Historical Review

Venous Thrombosis: On the History of Virchow’s Triad

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Abstract
Rudolf Virchow, the renowned father of Modern Pathology, is credited with many monumental medical findings that continue to pervade the realms of modern medicine. His numerous discoveries notwithstanding, Virchow is remarkable in that he is attributed a theory on the complex pathogenesis of venous thrombosis – in an age limited by a rudimentary understanding of pathobiology and crude experimental resources – and this triad remains clinically relevant to date. The importance of Virchow’s Triad is impressed upon generations of students of medicine; consequently, this paper traces the history of venous thrombosis, focusing on its relationship to Virchow’s Triad and highlighting major trends in our understanding of the pathogenesis of this condition. Utilizing the Index Medicus, Surgeon General’s Catalogue, and period texts, a comprehensive review of both the English and French literature was undertaken. The results suggest that the ideas presented in the triad were neither original to Virchow, nor did he appear to synthesize them in the manner in which they are currently held. It is not until the middle of the 20th century that the triad ascribed to Virchow appears in the literature, and considerably later in most major pathology texts.

Introduction
Rudolf Ludwig Karl Virchow (1821 – 1902) is recognized for numerous medical discoveries that continue to influence generations of pathologists and clinicians alike. Ideally situated at the cusp of a revolution in medical advance, many of Virchow’s accomplishments continue posthumously to bear his name. One such attribution is a theory delineating the pathogenesis of venous thrombosis: Virchow’s Triad, which proposes that venous thrombosis occurs as a result of (i) alterations in blood flow, (ii) vascular endothelial injury, or (iii) alterations in the constitution of the blood. Proposed at a time when both pathology and haematology were in their infancies, the triad remains clinically relevant over 150 years later. Considered standard knowledge for all students of medicine, the triad is of obvious historical importance; consequently, this paper traces the history and application of Virchow’s Triad from its preconception to the present day.

Etiology
In reviewing both the English and French literature on the history of venous thrombosis and Virchow’s Triad, several resources were employed. The following search terms were used in the Index Medicus, Surgeon General’s Catalogue, and Medline. These terms included, but were not restricted to: Virchow, Virchow’s Triad, thrombosis (venous), embolism (pulmonary), phlebitis, hypercoagulable, inflammation (venous), stasis (blood), and clot (blood). Brackets denote the use of the more specific term, where applicable. Some indices included references to texts, in addition to journal articles (e.g., Surgeon General’s Catalogue). Other texts were identified applying the same search terms into the library catalogue at the University of Toronto, during the spring of 2003.

Early History of Venous Thrombosis
Pathologic haemostasis was described as early as 2650 BC by the Chinese physician Huang Ti; unfortunately, this account fails to distinguish between venous and arterial thrombosis. Anning suggested the earliest recorded observation of venous thrombosis occurred around 1400 AD as depicted from the account of the Consilia of Ugo Benzi of Sienna. More recently, rediscovery of an illustrated manuscript presented to the Cardinal of Bourbonnoys in the 15th century suggests the first documented account in a young man clearly suffering from venous thrombosis in 1271 AD.

More steadfast reports of venous thrombosis emerged towards the end of the 17th century. Wiseman (1686) offered an early theory on the etiology of venous thrombosis, which bears interesting resemblance to Virchow’s Triad:

The cause of which may be referred either to the coagulation of the Serum, or granulation of the Blood, or to the obstruction of the Vein somewhere in its passage by some anguiation upon it by part of the tumours from whence it will often happen that the Vein beyond it hath its current stopped, and is forced to swell. Nay, not only the contraction of the Vessels by preternatural Tumours doth this, but also any other preasure.
Wiseman thus attributed the cause of thrombosis to: (i) coagulation of the serum; (ii) thickening of the blood; and, (iii) decreased venous blood flow by either impingement by tumour or any other back pressure on the venous system (Table 1). He proceeded to describe the increased occurrence of thrombosis during pregnancy and malignancy; Van Swieten (1705) is credited with describing the incidence and outcome of clots during the puerperium. White (1784) illustrated that phlegmasia alba dolens is associated with thrombosis of the iliac or femoral veins. That same year, Hunter published Observations of the inflammation of the internal coats of veins where phlebitis is first described.

