INTRODUCTION

Aspects of the history of medicine help us to appreciate our traditions of thought and practice, and in some cases they elucidate present-day understanding of disease pathology, therapy and prophylaxis. This point is well illustrated by modern perspectives on deep venous thrombosis (DVT) and its treatment and management. In the present paper we re-evaluate the contributions of Hunter, Cruveilhier and Virchow to this field. Most modern medical textbooks and teaching courses misconstrue Virchow’s seminal work on thrombosis and embolism and say little or nothing about his predecessors. Our discussion will explore the evolution of ideas about the aetiology of DVT, and will inter alia consider the way in which the word ‘inflammation’ has been used in relation to what we now call ‘deep venous thrombi’ and ‘emboli’.

INTRODUCE REVIEW

Deep Venous Thrombosis: Hunter, Cruveilhier, Virchow, and Present-Day Understanding and Clinical Practice

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ABSTRACT

During the past 50 years, systematic misunderstandings of Virchow’s contribution to the study of deep venous thrombosis (DVT) have distorted thought and opinion in this field. Virchow’s main concern was with the formation of pulmonary emboli, not with the generation of venous thrombi per se. In particular, the elements of what has become known as ‘Virchow’s triad’ had nothing to do with the formation of thrombi but with their metastasis to produce emboli. Nevertheless, Virchow made two particularly important observations about venous thrombogenesis that have been largely overlooked since the 1950s: thrombi are initiated in valve pockets; and their initiation is associated with a massive local accumulation of leukocytes. He also distinguished clearly between in vivo thrombi and ex vivo blood clots. In this paper we explore the background and motivation to Virchow’s work, which lies in the earlier studies of John Hunter and Jean Cruveilhier, and the methods he used, particularly his reliance on the recently-improved microscope. We also consider the work of Virchow’s successors and explore the circumstances leading to the eventual distortion of his legacy.

The article is organized as follows. The first substantive section summarizes and compares two modern-day accounts of the aetiology of DVT. The second examines some aspects of Virchow’s writings about venous thrombi and emboli and corrects a common misconception. The third considers the origin and fate of the ‘phlebitis’ concept and evaluates the idea of ‘inflammation’ in relation to DVT. The fourth reflects on the involvement of venous valves in thrombogenesis and argues that this involvement was implicitly recognized by John Hunter. Finally, a concluding section comments on the implications of this study for our appreciation of recent medical history and our current understanding and management of DVT.

The pathological lesion that Hunter termed ‘inflammation of the internal coats of veins’, mistranslated as phlebitis by his successors after his death, was renamed ‘thrombosis’ by Rudolf Virchow circa 1856. We contend that John Hunter’s theory of life, and his naked-eye inspection of the lesions, provided the original framework of reference in terms of which scientists – including Virchow – sought to understand the phenomenon for 154 years (until 1947). Those who prefer mechanical prophylaxis to anticoagulant treatment for DVT today are still adhering to Hunter’s (and by implication, Virchow’s) viewpoint, but they have become a minority.
THE ETIOLOGY OF DVT

Two accounts of the aetiology of DVT are current.\(^1\) The consensus model views DVT as a haematological disorder and attributes it to some combination, not well characterized, of ‘stasis’, ‘hypercoagulability’ and ‘vessel wall injury’. The valve cusp hypoxia hypothesis (VCHH) holds thrombogenesis to be initiated in venous valve pockets under conditions of suffocating hypoxaemia; given certain well-defined circumstances, these incipient nidi may develop into fully-fledged thrombi.

**The consensus model**

The consensus model is the more widely-held account. It provides a prima facie rationale for anticoagulant and thrombolytic prophylaxis and treatment, and indeed it has evolved along with these pharmaceutical approaches to clinical practice. Scientifically, it has motivated research into hereditary and acquired thrombophilias, and into the molecular responses of the venous endothelium to hypoxic conditions.\(^7\) Research in both these areas has proved fruitful. The drawback of the consensus model is that it does not provide a clear aetiological account of DVT. Indeed, the terms ‘stasis’, ‘hypercoagulability’ and ‘vessel wall injury’ are not clearly defined or consistently used.

