Looking for the word "angiogenesis" in the history of health sciences: from ancient times to the first decades of the 20th century

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Editor-in-Chief
John G. Hunter
World Journal of Surgery

Dear Prof. Hunter,

As suggested by the recent e-mail of Laura Shearer, the Managing Editor, I am submitting to World Journal of Surgery an articulated review which investigates the origin of the term "angiogenesis", from ancient times to the first decades of the 20th century, and the central role of the surgeon John Hunter. The work has not been published previously; it is not under consideration for publication elsewhere; its publication is approved by all authors (G. Natale, G. Bocci and P. Lenzi) and tacitly or explicitly by the responsible authorities where the work was carried out; if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Each author declares the individual contribution to the article. All authors participated in the historical research and article preparation and have approved the final article.

Our present historical research discloses new perspectives both on the role of Hunter and on the "angiogenesis" term. The present extensive review does not claim to provide definitive answers but wishes to open a debate and improve the knowledge on this important research area, also from a historical point of view. We are convinced that this topic deserves a particular attention in a scientific journal dealing with the history of surgery.

If I can be of any assistance during the review process, please do not hesitate to contact me at the address reported on the manuscript.

Thank you for your kind attention.

Sincerly yours,

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Looking for the word "angiogenesis" in the history of health sciences: from ancient times to the first decades of the 20th century

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Abstract

This review deals with the origin of the term "angiogenesis", with an attention to John Hunter who is credited with this neologism. A part of the literature refers to a Hunter's work dating 1787 and the other part claims the first use of the term "angiogenesis" in the Hunter's masterpiece published in 1794. Since we were unable to find the term "angiogenesis" in Hunter's works, this review attempts to bring a new contribution to the historical research of this important concept, moving from ancient times to the first decades of the 20th century, when "angiogenesis" begun to appear on titles of scientific articles. The development of the knowledge on the cardiocirculatory system and the principal steps of this fascinating subject were examined, with particular regard to microvascular bed and vessel sprouting, and intriguing observations on blood vessel neoformation have been also made in the premicroscopic era. In Hunter's works the concept of angiogenesis indeed emerges, but not the term "angiogenesis". The scientific language occurring during Hunter's time was still old-fashioned and the term "angiogenesis" was not one of those he used, rather a much later neologism that sounds too modern to appear in that context. To our knowledge, the first appearance of the term "angiogenesis" in the title of a scientific article was in 1900, when Flint described the vascularization of the adrenal gland. All historical researches cannot be conclusive and the present study wishes to open a discussion to better define this matter and other contributions are welcome.

Keywords: Angiogenesis; John Hunter; Cardiocirculatory system; History of medicine

No conflicts of interest were declared

1. Introduction

Since ancient times the occurrence of new blood vessel formation was described in both physiological and pathological conditions. However, only in recent times the modern techniques of light and electron microscopy, and immunohistochemical and molecular investigations allowed to define specific patterns of vascular growth in *in vitro* and *in vivo* models for which distinct terms have been adopted [1-3].

The term angiogenesis derives from the Greek word *angêion* (vessel), and *genesis* (birth), and indicates the growth of new blood vessels from pre-existing vasculature in response to chemical and mechanical stimuli. This process is crucial to many physiological (embryonic development, ovulation, wound healing) and pathological events (tumour growth, arthritis, diabetic retinopathy). Typically, the new vessels are very thin, corresponding to capillaries, and are lined up by an array of tightly adhered endothelial cells. Furthermore, different forms of angiogenesis can be distinguished: sprouting and splitting (intussusception) angiogenesis [2,4,5]. Differently, the term vasculogenesis indicates the *de novo* formation of blood vessels directly from mesoderm cell precursors [2,4].

This investigation aims to outline the history of new blood vessel formation, with special attention to the birth of the modern term "angiogenesis". In particular, our research moves from ancient times, when the knowledge of the cardiovascular system was quite general and incorrect, to the first decades of the 20th century, when the term "angiogenesis" begun to appear on titles of scientific articles. In particular, our attention has been focused on the intriguing question whether the British surgeon John Hunter was really the first to coin the term "angiogenesis". In this respect, in a brief communication we introduced the debated issue about the role of Hunter in the creation of the "angiogenesis" neologism [6], while a large body of evidence is provided in the present paper.