Virchow: Thrombosis and Emboli
Upon his appointment to the Charité Hospital in Berlin, Virchow came under the direction of Robert Froriep (1804–1861), who tasked him with investigating the assertion of the leading French pathologist Cruveilhier (1791–1874) that “La phlébite domine toute la pathologie [Phlebitis dominates all pathology].” It bears mention that phlebitis and thrombosis, until Virchow’s urging, were described synonymously.

Virchow combined clinical and experimental investigations in pursuing Cruveilhier’s clinical. In a series of 76 autopsies he identified 18 cases of ‘venous plugs’, 11 involving concurrent pulmonary emboli. In several instances he noted that the distal margin of the clots isolated from pulmonary arteries “… fit to the end of the [venous] thrombus like a cap… it was easy to demonstrate the separation of these pieces from a certain location by the upper concave, the lower convex, and inversely terraced surfaces.” Thus, he correctly determined that the clot wedged in the vasculature of the lungs represented a fragment derived from a distal source. Virchow coined the term embolism to describe this process and reasoned that the majority of clots originate from the deep veins of the lower extremities, thereby contradicting the prevailing belief that thrombosis occurred in the lungs de novo as a result of inflammation of the veins. Virchow substantiated his necropsy observations by a series of studies in which he injected various materials into the venous circulation of dogs, ultimately examining the characteristics of the material lodged in the pulmonary vasculature. In addressing the pathogenesis of the pulmonary embolism, it was presupposed that Virchow proposed his triad to describe the precipitants of the original venous thrombus.

Virchow’s Triad
Alterations in Blood Flow
Prior to Virchow’s work, the role of stasis towards venous thrombosis was already well established, as exemplified by Wiseman’s work in 1686 (previously quoted herein). As well, Baillie (1793), Davies (1823), Andral (1830) and Bouchut (1845) are all credited with observing that stasis contributes to an increased risk of venous thrombosis.

Humphry (1881), after personally incurring venous thrombosis, proposed that clotting also stemmed from turbulence in blood flow. He reasoned that eddies, generated as a result of the venous valves, facilitated clotting; the idea of ‘valve pockets’ was re-popularized nearly 100 years later.

By the 1930s, consensus emerged that stasis alone was insufficient for generating thrombosis. Nevertheless, it was appreciated that reduced blood flow contributes to thrombosis, which is speculated to facilitate interactions between blood constituents and the vessel wall, or alter the balance of activated clotting factors and inhibitors within the blood stream. Additional support for this hypothesis came from emerging observations of an increased risk of thrombosis in patients paralysed from stroke and spinal cord injuries, as well as patients confined to bed-rest or immobility. The theory in this instance being that the veins, dependent on the pumping action of adjacent muscles to return blood to the heart, developed increased pooling of the blood which potentiates interactions between the erythrocytes and the endothelium.

Recent media attention has revived interest in the contribution of venous stasis, particularly as it pertains to passengers on long trans-oceanic flights with the ‘economy class syndrome’. It remains noteworthy, however, that consistent with studies almost 150 years earlier, stasis alone does not appear to cause thrombosis; rather, it requires the addition of vessel injury or hypercoagulability.

Endothelial Injury
The notion that injury to the intima causes thrombosis – also known as the ‘doctrine of Cruveilhier’, reflecting its obvious origins – was known prior to Virchow’s research on venous thrombosis. Hodgson (1815), followed by others, described how trauma to a vein predisposes to thrombosis. Meanwhile, Davies (1823), Andral (1830), and Lee (1842) were of the opinion that inflammation of the endothelium could also contribute to this phenomenon.