The consensus model was first articulated during the early 1960s, coinciding with the acceptance of anticoagulants for clinical use against DVT and embolism.\(^3,4\) Its roots lie in the scientific study of blood coagulation, which dates from the early 19\(^{th}\) century but underwent rapid development during the mid 20\(^{th}\) century. At its outset, this development was largely driven by the identification of haemophilia in the British royal family and the need to determine the cause of the condition and find an effective treatment. A review by Eagle in 1938 summarised what was then known of the coagulation mechanism.\(^5\) Strikingly, although Eagles mentioned Andral’s isolated description (1843) of an excessive tendency to coagulate,\(^6\) he made no suggestion that haematological research could have any significance for our understanding of DVT.

Immediately after the Second World War, however, the picture changed. The burgeoning of haematology as a distinct discipline, fostered by methodological and conceptual advances in biochemistry, heralded the birth of the consensus model. During the 1930s, Dr Paul D White, General Eisenhower’s physician and a founder of the American Heart Institute, had been surprised to realise that DVT killed many of his heart failure patients as well as surgical and decubitus patients.\(^7\) His reaction may have contributed to the quest for pharmaceutical rather than mechanical approaches to prophylaxis and treatment and thus, later, to the consensus model. The mechanical and pharmaceutical paradigms associated with the two accounts of the aetiology of DVT may thus be viewed as reflections, respectively, of surgical and medical ideologies and approaches. But the pharmaceutical paradigm soon became pre-eminent.

A 1947 article by Pulvertaft revealed the bewilderment and anger that this development inspired among followers of the Hunterian tradition.\(^8\) In his introduction, Pulvertaft wrote:

‘The presence of large and well-organized clots of blood in the pulmonary arteries has long been recognized, but in spite of Harvey's demonstration of the mechanics of the circulation of the blood, it was left to Virchow to explain their true nature a hundred years ago. Since then an enormous literature has developed around the subjects of thrombosis and embolism... They have perhaps attracted an attention greater than their clinical importance warrants, but elementary students of physiology are sometimes puzzled to hear so many of their masters weaving a tortuous and highly individual path through the polysyllabic mazes of blood coagulation... Yet the penultimate word on the question was written by Welch in Albutt's System of Medicine in 1897,\(^9\) and much that has been written since has been a bungalow growth rather than an architectural synthesis; on re-reading Welch’s excellent study, one feels that today’s students would be well advised to remember that there were great men before the Agamemnons of modern medicine.

Welch’s seminal study of thrombi (actually published in 1899)\(^9\) was decidedly in the tradition of Virchow and was justly celebrated. Yet within a decade of Pulvertaft’s diatribe against the incursion of haematology into the study of DVT, Virchow’s name had become associated with the so-called ‘triplet’ of stasis + hypercoagulability + vessel wall injury, the ‘Agamemnons of modern medicine’ had begun to articulate the consensus model, and Welch’s contribution had been more or less forgotten.

**The valve cusp hypoxia hypothesis**

The VCHH\(^1\) may be less familiar to many readers than the consensus model, so a more detailed description is needed here. It holds that DVT may occur if there is sustained non-pulsatile (streamline) venous blood flow, so that the valve cusp leaflets are not ‘flapped’ and the blood in the valve pocket is therefore not exchanged with that in the vein lumen. This leads to suffocating hypoxaemia in the valve pockets, resulting in hypoxic injury to the inner (parietalis) endothelium of the cusp leaflets. Such prolonged oxygen insufficiency of the endothelium stimulates the elk-1/egr-1 pathway, which initiates most of the constellation of responses of endothelial cells to hypoxia and activates a number of chemoattractant and procoagulant factors.\(^2\) When normal pulsatile blood flow is restored, even transiently, leukocytes and platelets (attracted by these factors) marginate and sequesterate at the site of injury to ‘cover and heal’ the now moribund endothelial layer. These cells self-attach to the necrotic epithelium and constitute the
first layer of what may become an incipient venous thrombus.

