Hypertrophic pulmonary osteoarthropathy and the vagus nerve: an historical note

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Fifty years ago Geoffrey Flavell¹ working at The London Hospital published the result of a remarkable clinical experiment. He asked a patient with lung cancer if he would consent to a two stage operation; at first Flavell would only divide the vagus and then a week later reopen his chest to remove the cancerous lobe of the lung.² The patient had severe hypertrophic osteoarthropathy (HPOA) and Flavell wanted to test his hypothesis that the vagus nerve was a critical pathway in the still unknown mechanism that causes osteoarthropathy in some cases of lung cancer. The man had first developed painful swelling of the ankles in August 1955 and over the next couple of months the knees, then the wrists, elbows and fingers also became stiff and painful. 'Radiography showed typical hypertrophic osteoarthropathy of all the long bones.' There was a small opacity in the upper lobe of the left lung which was diagnosed as lung cancer on sputum cytology. 'The patient agreed to a two-stage operation.'

At the first operation on 23 November 1955 Flavell disturbed nothing but the vagus nerve, dividing it just distal to its recurrent laryngeal branch, below the aortic arch. The following morning the patient was asked if he felt any different. 'Goodness me, yes,' Flavell quotes 'all my pains are gone; and look—I can bend my knees for the first time in weeks!' The swelling went in 48 hours and the pain never recurred. A week later Flavell removed what proved to be a squamous carcinoma without lymph node metastases.

HPOA is the severe end of a spectrum of clinical signs that includes digital clubbing. The vagal mechanism has not been disproved but is given little credence in present day teaching and yet it has not been replaced with any better explanation. The background as Flavell wrote is this: 'It has long been known that resection of the growth is followed instantly by cessation of all pain . . .'. This is generally accepted: it is a striking and consistent observation. Flavell made the further observation that patients in whom resection had failed, but a preparatory dissection around the hilum had been performed, were also relieved of the pain. He describes two such cases in his paper.² In a third he discovered the cancer was already disseminated after

performing a right thoractomy so he only divided the vagus. In the fifth, and last, case in his report a right-sided cancer was known to be inoperable at bronchoscopy; so he performed a minimal thoracotomy and just divided the right vagus. In all cases, the patients' pain was completely abolished. In his conclusion Flavell proposed division of the vagus nerve in inoperable cases with the objective of relieving pain.

Magdi Yacoub who was a senior resident at the nearby London Chest Hospital in the mid 1960s took up the suggestion and described two cases.^{3,4} The first was a man admitted to hospital in 1962 with left-sided cancer which had already destroyed the recurrent laryngeal nerve. The pain from HPOA was so severe that he could not sleep. Division of the vagus in the neck gave dramatic relief. In the second case, in 1964, the patient had lost the use of his hands due to the severity of HPOA. Yacoub passed a mediastinoscope from the neck down to the right hilum and divided the vagus nerve in the tracheo-oesophageal groove. 'The joint and bone pains subsided immediately, and five days later he could close his fists easily.'

Flavell and Yacoub, in these case reports and other articles,^{5–7} review the evidence for proposed mechanisms. They concluded that the ipsilateral vagus nerve was the key afferent pathway but clinical texts on lung give it little or no credence. The possibility of a vagal mechanism is mentioned in some texts but usually no source is cited and various rather vague humoral mechanisms are postulated. There are fewer than 100 references to HPOA in PubMed since 2000: predominately case reports of rare associations and phenomena. Lung tumours cause a wide range of paraneoplastic syndromes due to the release of proven or postulated substances and neural and humoral mechanisms could co-exist. However, the vagal mechanism is not favoured. It appears to be largely discounted and if so, why? Is it that the veracity of these surgical reports is in doubt? Cardiothoracic surgery was then and still is a very public specialty. The London Hospital and the London Chest Hospital were both major contributors to teaching, training and clinical reports in the 1950s and 1960s. Flavell named each referring physician in his *Lancet* paper. Yacoub acknowledged his senior colleague Jack Belcher when he wrote in the *British Journal of Diseases of the Chest*. Erroneous or over enthusiastic assertions could hardly have gone unremarked.

(a)

(b)

Figure 1 X-ray of HPOA (hypertrophic pulmonary osteoarthropathy). a, lateral; b, AP

There is the possibility that the dramatic relief reported by Flavell and Yacoub was a placebo effect—a result of suggestion. We tell patients with HPOA that the pain will go away when the cancer is removed. A thoracotomy would surely qualify as an ‘invasive, authoritative and dramatic intervention’ sufficient to prompt a placebo effect.⁸ And yet the physical and radiological changes regress, along with the pain. Placebo effect seems unlikely.

The clinical features and the place of HPOA in diagnosis remain unchanged. It is generally regarded as at the severe end of the clinical spectrum of the physical changes that are seen under the general heading of finger clubbing. Clubbing is said to have been described by Hippocrates in his account of empyema and is seen in about a third of cases of lung cancer.⁹ The occurrence of ‘hypertrophic pulmonary osteoarthropathy *without* clubbing of the digits’¹⁰ is so rare as to be published only in as few as four case reports. The incidence of HPOA in lung cancer was about 3% (9 out of 280) in a consecutive series seen between about 1970 and 1975.¹¹ Even in 1942 there was a ‘welter of hypothesis’¹² and publications in the last 10 years are predominantly case reports. The mechanism remains unexplained. Is there any unifying hypothesis? There was an interesting suggestion that it was related to megakaryocyte fragment passing

through the lungs¹³ to reach the vascular bed of the fingertips where they release platelet derived growth factor and cause clubbing.¹⁴ This theory did not gain acceptance and does not feature in standard texts.

The vagal theory is played down because the mechanism seems to be implausible. Although there is strong empirical evidence for a central role for the vagus from the surgical ‘experiments’ of Flavell and the clinical application by Yacoub, the vagus theory does not fit with physiological mechanism in current accepted scientific knowledge. In the 1840s, Semmelweis showed that hand washing with chlorinated water between the post mortem room and the labour ward dramatically reduced the death rate from puerperal sepsis, but his contemporaries were able to discredit him because the microbes had ‘never yet been seen’.¹⁵ The discrediting of Semmelweis and the forgetting of Flavell is too strong a parallel to draw, but the more gentle message from Belloc¹⁵ is worth recalling:

‘Oh! Let us never never doubt what nobody is sure about.’

With our modern minimal access methods, perhaps we should look again at division of the vagus to palliate HPOA.

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