2. The description of circulation, vascularisation and "angiogenesis" in ancient times

To better understand the origin of the morphofunctional concept of angiogenesis, it is advisable to see throughout a brief history of medicine, in particular the progress in the knowledge of the cardiovascular system (Fig. 1).

The earliest pictures of heart were found in prehistoric cave paintings. In these pictures the prey is riddled by the arrow at the heart level [7]. Nevertheless, the description of the cardiovascular system dates back to ancient Egyptians. In medical papyri, such as the Edwin Smith Surgical Papyrus (ca. 1600 century BC), the Ebers Papyrus or the Greater Berlin Papyrus (ca. 1550 BC), and

the Brugsch Papyrus (ca. 1300 BC), the description of the blood circulation precedes that of the Greek Democritus by over two millennia [8]. The Smith papyrus is the oldest known medical document. Indeed, some historians have dated it as far back as 3000 BC and they believe that the treatise was copied by an older document written by the important priest and physician Imhotep (ca. 2600 BC). In both Smith and Ebers papyri, the pulse is directly correlated to the heart activity [8]. Accordingly, many authors agree that the Egyptians were the first to recognize the important role of pulse and its relationships with the contractions of the heart [8-10]. Interestingly, in the Ebers Papyrus there is also the description of a type of "vessel-tumor", interpreted as coming from the wound of a vessel [8].

In the Chinese treatise *Huang Ti Nei Ching Sur Wên* (*Yellow Emperor's Canon of Internal Medicine*) (ca. 2689-2599 BC), it is stated that the heart controls the blood that flows continuously: *the heart governs the blood* [11,12]. Moreover, the blood was considered one of the chief doctrines and 28 different types of blood pulse, which are at the basis of acupuncture, were recognized [13].

In ancient India only Brahmins had the privilege to exercise the function of priests and physicians. Loukas et al. [14] report that the ancient Indian medical knowledge was collected in a text named *Vagadasastir* (or *Wagadasastir*) after the missionary Gründler [15]. This collection, also mentioned by Renouard in 1856 [for the modern edition see reference 16], is not recognizable at the present within a modern classification. However, in *editorial compilations and comments* published in *The National Medical Review* (Vol. 1, N. iv, March 1879, p. 155) concerning the ancient medicine, the contribution of the *Vagadasastir* to the circulation was fully reported: *According to their medical works there were in the human system one hundred thousand parts, of which seventeen thousand were vessels. Each one of these was described as composed of seven tubes, giving passage to ten species of gasses, which, by their conflicts, engendered a host of diseases. They placed the origin of the pulse in a reservoir situated beneath the umbilicus. This reservoir was four fingers wide by two long, and divided into seventy-two thousand canals, which were distributed to all parts of the body.*

In ancient Greece the condition of medicine was not different from that of the primitive civilizations. Nevertheless, Greek physicians became the most brilliant scientists. The earliest Greek reports on anatomy and physiology appear in Homer (900 BC) and Hesiod (750 BC) [7]. Probably, the anatomical and physiological descriptions were due to the observations of wounded soldiers during the Trojan War [14].

Alcmaeon of Croton (approximately 500 BC), thanks to the animal dissection, described arteries and veins as distinctive vessels [17]. Aristotle (350 BC) recognized that the heart was connected to blood vessels, thus identifying a functional link between them. Moreover, Aristotle

sustained that blood vessels were the first structures to undergo remodeling during the early embryologic life and that they extend throughout the entire body from the heart [18]. Even more interestingly, Hippocrates of Cos (ca. 460-370 BC) observed the tumor spreading associated with swollen blood vessels tortuously arranged around the tumor itself reminiscing the claws of a crab (this iconography was referred in particular to breast cancer), and he named the tumor *karkinos* and *karkinoma* (the Greek name for crab): *karkinos was used for any non-healing swelling or ulcerous formation, even hemorrhoids, whereas karkinoma was reserved for non-healing "cancer"* [19].