A frank thrombus may subsequently develop if regular contractions fail again for a prolonged period, so the valve pocket is not emptied and refilled with adequately oxygenated blood. Each further period of non-pulsatile flow kills all accumulated blood cells in such a valve pocket. Cells oxygen-starved by each subsequent immobilization, and expelled back into the vein lumen, are repetitively replaced by more live cells charged with oxygen, which are fated to die when immobilised on the growing sequence of layers that build up to form the core of the nascent thrombus. If periods of non-pulsatile and pulsatile flow continue to alternate, serial deposition of white cells and fibrin may ensue, sequentially or at distinct intervals, and this results in the characteristic ‘Lines of Zahn’ morphology of a venous thrombus. Only the blood cells on the outermost layer of a thrombus are still living.

The VCHH thus re-explains many of the recognized causes of (risk factors for) DVT (e.g. prolonged inactivity, especially a motionless state while undergoing muscle-relaxant anaesthesia) and it accounts for the morphology of thrombi. It also predicts that a venous thrombus will readily embolise, because the area of endothelium to which it is anchored, the valve cusp parietalis on which it has grown, is necrotic (by definition) and is therefore readily detached by the restoration of pulsatile blood-flow past the obstruction. It provides a **prima facie** rationale for accepted non-pharmaceutical approaches to prophylaxis (e.g. early ambulation, flexion and extension of the ankles, support stockings and intermittent pneumatic pressure leg devices).

It also suggests a new approach to preventing hospital-acquired venous thromboembolism. Having indicted the pathogenicity of venous valve pockets undrained for many hours, it follows that the risk of DVT can be eliminated by ensuring that all venous valve pockets in the lower limbs are emptied gravitationally at (minimally) half hourly intervals by slight head-downward tilting of the bed, alternating every 1–1.5 hours with slight foot-downward tilting to preclude the risk of thrombogenesis in the valve pockets of the upper limb veins.1

Like the consensus model, the VCHH was also conceived in the 1960s and received powerful experimental and clinical evidence in the late 1970s and early 1980s,10 but its roots are much older.11 They can be traced to Virchow, and beyond Virchow to Cruveilhier and Hunter. We shall explore this historical development in what follows.

**A seeming paradox**

After 1962, the consensus model marginalised and even eclipsed the pathophysiological tradition of Hunter and Virchow, at least temporarily; Ockham’s Razor seems to forbid the coexistence of two explanations for the same phenomenon. However, the originators of the consensus model attached the label ‘Virchow’s triad’ to the alleged pathogenic circumstances (stasis + hypercoagulability + vessel wall injury). It may seem surprising that both the VCHH and the consensus model claim to be rooted in the work of Virchow, who clearly did not advance two apparently incompatible accounts of the same process. We need to examine Virchow’s work to resolve this seeming paradox.

**WHAT VIRCHOW WROTE AND DID NOT WRITE**

**Virchow’s motivation and approach**

Rudolf Virchow (1821-1902) began to work on the aetiology of pulmonary emboli in 1844, under the direction of Robert Froriep, who set him the challenge of examining the ‘ Doctrine of Cruveilhier’ (i.e. that ‘phlebitis is the root of all pathology’).12 By 1848, he had shown that the semi-solid masses of blood that form, often fatally, in pulmonary arteries are not produced in situ but have metastasised from the peripheral circulation. The papers he published on these studies, some based on animal experiments and some on clinical cases, were brought together in his *Thrombose und Embolie*,13 published in the year (1856) that he took up the post of Professor of Pathological Anatomy created for him in Berlin.

*Thrombose und Embolie* was a remarkable work, emphasizing a reliance on scientifically demonstrable fact rather than conjecture, and introducing nomenclature that still survives. (For example, Virchow gave ‘thrombus’ and ‘thrombosis’ the definitions we accept today, and he invented the words ‘embolus’ and ‘embolism’.) It may be argued that the discovery that all pulmonary emboli originate from peripheral vein thrombi was not original with Virchow, since Joy14 had come close to this realization in 1840 and van Swieten15 had broadly grasped the idea as early as 1776. However, the overwhelming mass of experimental and clinical evidence in *Thrombose und Embolie* was entirely Virchow’s, and it made the conclusion irrefutable.

