heart beat, and also by the reduction of activity in the antagonist stimulant nerves, whose function is to increase the cardiac rate. He further showed the role played by the different vascular areas in the modifications of blood pressure when the sinus pressure is increased or lowered. He also indicated that the suprarenal medulla was probably influenced by reflexes arising from the carotid sinus, bringing it to increase or decrease adrenaline secretion into the blood.

Systematic research was carried out with the aim of discovering if respiratory reflexes could also arise from the sinus. On this specific subject a number of significant facts had already been noted. For instance, Sollmann and Brown had observed that stretching of the common carotid artery initiated respiratory reflexes, and others, among them Hering and Heymans himself, had noted that an increase of pressure in the carotid artery could inhibit respiration, while a lowering of pressure in the sinus area stimulated respiration. In 1930, Heymans and Bouckaert were able to show that even slight variations in pressure could lead to marked changes in the respiration, and that these changes were due to a reflex mechanism.

Research was then concentrated on establishing whether the sinus area was sensitive as regards chemical stimuli in the same way as the area covered by the depressor nerves. In a number of papers, first in collaboration with Bouckaert and Dautrebande in 1930-1931, and then also with von Euler, Heymans gave irrefutable evidence that chemical stimuli played an important part in the control of blood pressure and respiration. In his experiments blood containing varying proportions of carbon dioxide and oxygen, and varying H-ion concentrations, was pumped into the sinus area. Blood could also be transfused from another dog which was inhaling mixture with a given proportion of gases so as to obtain the required chemical change in the blood. These experiments have shown that the increase in carbon dioxide tension, or the decrease of oxygen contents can increase respiration by acting upon the sinus area. By cutting the nerve fibres which travel from the

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sinus to the medulla, it was demonstrated that the increase in respiration after inhalation of air of low oxygen content, did not occur at all, and that consequently the stimulating reaction depended entirely on the sinus reflex. A similar experiment demonstrating the role of carbon dioxide showed that this gas stimulated respiration both by direct action on the respiratory centre and indirectly by means of the sinus mechanism.

Thus Heymans's work led to the theory that four different types of reflexes could originate in the sinus area. On the one hand, the circulation, or more precisely the blood pressure and cardiac rhythm, and the respiration could be modified by pressure changes in the sinus and, on the other hand these two groups of physiological functions could also be modified by variations in the chemical composition of the blood. Heymans went on to make further contributions to our knowledge in this field. Since the end of the 18th century we know of the existence of a curious structure in the region of the sinus, the glomus caroticum or carotid body which, in man, extends over only a few millimetres. The glomus consists of a small mass of very fine intertwining vessels arising from the internal carotid and enclosing various different types of cells. It has been considered by some as being a sort of endocrine gland similar to the medulla of the suprarenal glands. De Castro, however, in 1927 demonstrated that the anatomy of the glomus could in no way be compared to that of the suprarenal medulla. De Castro suggested rather that the glomus was an organ whose function was to react to variations in the composition of the blood, in other words an internal gustatory organ with special «chemo-receptors». In 1931, Bouckaert, Dautrebande, and Heymans undertook to find out whether these supposed chemo-receptors were responsible for the respiratory reflexes produced by modifications in the composition of the blood. By localized destruction in the sinus area they had been able to stop reflexes initiated by pressure changes, but respiratory reflexes could still continue to occur in answer to changes in the composition of the blood. Other experiments showed that Heymans's concepts on the important role played by the glomus in the reflex control of respiration by the chemical composition of the blood were undoubtedly correct. Recently it has been shown that similar chemo-receptors located in the area covered by the depressor

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nerves (glomus aorticum) have an analogous structure to that of the glomus caroticum (Comroe, 1939). It seems likely however that this depressor nerve mechanism plays only a small part in the respiratory reflexes produced by a marked lowering of oxygen contents and that the essential pathway is via the glomus caroticum. No doubt remains that the whole system plays an important part in the regulation mechanism as regards respiration.

By using modern amplification techniques, it has become possible to record exceedingly small variations in electrical potential within the body and to carry out research on action potentials detected in nerve fibres during transmission of an impulse. Even in the case of the smaller branches of the glossopharyngeal nerve which originate in the sinus area, action potentials of this type have been detected (Bronk, 1931). In 1933, Heymans and Rijlant demonstrated that these potentials were of two different kinds, the greater being produced by blood pressure in the sinus, the other by chemical stimulation in the glomus. We are thus in possession of a solid basis for further research as regards these two types of potential under various conditions.

Heymans not only discovered the role, hitherto quite unknown, of certain organs (glomus caroticum and glomus aorticum), he also greatly enlarged our field of knowledge concerning the regulation of respiration. He showed that the various methods used for stimulating respiration had quite different mechanisms. In certain cases (lobeline, nicotine, cyanide, sulphide, etc.) the drug acts on the glomus, in others (e.g. Cardiazol) it acts by central stimulation and again in other cases (e.g. Coramine) it acts centrally and peripherally. It seems likely that this increase in our knowledge of the chemo-regulation of respiration will also be of great use in research on a number of diseases.

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