During the Alexandrine period, vivisection was performed on human beings condemned to death penalty. This practice, obviously and ethically unacceptable in contemporary times, anyhow allowed obtaining both anatomical and physiological observations. In this context, the earliest anatomical treatise, written by the physician Herophilus of Chalcedon (ca. 335-280 BC), distinguished arteries from veins, the latter containing air rather than blood [20]. In particular, arteries were defined as vessels thicker than veins [17]. Furthermore, Erasistratus of Ceos (ca. 315-240 BC) was the first experimental physiologist who described the heart as a pump and postulated the first theory of blood circulation. Furthermore, in order to explain his doctrine of *horror vacui*, as the tendency of nature to fill a void, he formulated the theory according to which the presence of *synanastomoses* allows the blood flowing from veins to an artery when cut to fill the vacuum caused by the sudden escape of the air or *spirit* present in arteries [21]. Erasistratus also described a structure characterized by a network of veins, arteries and nerves, which was termed *triplokia*. This anatomical organisation might be compared to the modern *vasa* and *nervi vasorum* and *nervi* and *vasa nervorum* [22].

The hippocratic observation on neoplastic blood vessel formation was also confirmed by the physician Galen of Pergamon (ca. 129-200): *the cancer is completely similar to the animal that is called crab, because as this has the legs to the sides of the body, so in this pathology the veins that extend from the centre of the tumour at its periphery, represent, for their tension, branches almost similar to these legs*. Tumours, remembered Galen in *Methodus medendi*, have a hard consistency, a roughly round shape, a darker colour than that of an inflammatory swelling, but they were less warm. This can be considered the first gross description of blood vessels related to the tumour growth [23]. According to the Galen's open-ended vascular system theory, which was successful for several centuries, the liver represented the organ for blood production and the source of all veins. Indeed, nutrients were concocted in the gut and transformed into blood by the liver. Then, from the hepatic vein the blood moved to the lower vena cava and distributed to all parts of the body. In contrast to Erasistratus' theory, Galen assumed that arteries were filled with blood, which was infused with the vital spirit by a mixture of air coming from the lungs through the pulmonary

vein and heat coming from the heart. Finally, the blood moved from the right to the left ventricle through invisible (indeed inexistent) pores of the inter-ventricular septum [24].

Hundreds of years later, the Islamic medicine gave a great contribution to the development of anatomy, including the cardiovascular system. In this respect, among physicians and scientists, Ibn Sina (980-1037), known with the Latin name Avicenna, Ibn al-Nafis (ca. 1210-1288), and Ibn al-Quff (1233-1286) improved the concept of blood circulation [25,26]. Although reporting many galenic misconceptions in his masterpiece *Al-Qanun fi al-Tibb* (*The Canon of Medicine*), Avicenna described new anatomical issues, such as the blood circulation of the brain, anticipating the Willis' circle [27], the arterial and ventricular contractions in the cardiovascular system [28] and the connection between arteries and veins [29]. In particular, in the *Canon* the connection between arteries and veins was described as follows: *…there are fenestrations between them [arteries and veins] whereby the venous blood receives the inherent heat of the heart present in the arterial blood ...The proof of a connection between the arteries and veins is that, when a vein is cut, the blood will empty from both the arteries and the veins* [29]. Interestingly, although not observed because of their size, a large peripheral network of capillaries was theorized: *The good blood ascends into the superior vena cava, and its subsequent course is into smaller and smaller veins: and finally into the finest hair-like channels. Having reached these hair-like channels it "sweats out" through their orifices and bathes the tissues, according to the decree of Allah* [30]. In the first description of the pulmonary circulation, Ibn al-Nafis alluded to the presence of pulmonary capillaries [31,24]. The theory of capillary network was also reported by Ibn al-Quff in his book *Basics in the Art of Surgery*: *Due to the dependency of this blood system* [venous system] *to the other one* [arterial system]*, these two systems are mostly located near each other within the body. ...to connect one system to the other ...through the communicating fenestrations between one system and the other. These fenestrations are hidden from the eye…* [32].