**What is now called ‘Virchow’s triad’ arises from a misunderstanding of Thrombose und Embolie**

For the purposes of the present article, the important point is that *Thrombose und Embolie* addresses the cause of emboli, not the cause of venous thrombi. In other words, it is not about the aetiology of DVT at all. The earliest reference we can find to ‘Virchow’s triad’ as an alleged account of the aetiology of DVT (usually interpreted as stasis + hypercoagulability + vessel wall injury) is the 1957 paper by Anning.16

written almost exactly 100 years after Virchow’s seminal publication. The ‘Virchow’s triad’ concept seems to have arisen from a misinterpretation of the following passage from *Thrombose und Embolie* (pp. 293-294 of the Matzdorf-Bell translation):-
Thrombi resemble blood clots but are not the same as blood clots

Nowhere is Virchow’s emphasis on the tangible and demonstrable better illustrated than in his comparison of thrombi with blood clots. Everyone has seen blood clotting \textit{ex vivo}. Virchow’s microscopic studies of thrombi (which his readers had not seen) led him to say that in certain ways they resemble clots (which they had seen). He criticized Cruveilhier for refusing to use the microscope (Cruveilhier was 35 years old before Lister’s achromatic lens made the microscope into a reliable instrument, so his lifelong doubts about the instrument are understandable) and was himself a committed microscopist. However, he was careful to point out some important morphological differences between \textit{in vivo} venous thrombi and \textit{ex vivo} clots:

1. the structure of the thrombus is in layers [i.e. the lines of Zahn];
2. the fibrin content is denser;
3. the population of colourless corpuscles is denser, and to a striking degree; these corpuscles were present in the blood from the beginning, and were separated from it with the fibrin... Thus there is evidence for spontaneous coagulation of the blood within the vessels, visible where the continuity of the vessels is interrupted, e.g. by a wound. This large segregation of colourless corpuscles is clearly associated with the retardation of the circulating blood.’

In other words, a thrombus is not a clot, or even like a clot; the resemblance is superficial. (We might say that this tripartite distinction between ‘clot’ and ‘thrombus’ has a better claim to bear the epithet ‘Virchow’s triad’ than the modern-day consensus-model mantra ‘stasis + hypercoagulability + vessel wall injury’.) The first point of distinction, the layered structure of the venous thrombus, had been recognized by Lobstein and Bristowe but not described so informatively. There was no more detailed exploration of thrombus structure until 1876, when the newly-improved Zeiss microscope became available to Zahn. Virchow’s precise drawings of thrombi make his skill and care as a microscopist evident.

The third point of distinction between thrombus and clot states that the ‘colourless corpuscles’ forming much of the ‘root’ of the thrombus originate from the circulating blood. This is ‘obvious’ to our minds, so why was Virchow so emphatic about it? We shall return to that question in the following section.

The third point of distinction also indicates the association of thrombi with injured areas of the vessel wall. In this, Virchow tacitly echoed Cruveilhier, who believed that what we now call ‘thrombi’ were always caused by vessel wall injury. The principal questions are: how may a vein wall be injured without outside (experimental) intervention, and which specific parts of the vein wall are at risk of such injury?

Venous thrombi form in valves

Virchow’s careful drawings of thrombi depicted them more or less in the centre of the vein lumen, with streaks of white material running throughout their length. Although no valves are shown in most of these illustrations, Virchow nevertheless stated that ‘the thrombi are seated on the valves’. Notwithstanding...
ing the fact that Thrombose und Embolie is about the pathogenesis of emboli, not DVT per se, this brief remark was of the greatest importance for elucidating the aetiology of DVT and was enough to establish Virchow’s pre-eminence in the history of thrombosis research. In his 1858 collection of lectures, Cellular Pathology, there is a clear illustration of a thrombus anchored to a valve.\

**Virchow and the two accounts of DVT aetiology**

We can now propose an answer to the question posed earlier: why do the two different present-day accounts of the aetiology of DVT, the consensus model and the VCHH, both claim Virchow as precedent? In the consensus model, the ‘stasis + hypercoagulability + vessel wall injury’ concept is wrongly attributed to Virchow and seems to have arisen from a misreading of a passage in Thrombose und Embolie. As for the VCHH: although Virchow said little about the causes of DVT, he demonstrated (a) the involvement of leukocytes in the pathogenesis of venous thrombi and (b) the fact that thrombi are formed on valves. These two crucial discoveries will be explored further in the following sections.