Baumgarten (1876) demonstrated that blood trapped in a doubly ligated vein for months failed to clot, but inoculation of the isolated blood with infectious material resulted in prompt thrombosis. Injury alone was subsequently demonstrated to be insufficient for generating thrombosis. Barrett (1924) inflicted aseptic trauma to veins, noting that coagulation failed to occur even in subsequent experiments when he injected bacteria at the site of injury. It was only when he anchored bacteria-inoculated threads in the vasculature did he generate a venous thrombus and in some cases a pulmonary embolus. Advances in anaesthesia – which enabled longer and more invasive surgical procedures – along with subsequent casualties from the Great War, heralded the contribution of the endothelium which hitherto had been considered a minor contributor to venous thrombosis. Injury to the intima was thought to be due to direct trauma, but more importantly from damage as a result of infection and bacterial toxins, thus “some workers go so far as to say that there cannot be any thrombosis in the absence of infection.”
### Table 1
**Historical Summary of the Proposed Contributors to Venous Thrombosis**

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>YEAR</th>
<th>ETIOLOGY</th>
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| Wiseman    | 1686 | 1. Coagulation of the serum  
                        2. Thickening of the blood  
                        3. Decreased venous blood flow by impingement or backward pressure on the venous system |
| Loeb       | 1903 | 1. Constitution of the blood  
                      2. Influence of surrounding tissue upon coagulable fluids  
                      3. Influence of foreign elements such as bacteria and ligatures |
| Bland-Sutton | 1909 | 1. Mechanical disturbances in the blood  
                          2. Lesions of the endothelium  
                          3. Alterations in the blood  
                          4. Sepsis |
| Wilson     | 1912 | 1. Slowing or stagnation of the blood stream  
                      2. Injury of the vascular walls  
                      3. Disintegration of the corpuscles of blood from toxic substances  
                      4. Bacteraemia |
| Duckworth  | 1913 | 1. Feeble state of the circulation due to cardiac debility  
                      2. Injury to, or alteration of, the intima of vessels  
                      3. Direct blocking of their lumen by the intrusion of foreign or toxic material  
                      4. Increased blood viscosity. |
| Aschoff    | 1924 | 1. Changes in blood-plasma (coagulability)  
                      2. Changes in blood elements (agglutination)  
                      3. Changes in blood flow (slowing, or eddies)  
                      4. Changes in vessel (endothelial damage) |
| McCartney  | 1927 | 1. Slowing of the blood stream  
                      2. Injury to vascular endothelium  
                      3. Changes in the composition of blood |
| Bancroft   | 1931 | 1. Trauma  
                      2. Infection  
                      3. Slowing of the blood stream  
                      4. Dehydration |
| Vance      | 1934 | 1. Slowing of the blood stream  
                      2. Injury to vascular endothelium  
                      3. Changes in the composition of blood |
| Anning     | 1957 | 1. Changes in the velocity of the blood stream  
                      2. Lesions of the vascular intima  
                      3. Alterations in the constitution of blood |

### Table 2
**Summary of Relevant Terms**

**Venous Thrombosis**
The antemortem occurrence of coagulated blood within a vein.

**Pulmonary Embolism**
The process by which a lesion derived from the downstream venous circulation migrates to the pulmonary vasculature. This is most commonly attributed to a fragment of venous clot; however, it could also include other material such as air, amniotic fluid, and fat.

**Phlebitis**
Inflammation of the vein.
Appreciation for the complex intrinsic biology of the endothelium reveals how interdependence amongst many factors governs the dynamic interplay between the occurrence of thrombosis and thrombolysis. For example, exposure to the circulation of factors which are normally sequestered in the subendothelial space, disorganization of the cell matrix, or alterations of the structure and function of the endothelial cells proper may all off-set this delicate balance.22

Alterations in the Constitution of the Blood
It is paradoxical that Virchow would endorse a role for hypercoagulability as a contributor to venous thrombosis, given the lack of tangible evidence – only now revealed with the multitude of experimental resources at our disposal – for such a nebulous assertion. Re-examination of Virchow’s original intent demonstrates that by ‘alterations in the constitution of the blood’ he implied more banal factors such as changes in the relative amount of fibrin8 and platelets, and dehydration, rather than foreshadowing a myriad of amorphous illnesses.

Wiseman (1686) proposed that either coagulation of the serum, or thickening of the blood contributed to venous thrombosis.4 Andral (1830) also preceded Virchow by suggesting that venous thrombosis may be the result of an increased tendency of blood to coagulate.10 Nevertheless, prior to the 1930s, tangible factors contributing to thrombosis by altering the composition of blood were lacking.15,23 While it was known that the injection of certain snake venoms could precipitate thrombosis, few endogenous factors were known to have a similar effect.14 Lotheisen (1901) theorized that pregnancy, malignancy and chlorosis, amongst other factors, may affect thrombosis in this regard.23 Subsequently, increases in globulin, fibrinogen, and calcium were all postulated to increase agglutinability; as well, it was suggested that obesity and infection may potentiate coagulability.15,23

Hypercoagulability ranks unequivocally as the broadest category contributing to the triad at present.25 We better appreciate the host of genetic and environmental factors contributing to alterations in blood coagulability, far too innumerable to summarise herein.