Interestingly, during the Renaissance period, an important terminological definition was achieved by Leonardo da Vinci (1452-1519) who first named in the pre-microscopic era of the western medicine the lesser blood vessels visible at the naked eye as "capillaries" [3]. Indeed, as reported by his biographer Paolo Giovi, Leonardo *learned to dissect the cadavers of criminals under inhuman, disgusting conditions ... because he wanted* [to examine and] *to draw the different deflections and reflections of limbs and their dependence upon the nerves and the joints. This is why he paid attention to the forms of even very small organs, capillaries and hidden parts of the skeleton* [33]. Then, Leonardo described as capillaries arterioles and venules, but of course he was unable to see the real microscopic connection between them.

In the 16th century, Andreas Vesalius (1514-1564), who is defined as the "father of the modern anatomy", studied blood vessels, in particular the venous valves, and in his masterpiece *De humani corporis fabrica* corrected the Galen's assumption that the great blood vessels moved from liver to supply all part of the body. In the same period, the philosopher Michael Servetus (1511-1553) and the anatomist Realdo Colombo (1516-1559) studied blood circulation, and hypothesized that blood flowed from the right ventricle into the lungs where it was mixed with the air to be returned to the left ventricle [17].

In the late 16th century, Andrea Cesalpino (1524-1603) described the pulmonary circulation and he was the first to coin the word "circulation" [34]. These observations pre-dated Harvey's theory, which demonstrated the correct circulation of the blood and described the heart as a pump [3]. However, William Harvey (1578-1657) was unable to observe microcirculation and in his work *De motu cordis* (1628) supposed the presence of *pulmonum caecas porositates et vasorum eorum oscilla*: the blood would have reached the lung parenchyma passing through invisible porosity and cavities of vessels [35].

The study of blood circulation improved with the invention of the microscope by Hans and Zacharias Janssen in the Netherlands at the end of 16th century. By using pioneering microscopes, Marcello Malpighi (1628-1694) detected in the frog lung tiny capillaries through which blood flowed from arteries to veins, thus completing the Harvey's missing link on the blood circulation. Furthermore, he also described the particular capillaries of the renal glomerulus and the blood circulation of the chick embryo chorioallantoic membrane [36]. Pearce [33] noted that in the same period, from a review of the book by the English physician and anatomist Needham (1667), entitled *Disquisitio anatomica de formato foeto*, published in the *Philosophical Transactions of the Royal Society* [37], the idea of capillary as one of a number of minute blood vessels also emerged: *He annexes a particular description of the* Placenta *of a Woman, as the most considerable, and teaches, how it may be most conveniently severed from the Vessels, to render them conspicuous, which are a numerous off-spring of Arteries, Veins, and Fibres; of the last whereof he inquires, whether they be capillary's of the Arteries, and Veins, or nervous.*

3. "Angiogenesis" in Hunter's works

In recent articles, the first appearance of the term "angiogenesis" has been generally attributed to the British surgeon John Hunter (1728-1793) [38], and two different opinions are emerging from the scientific literature.

In his paper entitled *The role of angiogenesis in cancer*, Hall [39] 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 [40] 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. [41]: *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*. Ghosh [42] also advocated that opinion. Ribatti and Crivellato [5], and more recently Vandekeere et al. [43] 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* [44-46], but none of them are dealing in particular with blood vessels, neither they contain the neologism "angiogenesis".

According to the other opinion, the term "angiogenesis" would appear in a famous posthumous Hunter's book. Indeed, Mariotti and Maier [47] 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* Ribatti [48] 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. [49] indicated Hunter as the first who coined the term in 1794 *…to describe the formation of new blood vessels from extant vasculature* and Pories and Wulf [50] cited an old book by Kobler [51], and 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 would appear in the book entitled *A treatise on the blood, inflammation, and gun-shot wounds* [52].

The report itself of two different opinions on the same author appears suspect already. After an accurate examination of the Hunter's masterpiece, we were not able to find the description of blood vessels growth in reindeer antlers, and we never met the term "angiogenesis", but we faced with several descriptions dealing with that concept [52].