**White cells and venous thrombogenesis: Hunter and the concept of ‘inflammation’**

The term ‘inflammation’ is at least 2000 years old. For around 1700 years the leading authority on the subject was De Medicina, compiled by the 1st century Roman writer Celsus, in which the four traditional signs of inflammation - rubor, calor, tumor and dolor (redness, heat, swelling and pain) – were identified. These signs describe manifestation, not cause. What we recognize nowadays as typical concomitants of the inflammatory response, such as phagocyte invasion and the release of various cytokines and complement factors, are not signs appreciable by examining physicians; they are detectable only by specific laboratory investigations.

The early microscopists of the 17th century, van Leeuwenhoek, Janssen, Kepler, Malpighi and Huygens, studied ‘inflamed’ tissues and challenged the doctrine of Celsus. Their findings enabled John Hunter (1728-1793) to define ‘inflammation’ more precisely. He wrote: ‘Inflammation is to be considered only as a disturbed state of parts... it is not to be considered a disease, rather a salutary operation [‘healing’ in today’s terms] consequent on either violence or disease’. In other words, inflammation is a response to tissue injury; the term ‘inflammation’ is descriptive but has no aetiological implication. Hunter then distinguished two types of ‘inflammation’, ‘adhesive’ and ‘suppurative’. In today’s terminology, these presumably equate to ‘degenerative inflammation’ (e.g. arthritis) and ‘infection-related inflammation’, though when Hunter was writing the concept of ‘infection’ lay more than 60 years in the future.\

‘Inflammation of the internal coats of veins’, the title of Hunter’s 1793 publication, denotes what we now (following Virchow) call venous thrombosis. What Hunter observed were intravenous coagula. Why did he use the word ‘inflammation’ in this context, and why did he specifically implicate ‘the internal coats of veins’? The latter question is challenging because he, like Cruveilhier and Virchow after him, observed the white-streak-coagulum in the middle of the vein lumen. The former question invokes what Hunter accepted as a signifier of inflammation, ‘pus’.

**The concept of ‘pus’ in the 18th and 19th centuries**

In Hunter’s day, it was well known that vein lumens could become occluded with what he termed ‘coagulated lymph, pus and blood’. Pu was considered to betoken inflammation, and inflammation was manifest as pus. Although ‘pus’ and ‘purulent inflammation’ are irrevocably associated today with bacterial activity, that association would not be established until the work of Pasteur and Lister in the 1850s. In Hunter’s day, any white amorphous material in the body was ‘pus’. It was considered to enter blood vessels from the surrounding tissues, which made its appearance in the centre of the vein lumen surprising.

Therefore, when Hunter observed an accumulation of white material in intravascular coagula, he identified it as ‘pus’ and inferred ‘inflammation’. Since ‘inflammation’ was traditionally associated with heat, he devoted considerable time and attention to determining whether blood coagulation liberates heat, but found it did not. However, in view of the invariable association of intravascular coagula with ‘pus’, he continued to describe the formation of such coagula as ‘inflammation’ of the ‘internal coats of veins’.

It was a few decades later, shortly after cell theory was articulated, that leukocytes were recognized as distinct entities. The source of ‘pus’ and its relationship to leukocytes was intensely debated during the 1840s. The English microscopists Addison and Waller concluded that ‘pus globules’ and ‘leukoeytes’ were identical, and that pus was normally formed by diapedesis of leukocytes from the blood vessels into the tissues, not the other way round, as previously believed. Remarkably, Virchow rejected that inference. He believed that the admixture of white material in the interstices of red venous thrombi represented a venous coagulum associated with a focus of pus. His generation of scientists therefore considered ‘coagulated blood inside vessels’ to merit the suffix ‘itis’. Nevertheless, he amassed evidence to show that the leukocytes constituting the white parts of thrombi originated from within the blood stream, not within the surrounding tissues, and he used this discovery to further his attack on Cruveilhier. This, it seems, is why he was so emphatic about an observation that we accept nowadays as a near-truism (see previous section).
Cruveilhier