Virchow’s Triad Revisited
In its simplest form Virchow’s Triad is thus summarized: (i) alterations in blood flow, (ii) vascular endothelial injury, and (iii) alterations in the constitution of the blood.2 The literature references several of Virchow’s works as the source for the triad, including Die Cellularpathologie [Cellular Pathology], Thrombose und Embolie [Thrombosis and Emboli], and Gesammelte Abhandlungen zur Wissenschaftlichen Medicin [Collective Treatises on Scientific Medicine]. The former two texts have been translated into English and fail to explicitly mention a triad. This author’s efforts to obtain translation of the most frequently cited portions of the latter text also fail to identify the triad (data not shown). Virchow does outline a tetrad for the etiology of pulmonary artery thrombosis bearing some resemblance to the triad; nevertheless, this theory is specifically intended to explain thrombosis in the pulmonary artery. Consequently, it remains unclear if Virchow considered the pathogenesis of thrombosis in the pulmonary artery similar – except for the fourth criteria – to that of venous thrombosis.

Owing to the fact that each of the three elements of the triad may be assembled from various parts of Virchow’s extensive writings, it would seem that he appreciated the contributors to venous thrombosis; nevertheless, he never assembled a formal triad to delineate the contributors to venous thrombosis24 (A Matzdorff, personal communication). Given that each of these three elements was previously established as contributing to venous thrombosis, it can only be assumed that Virchow was aware of this literature; further, there is no direct evidence to suggest that he ever laid claim to these observations. Matzdorff (2004) points out that Virchow constructed a triad, bearing resemblance to that which we associate today as Virchow’s Triad, but that he expressly intended it as an explanation for the adverse consequences in the pulmonary vasculature following a pulmonary embolism.21 It remains yet to be discovered if and how this triad became misapplied to describe the pathogenesis of venous thrombosis in the literature.

Diagnosis and Treatment
Since Virchow’s lifetime, the utility of a clinical diagnosis of venous thrombosis remains relatively unchanged. A thorough history may identify pertinent risk factors, or a complaint from the patient regarding anxiety, anorexia, or insomnia.10 Examination of the limbs infrequently yields a diagnosis, but may reveal a warm, swollen, edematous, or discoloured appendage;4,20,27 dorsiﬂexion may exaggerate tenderness, denoting ‘Homan’s sign.’10 Venography allowed X-ray visualization of the patency of veins around the early 1930s,28 which at present remains the ‘gold standard.’29 Less invasive, but operator dependent, ultrasound offers an efﬁcient tool for examining the patency of veins. In the future, spiral CT venography, and MRI are predicted to facilitate the diagnosis of venous thrombosis.30

In Virchow’s era, treatments for venous thrombosis included leeches, bed-rest, and warm compresses alternated with various lotions and liniments;11,27 a subtle improvement from the purging and bleeding advocated in the 1680s.4 Surgical interventions, such as the proximal ligation and excision of thrombosed veins, were favoured in the 1860s but were employed as early as the 1680s albeit with limited success.31

Identification of some of the risk factors for venous thrombo- sis – namely venous stasis and bacteremia – led to the suggestion that they could be minimized via prophylaxis.32 Examples included early ambulation following surgery, breathing exercises, and in some cases intraoperative exercise.10,32 Optimizing venous return to the heart was the goal of most early therapies. Attempts to improve cardiac output were attempted with digitalis, intravenous ﬂuids, thyroid extract, alcohol and carbon dioxide.30,31 Elevating the foot of the bed was initially recommended but later abandoned as potentially dangerous, in favour of raising the head of the bed.10

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Researchers predicted early that anticoagulants and thrombolytic treatment might be efficacious in preventing and treating this condition.\textsuperscript{19} Initial anticoagulants included the application of leeches (\textit{Hirudo medicinalis}) which in 1884 were discovered to have anticoagulant properties.\textsuperscript{23} It was some 20 years later before the anticoagulant hirudin was extracted and purified\textsuperscript{23} but it was not until the early 1900s that it found clinical acceptance;\textsuperscript{23} unfortunately, low yields of the active ingredient ultimately limited its applicability.