Hunter observed that an increase in vascularity occurred not only during the growth of young animals but also in disease conditions and healing processes (p. 156): *As a further proof that this is a general principle, we find that all growing parts are much more vascular than those that*

are come to their full growth; because growth is an operation beyond the simple support of the part: this is the reason why young animals are more vascular, than those that are full grown. This is not peculiar to the natural operation of growth, but applies also to disease, and restoration. Parts become vascular in inflammation; the callus, granulations, and new formed cutis, are much more vascular in the growing state, or when just formed, than afterwards; for we see them crowded with blood-vessels when growing, but when full grown, they begin to lose their visible vessels, and become not even so vascular as in the other neighbouring original parts, only retaining a sufficient number of vessels to carry on the simple oeconomy of the part; which would now seem to be less than in an original part. This is known by injections, when parts are in the growing state, or are just grown, and for some time after.

In particular, during a disease state, the vessels increased in size, in strength and their arrangement (p. 158): *In diseases where there is an increased size of the part, as in tumors etc. the increase of vessels is no less conspicuous; and they have the power of dilatation, and increase of strength, in proportion to the size of the vessels; which are now endowed with new dispositions, and actions, different from those they had before.*

Moreover, describing the inflammation status, Hunter observed that new and enlarged vessels are formed by inducing a more vascular appearance of the inflamed part which results red: *The part inflamed, I have already observed, becomes to appearance more vascular than when in the natural state, and it is probable that it is really so, both from new vessels being set up in the inflamed part, as well as the new and adventitious uniting substance becoming vascular. Besides, the vessels of the parts are enlarged, so that the red blood passes further than common, which increases those appearances* (p. 283). *Besides, I observed in the introduction to inflammation, and when treating of the adhesive state, that the old vessels were dilated, and new ones were formed; these effects, therefore, are here carried still further in the surrounding parts, which do not suppurate, and constitute two other causes of this redness being increased, by the vessels becoming still more numerous, and the red part of the blood being pushed more forward into many vessels, where only the serum and coagulating lymph went before* (p. 378). Hunter named *this new structure, or disposition of vessels*, *glandular* (p. 417).

Finally, we found interesting information also in the iconographic section of the book. Indeed, in the first plate, it is illustrated the physiological process of the vascular neo-formation in a chick embryo at three different stages. The new vessels are not *always elongations from the original ones, but vessels newly formed, which afterwards open a communication with the original* (p. 567). In particular, the legends of Figures II and III of the first plate report: *…vessels appear to be rising up spontaneously in different parts of the membrane…* and *The number of blood-vessels is very*

considerably increased; they now form a regular system of vessels, composed of larger trunks, and a vast number of ramifications going off from them.

Furthermore, Hunter documented blood vessel formation observing coagula in uterus and in human testicles (second plate, p. 568, and third plate, pp. 569-570, respectively). The blood vessel growth is described to arise from the coagula due to the ruptured vessels in the uterus: *...the vascularity of the uterus, whose vessels are distinctly seen, continued into the coagulum, and passing about halfway through its substance* (second plate, Figure II). Blood vessels in the testicles were described during the dissection from a patient treated at St George's Hospital for hydrocele. Hunter noticed blood vessels forming inside the coagulated lymph (third plate, p. 569, and four plate, p. 571): *Over the whole surface of the tunica vaginalis there were vessels filled with blood, and clots of extravasated blood in different parts*; *the whole surface of the testicle now appeared to be a layer of coagulating lymph become vascular* (Fig. 2). This observation gave the opportunity to Hunter's belief to claim that the blood contained an active principle responsible for the organisation of the living matter. Hunter clearly confirmed his opinion, as announced to his pupils: *By way of news I have to inform you Gentlemen that I have within these few days got into my possession a preparation which must convince the greatest unbeliever in my Doctrine that the blood is alive*. This phenomenon was difficult to demonstrate, but Hunter restored the vascular appearance of the coagula after dissection by injecting the testicle through the spermatic artery [53]. The injected human testicle is one of the most important preparations of *The Hunterian Museum* at the Museum of Health and Medicine in London. The caption to the item mentions posthumously the term "angiogenesis" referring to the testicle coagulum.