Gilbert Brechet (1784-1845) appears to have read Hunter’s ‘inflammation of the internal coats of veins’ as ‘inflammation of the veins’ and translated it to the Greek-derived word ‘phlebitis’. He may have used the word originally in a memoir read to the Paris Académie des Sciences in 1832. Brechet was a close friend of Jean Cruveilhier (1791-1874) and succeeded him as Professor of Anatomy in 1836. Cruveilhier adopted his interpretation of Hunter and made free use of the neologism ‘phlebitis’. Virchow subsequently attributed the concept of ‘phlebitis’ to Hunter. Much more recently, Browse et al. attributed the strange hybrid term ‘phlebothrombosis’ to the same source.

Cruveilhier wrote:

‘In a way, phlebitis dominates all pathology… The first effect of all phlebitis is coagulation of the blood and its adherence to the walls of the vessel/s… Stagnation of the venous blood, and ‘serosity’ [oedematous swelling?] in the corresponding parts, result from obstruction of the venous circulation in the inflamed vessel when the collateral veins are not sufficient for circulation…’

In lecture 10 of Cellular Pathology, Virchow wrote:

‘It was imagined by John Hunter that pus… was furnished as a product of secretion by the wall of the vessel. This doctrine, however, presented some difficulty … Cruveilhier was right… that the so-called pus in the veins never, in the first instance, lies against the wall of the vein, but is always seen first in the centre of the previously existing coagulum which marks the start of the process. He imagined that the pus was secreted from the vessel wall, but did not remain there, but by means of ‘capillary attraction’ made its way into the centre of the coagulum.

Having made this admission, however, he proceeded to attack Cruveilhier’s ‘capillary attraction’ explanation, declaring it to be ‘mystical’. Later in the same lecture, however, he distinguished the ‘reactive blood semi-solidification’ of thrombogenesis from the ‘inflammatory state’ of the vein wall that had previously been alleged to cause it.

‘Pus’, infection and confusion

Virchow made a remarkable statement about the ‘white substance’ (the collected leukocytes) involved in thrombus formation: he said it was puriform but not purulent’. The phrase was remarkable because it preceded Pasteur’s recognition of bacterial action, and also preceded Lister’s realisation that bacterial action, infection and pus formation were interrelated. Lister recognised that the leukocytes associated with venous thrombi had nothing to do with bacteria; his Croonian lecture clearly distinguished between infection and intravascular coagulation. Nevertheless, another 80 years was to pass before it was generally accepted that bacterial infection was not involved in the aetiology of DVT. The longevity of the term ‘phlebitis’ to denote DVT testifies to the persistence of that confusion, notwithstanding the best efforts of Virchow, Lister and Pasteur.

The President of the Royal College of Surgeons during Lister’s early years, Sir James Paget, was critically dismissive of the new notions about ‘pus’ until 1879, when Lister received a standing ovation in an international meeting in Amsterdam. This is not to criticise Paget, but to indicate how difficult it is for senior generations to assimilate new developments. Anyone seeking to revise ‘received wisdom’ must re-educate their seniors, whose lessons have ossified. The same phenomenon affected Cruveilhier – and Semmelweiss - but perhaps in reverse.

Venous thrombi originate in valve pockets

Cruveilhier, like Hunter, was puzzled by the location of the ‘pus’ in the middle of intravenous coagula. Until Virchow discovered otherwise, it was held that pus was ‘exuded’ from the vessel walls and tissues external to them, so it should have been found immediately adjacent to the vein wall, not in the middle of a coagulated red blood mass. Cruveilhier seems not to have found a way of explaining this mysterious observation. However, perhaps Hunter had already done so.

