

Angiogenesis

JOHN HUNTER AND THE ORIGIN OF THE TERM "ANGIOGENESIS"

--Manuscript Draft--

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Response to Reviewers:	<p>Dear Prof. Griffioen,</p> <p>I would like to thank you so much for your kind and prompt e-mail. All the authors are happy with your decision to accept the manuscript. Here is attached the revised text with the changes you requested in red. Moreover, and above all, we included only 9 references in the manuscript (now 873 words).</p> <ol style="list-style-type: none"> 1. As you will see, we have included a final paragraph to answer your question about the first use of the term angiogenesis. 2. As written now clearly in the text, the Hunter's book was posthumously published in 1794. 3. The posthumous Hunter's book is now well defined into the text. 4. The last two sentences have been deleted and rephrased.

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JOHN HUNTER AND THE ORIGIN OF THE TERM “ANGIOGENESIS”

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In temporary articles, the first use of the term angiogenesis has been generally attributed to the British surgeon John Hunter (1728-1793) (Fig. 1), and two different opinions are emerging from the literature.

Hall [1] wrote the paper entitled *The role of angiogenesis in cancer* where he started the paragraph *What is angiogenesis?* with the following sentence: *The history of angiogenesis goes back to at least 1787 when a British surgeon, Dr. John Hunter, first used the term “angiogenesis”*. Unfortunately, the manuscript did not report any reference for this important statement.

Hall’s sentence was taken up again by Folkman [2] in the chapter *History of Angiogenesis (The first use of the term angiogenesis was in 1787 by John Hunter, a British surgeon)*, and by Stephenson *et al.* [3] “*The founder of “scientific surgery” John Hunter (1728–1793), who sought to provide an experimental basis to surgical practice, first used the term angiogenesis in 1787*”. Ribatti and Crivellato [4] simply recognised that the concept – not the term – of angiogenesis is attributed to Hunter’s work dating back to 1787. However, stimulated by these articles, we decided to deeply go through the work of Hunter during 1787. As far as we discovered, in 1787 Hunter published three articles in *Philosophical Transactions of the Royal Society of London*, but none of them are dealing in particular with blood vessels, neither do they contain the neologism “angiogenesis”.

According to another opinion, the term angiogenesis would appear in a famous book posthumously put together on Hunter’s work, entitled *A treatise on the blood, inflammation, and gun-shot wounds* (1794, John Richardson publisher, London). Indeed, Mariotti and Maier [5] in *New Frontiers in Angiogenesis* stated that *the term angiogenesis was coined in 1794 by the British surgeon John Hunter to describe blood vessels growth in reindeer antlers as a result of long lasting exposure to cold*. In *History of Research on tumor angiogenesis* (2009, Springer publisher, UK) Ribatti also reported: *The term angiogenesis, meaning the formation of new blood vessels from preexisting ones, had been coined in 1794 by the British surgeon John Hunter to describe blood vessel growth in reindeer antlers as a result of long-lasting exposure to cold (Hunter, 1794)*. Again, Pathak *et al.* [6] indicated Hunter as the first who coined the term in 1794 *...to describe the formation of new blood vessels from extant vasculature* and Kobler in the book *The reluctant surgeon. A biography of John Hunter* (1960, Doubleday & Company publisher, New York) reported that *the term angiogenesis was first used in the 1700s by John Hunter to describe blood vessel growth in reindeer antlers in response to cold exposure*. In this way, the term angiogenesis appeared in the above mentioned posthumous book on the work of Hunter.

After an accurate examination of this masterpiece on the work of Hunter, we were not able to find the description of blood vessel growth in reindeer antlers, and we never met the term

“angiogenesis”, but we were faced with several descriptions dealing with that concept. Hunter described blood vessels in both human and animal organs. Indeed, several preparations came from animals: the fifth plate of his masterpiece shows the vascularisation of two rabbit’s ears, one in the natural state, and the other in an inflamed state. Thus, based on our historical research, we can conclude that Hunter described the process of growth of new blood vessels, but he did not coin the term “angiogenesis”. Surely, the scientific language occurring in the Hunter’s works is still old-fashioned and the word “angiogenesis” is not one of those he used. Indeed, this name seems to be a much later neologism that sounds too modern to appear in that context. Furthermore, Hunter certainly examined the formation of blood vessels as a rigorous scientific observer, but his interpretations still suffer from speculative and magical views considering that the process was described as arising from the effect of an innate vital principle within the blood.

In line with our observation, Adair and Montani [7] also claimed that the term “angiogenesis” does not appear in the Palmer’s editions of 1835-37 and 1840 of Hunter’s writings. In particular, the authors pointed Hunter as the first one to guess that overall regulation of angiogenesis follows a basic law of nature founded by Aristotle, which in essence is “form follows function”.

Furthermore, the term angiogenesis appears neither in the posthumous Hunter’s work collected and commented by Owen [8]. Finally, Shannon Compton in her online lesson at <http://study.com/academy/lesson/what-is-angiogenesis-definition-factors-quiz.html> correctly stated that Hunter *is describing what would later be called angiogenesis*. Nevertheless, the attribution of the term “angiogenesis” to Hunter still continues.

Vessel sprouting from preexisting vessels was already well recognized in the first half of the 19th century, also by using light microscopy. Despite our efforts looking at the library databases, we could not exactly go back to the scientist, or group of scientists, who firstly used or coined the word “angiogenesis”. However, to our knowledge, the first appearance of the term “angiogenesis” in an article title was in 1900, when Flint described the vascularization of the adrenal gland [9]. Since then, it is conceivable that the success of the word “angiogenesis” was also due to its use in the embryology field, also considering the general development of blood vessels and the term “angioblast”, used to name the progenitors of endothelial cells.

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Caption to the figure.

Figure 1. John Hunter's portrait from *A Treatise on the Blood, Inflammation and Gun-Shot Wounds* (1794).