The relevance of Hunter's findings with respect to cancer was well summarized by Androutsos et al. [38]:

Hunter above all estimates that cancerous formations result from secretion of a plastic substance transuding through blood vessels to pour out in other interstitial structures. He called this substance coagulable lymph ("cancerous tumefaction is produced as a result of the coagulable lymph's interstitial extravasation").

Following extravasation, this lymph is organised in random production, gifted with its own life, subject to the laws of biology instead of those of physics or chemistry, as was the view advanced by iatromechanics. In other words, it forms what biologists will call, at a later time, new tissue or neoplasm.

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 [52] 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 term "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. More correctly, Skalak [54] simply stated that Hunter *identified growing vessels in healing wounds and embryos from blood masses and enlargement of carotid arteries in deer*. The same concept was also expressed by Stapleton [55].

Interestingly, in line with our observation, Adair and Montani [56] also claimed that the term "angiogenesis" does not appear in Hunter's writings, referring to the Palmer's editions of 1835 and 1840 [57, 58]. 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 [59], which in essence is "form follows function".

Furthermore, the term "angiogenesis" appears neither in the posthumous Hunter's work, collected and commented by Owen [60]. 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*.

4. Angiogenesis in 19th and 20th centuries

Vessel sprouting from preexisting vessels was well recognized in the firs half of the 19th century, also by using light microscopy. Indeed, interesting findings were obtained by Van de Kolk, as reported by Rogers et al. [61]: *The uniqueness of the blood supply of spontaneous and transplanted tumors was recognized in 1826, by Schroeder Van der Kolk when he carried out the first injection experiments in neoplastic tissue.*

Other observations were carried out in *in vivo* experiments by Platner, [62] and Meyer [63] who described structures arising from capillaries in tadpole tails. Furthermore, similar features were clearly described during wound healing and in tumors by Billroth [64]. Virchow and Thiersch also contributed [61]: *Virchow and Thiersch further described the unique vascular network supplying a variety of cancers. Subsequent microscopic studies revealed defective and dilated capillaries in the periphery of tumors as well as destruction of newly formed vessels in their central zones often associated with necrosis.*

As reported by Skalak [54], during the 19th century the visualization of blood vessels was further improved by the use of india ink which allowed a better definition of the vessels under light microscopy.

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 [65]. Furthermore, three years later Flint [66] used the term "angiogenesis" studying the vascularization of the submaxillary gland. In the same period, by dissecting the vascular system in order to study the growth of malignant diseases, Goldmann [67] did not use the term "angiogenesis" but simply referred to the new formation of vessels whose first description was attributed to previous authors including, not surprisingly, John Hunter: *I now arrive at my second point: What are the general conditions of circulation in malignant growths? For information on this score we are obliged to go far back into the history of medical science, back to the writings of John Hunter, Schroeder van der Kolk, Broca and others*.

Sabin [68] focused on the origin of blood vessels (mesenchimal or not), but in his work there is no difference between angiogenesis and vasculogenesis. In 1935 Hertig applied the term "angiogenesis" in an attempt to explain the discrepancies existing in the formation of human extra-embryonic vascular system [69]. In his paper the author, reviewing the literature, stated: *the problem of angiogenesis has occupied the attention of numerous investigators in the field of human and comparative vertebrate embryology for more than fifty years.* Indeed, 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 term "angiogenesis". However, it is conceivable that the embryology is the field where the term "angiogenesis" could be appeared for the first time, also considering the general development of blood vessels and the term "angioblast" used to name the progenitors of endothelial cells. Several other studies were dedicated to the embryonic development of blood vessels. Indeed, two divergent theories on blood vessel origin arose: the *angioblast theory* [70] and the *local-origin theory* [71]. These two different points of view were well discussed by McClure [72].