Hunter was cautious about the use of microscopes and admonished his readers not to mislead themselves by ‘what can be seen through magnifying glasses … globules etc.’. Significantly, he wrote that warning - in a footnote on page 42 of his treatise - some 30 years before JJ Lister’s achromatic lens was introduced, when microscopes were unreliable; so his dubiety was justified. The consequence, however, was that he – like Cruveilhier - observed intravascular coagula only by naked eye. He never stated that thrombi are initiated on the valves, which are impossible to see with the unaided eye when they are smothered by a thrombus, but it seems highly likely that he made that interpretation. Harvey had described the valves as ‘eminences’ on the ‘internal lining (tunicula intima)’ of the vein. Hunter was familiar with Harvey’s masterpiece. Hence, we suggest, his nomenclature: inflammation (i.e. an accumulation of leukocytes) of the internal coats (the eminences on the internal linings, i.e. the valves) of veins. As we have seen, Virchow – aided by his skilled use of the improved microscope – recognized
that venous thrombi are initiated on the valves (his illustrations in Cellular Pathology explicitly showed them in the valve pockets) and that blood-borne leukocytes are involved in their formation. So whilst he acknowledged the importance of Hunter’s contribution, he was considerably less generous to Cruveilhier.

The significance of leukocytes in thrombogenesis was acknowledged by subsequent writers such as Welch,45 and Aschoff,46 and the role of platelets by Bizzozero,49 though all this is largely overlooked by proponents of the modern consensus model of DVT aetiology. As for the other major discovery of Hunter and Virchow: it is often acknowledged that thrombi are initiated at the venous valves, but the aetiological significance is seldom regarded. In fact, the association of thrombogenesis with the valves was overlooked for almost a century after Virchow, recognized during a period of two decades beginning in the 1950s, and then marginalized again as essentially irrelevant to the consensus model.

A paper by Hadfield50 published in 1950 contains line drawings that precisely reflect Aschoff’s ‘Kopfteil, Halsteil and Schwanzteil’ of thrombi.48 Remarkably, however, those drawings show no valves or valve pockets. Hadfield’s thrombi therefore arose, wholly imaginatively, from ‘wrinkles’ on the vessel wall, perhaps implying some unspecified abnormality of the endothelium. It seems that in Hadfield’s time, the first half of the 20th century, the presence and significance of valves in veins had come to be overlooked or ignored.

However, only a year after Hadfield’s paper appeared, Paterson and the McLachlin brothers produced a seminal paper on valve pocket thrombi.51 Subsequent papers by the same authors52,53 further established the valves as the site of thrombogenesis, as Virchow had described a century earlier. Later, an excellent series of pathological studies by Sevitt demonstrated that venous thrombi are rooted (and therefore presumably initiated) on the inner (parietal) surfaces of the valve cusps.54,55 These observations proved crucial for the development of the VCHH of DVT aetiology.11 The seminal work of Paterson, McLachlin and Sevitt is not cited by proponents of the consensus model and is therefore not well known.

CONCLUSION

This paper illustrates some of the ways in which salient discoveries by eminent researchers can be masked or distorted by subsequent commentators. Cruveilhier made a major contribution to understanding the aetiology of DVT and pulmonary embolia, but Virchow’s critique has marginalized him in the eyes of posterity. Virchow himself was concerned with the pathogenesis of embolism, not of DVT, yet – paradoxically – he made two crucial discoveries about venous thrombogenesis: the involvement of leukocytes and the role of venous valves. Yet posterity has not acknowledged these discoveries; indeed, the consensus model of DVT aetiology has no place for either of them. (We believe that Hunter had implicitly recognized both, but largely because of the limitations of contemporaneous microscopes he was unable to articulate either explicitly.) Likewise, Virchow’s tripartite distinction between in situ thrombi and ex vivo clots is largely ignored nowadays. Instead, most modern writers read Virchow’s summary account of the factors involved in pulmonary embolism as principles of the aetiology of DVT, hence the erroneous notion of ‘Virchow’s triad’.

Associated with the distortion and misrepresentation of Virchow’s work is the fact that the consensus model of DVT aetiology remains more widely accepted than the VCHH. A possible factor is the intimate connection of the consensus model with anticoagulant and thrombolytic prophylaxis and therapy, and of the VCHH with mechanical prophylaxis. The former approach to clinical practice entails profits for the pharmaceutical industry; the latter does not.

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