Heparin was discovered in 1916 as an anticoagulant, and its purification in the 1930s enabled its clinical introduction.\textsuperscript{34} In Toronto, Murray (1947) noted that heparin decreased the rates of pulmonary embolism in both postoperative patients, and those with known leg clots.\textsuperscript{34} Heparin remains a mainstay in the prophylaxis and management of thrombosis.\textsuperscript{22} Similarly, coumadin was introduced in the treatment of venous clots near the start of the 1940s and it too remains invaluable in limiting the incidence of clots.\textsuperscript{22,15} Meanwhile, intravenous filters, and in limited cases thrombectomy, can be offered to patients with contraindications to anticoagulation.

The discovery in the late 1950s that streptokinase lyases thrombi heralded its successful introduction into a clinical setting.\textsuperscript{36} Streptokinase speeds up resolution of venous clots; however, the use of this and other thrombolitics has generally fallen out of favour for fear of complications arising from haemorrhage.\textsuperscript{37}

\textbf{Conclusion}

Venous thrombosis and pulmonary embolism remain frequently encountered medical conditions; remarkably, despite significant advances in our understanding of haemostasis and thrombosis over the last 150 years, \textit{Virchow’s Triad} has endured as an explanation for the etiology of venous thrombosis. The diagnosis of thrombosis remains loosely rooted in the clinical tradition; however, investigations such as venography and ultrasound markedly improve our diagnostic capabilities. Treatment options have greatly progressed since Virchow’s time, although few significant breakthroughs have emerged since the introduction of heparin and coumadin therapy.

The origins and intent of \textit{Virchow’s Triad} remain nebulous; moreover, it is unclear to whom ownership should be duly ascribed. Clearly, the components of the triad were neither original to Virchow, nor did he purposefully organize them as a means to explain venous thrombosis. Almost 50 years after he published his work on pulmonary embolism there remains no evidence that he coined a triad for venous thrombosis; it is not until the 1930s that the three current components of the triad appear generally agreed upon in the literature (Table 1). \textit{Virchow’s Triad} itself does not seem to arise in the English or French literature until the 1950s\textsuperscript{2} and almost a decade later in most major pathology texts. Indeed, a comprehensive review of the German literature might be anticipated to advance the appearance date of the theory. Stanley Robbins’ (1962) renowned pathology text originally cites four factors as the cause of thrombosis: (i) derangement in the composition of the blood, (ii) stasis, (iii) turbulence, and (iv) alteration in the integrity of the endothelium.\textsuperscript{38} An earlier text by the Canadian pathologist William Boyd (1932) cites injury to the vascular surface from (i) trauma, or (ii) inflammation as the most significant causes of thrombosis.\textsuperscript{39} Both of the aforementioned texts neglect to mention Virchow as influential in the development of this theory; however, the 1964 re-edition of Boyd’s text offers a modified explanation on the etiology of thrombosis:

More than a hundred years ago Rudolf Virchow, . . . stated that there were three factors (Virchow’s Triad) involved in its causation. These were: (1) slowing of the blood stream, (2) changes in the vessel wall, and (3) changes in the blood itself. In the intervening years almost nothing of real importance has been added to our knowledge.\textsuperscript{40}

Its tenuous origins notwithstanding, \textit{Virchow’s Triad} remains clinically relevant. The persistence of this term, as it applies to the pathogenesis of venous thrombosis, may be attributable to several factors. First, broad ambiguity in the phrasing of the triad’s categories facilitates the assimilation of new discoveries into the paradigm (eg, hypercoagulable states). It is also possible that without a clearly established point of reference for its intent, the triad remains loosely open to interpretation (eg, its applicability to arterial thrombosis). As well, the possibility remains that the resilience of \textit{Virchow’s Triad} reflects the ongoing limits of our appreciation for the pathogenesis of venous thrombosis.

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\textbf{References}