In 1927 Lewis investigated the tumor environment suggesting its importance for the neovascular development during cancerogenesis [73]. Furthermore, this feature was emphasized by Rondoni [74], as reported by Ribatti [48]: *A tumor acts both angioplastically and angiotactically, in other words it promotes the formation of new vessels and attracts vascular outgrowths (capillaries and pluripotent perivasal cells) so as to build up and shape a stroma of it own, a newly formed stroma. It must thus be unreservedly admitted that tumors are partly vascularized by the already*

existing network of vessels around them. As in other pathological processes, therefore, such neoformation as takes place is a vascular neoformation from budding of the existing capillaries.

Later, angiogenesis appeared in the titles of the papers by Noback [75] and Greenblatt and Shubi [76], dealing with baboon and hamster models, respectively, until the pivotal and exceptional contribution of the work by Folkman [77] who described the essential role played by angiogenesis in cancer growth and, above all, firstly reported the concept of its inhibition by antiangiogenic drugs that, *de facto*, opened a completely new field in anticancer research and therapy.

Other than in cancerogenesis, altered angiogenesis is considered a common denominator in most other frequent pathologies, including ischemic heart disease, blindness, psoriasis, and arthritis [78]. The intriguing and complex questions emerged from the numerous investigations dedicated to the mechanisms involved in angiogenesis open new challenges for the future clinical implications, especially in the tumor treatment, as recently reviewed [43,79-82]. Nevertheless, the attribution of the term "angiogenesis" to Hunter still continues [83].

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Author contribution statement

All the authors contributed to the writing of this review

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Captions to figures.

Figure 1. Schematic diagram showing the principal steps of the scientific progress in the knowledge of cardiocirculatory system and blood vessel neoformation.

Figure 2. The original illustrations and caption of John Hunter's *plate third* from *A Treatise on the Blood, Inflammation and Gun-Shot Wounds* (1794, pages 569-570).
FIGURE I.
The testicle, with the tunica vaginalis slit open, exposing its surface.
AA. The body of the testicle.
B. A small hydatid arising from its surface, which occurs not unfrequently in that situation, viz. just where the epididymis takes its origin from the testicle.
C. The smaller coagulum lying in the angle between the body of the testicle and the epididymis.
D. The large coagulum adhering to the body of the testicle.
EEE. The tunica vaginal is turned back.
FIGURE II.
A portion of the tunica vaginalis magnified to shew the appearance of its vessels, and of the small specks of extravasated blood in different parts.

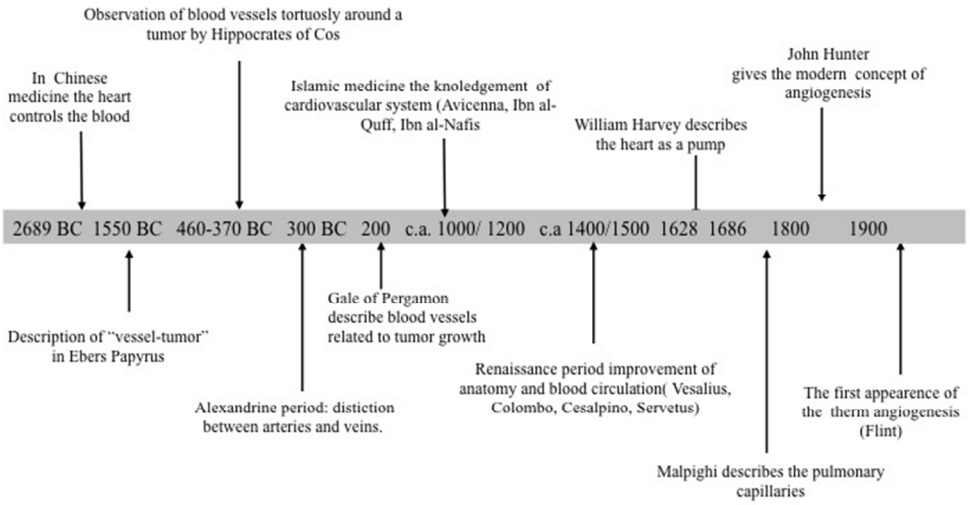

Figure 1
254x190mm (72 x 72 DPI)

Figure 2
134x226mm (96 x 96 DPI)