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Aetiology of Deep Venous Thrombosis - Implications for Prophylaxis

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1. Introduction

Clinical research on deep venous thrombosis (DVT) and thromboembolism (VTE) has focused in recent years on the contributions of potentiating factors, alone and in combination, to the risk of contracting these conditions. Many such 'risk factors' have been identified (Geerts *et al*., 2004) and are discussed elsewhere in this book. The National Institute for Clinical Excellence (NICE) in the United Kingdom has exploited this knowledge to make the prevention of DVT its main focus for 2011. In his keynote lecture introducing the policy and procedures adopted by NICE, Arya (2011) described the tools for evaluating risk in various patient groups and emphasised 'anticoagulation' in the design and implementation of evidence-based prophylactic measures. He claimed that the frequency of VTE in hospital patients should be reduced by 2/3 if the agreed protocols are followed. An achievement of that magnitude would be most welcome.

Comparable views have been articulated elsewhere in Europe. Although NICE is distinctive in recommending assessment for thromboprophylaxis for all medical inpatients, the health services of other European Union countries offer broadly similar guidelines, especially for patients with acute medical conditions with expected durations of hospital stay longer than 3-4 days (Khoury *et al*., 2011). Similarly, in the USA, the Surgeon General issued a 'Call to Action to Prevent Deep Venous Thrombosis and Pulmonary Embolism' in 2008 (Sliwka & Fang, 2010), and the Joint Commission on Accreditation of Healthcare Organizations requires prophylaxis for patients at moderate or high risk of VTE (Rothberg *et al*., 2010). In all these cases, the emphasis is on anticoagulation, typically with unfractionated or low molecular weight heparin or with Fondaparinux.

However, despite the progress made in recent decades, the incidences of DVT-associated mortality and morbidity among hospital patients have declined only minimally (Kahn & Ginsberg, 2004; Heit, 2005), perhaps suggesting there is scope for improvement in our understanding of the aetiology of DVT and *a fortiori* our approach to prophylaxis.

Because of the range and variety of established risk factors, there is a widespread view that DVT is 'multifactorial' or 'multicausal' (e.g. Rosendaal, 1999, 2005; Lippi & Franchini, 2008; Khoury *et al*., 2011). In a substantial minority of DVT patients, no known risk factor can be identified, and those cases are dubbed 'idiopathic'. While 'risk factors' determine the

probability that a venous thrombus will become clinically significant and make embolism and/or post-thrombotic syndrome more likely, they have not been experimentally shown to be implicated in the *initiation* of thrombosis (Malone & Agutter, 2008, chapter 3). It is therefore conceivable that venous thrombogenesis *per se* is not multicausal.

The *valve cusp hypoxia* (VCH) *hypothesis* was proposed in the 1970s and was subsequently corroborated by experimental evidence showing that all cases of DVT have a common underlying aetiology (Malone & Agutter, 2006, 2008; Agutter & Malone, 2011). The (empirically validated) VCH thesis of DVT aetiology is rooted in longstanding causal concepts, but since it may be unfamiliar to some readers, it will be summarised in this chapter before we discuss its clinical implications. In section 2 the contrast between VCH and current mainstream views will be highlighted, and in section 3 we will explore its roots in the historical literature, focusing on Virchow's seminal studies of venous thrombi and emboli, which raised key questions that must be answered by a plausible account of their aetiology. Section 4 comprises an overview of the VCH thesis and its experimental validation, and answers those key questions. In section 5 the VCH thesis is extended in the light of recent publications, potentially enriching our understanding of DVT aetiology. Section 6 presents a rational approach to prophylaxis based on our understanding of VCH, and outlines a programme of experimental research leading to clinical trial/s.

2. A departure from mainstream views

The VCH thesis is rooted in and informed by the classical work of Virchow, Welch and Aschoff, and its account of DVT aetiology logically implies a means by which venous thrombogenesis can be anticipated and prevented; i.e. it provides a rational basis for prophylaxis, though not for therapy. The mainstream (consensus) viewpoint, in contrast, emphasises 'risk factors' to provide a basis for preventing or retarding the growth of already-formed thrombi. The two perspectives might therefore be seen as complementary rather than as necessarily conflicting, though they are very different.

For example, it is well established that inherited and acquired thrombophilias are important contributors to the risk for clinically significant DVT. After hereditary antithrombin III deficiency was described almost half a century ago (Egeberg, 1965) a number of thrombophilias were identified, and the molecular bases of many of them are now known. Defects in the protein C pathway are the most common inherited disorders (Lane *et al.*, 1996). Acquired thrombophilias are many and varied; the most widespread is antiphospholipid syndrome (Asherton & Hughes, 1989). There are many reviews of the field, e.g. Mazza (2004), Rosendaal (2005), Hassouna (2009), Anderson & Weitz (2010), and the topic is explored elsewhere in this book. Broadly, the work surveyed in these reviews shows that overactivity of coagulation factors, underactivity of regulatory factors or slow lysis of coagula can increase the risk of clinically significant DVT and embolism. Since a patient with no identifiable thrombophilia might develop DVT, it is supposed that other risk factors must be present to carry such patient over the presumed 'thrombogenic threshold' (Mammen, 1992; Lippi & Franchini, 2008; Anderson & Weitz, 2010).

According to the VCH thesis, however, thrombophilias do not *cause* DVT (Malone & Agutter, 2008, chapter 3). A thrombophilia increases the likelihood that a venous thrombus

will become dangerous for the patient *after* it has formed, but it has no effect on the likelihood that thrombogenesis will occur in the first place. That does not diminish the relevance of thrombophilias to the *growth* of thrombi and *ipso facto* the likelihood of VTE, but it marginalises their significance for understanding aetiology and *a fortiori* for designing prophylactic measures. More generally: according to the VCH thesis, the situation or conditions under which venous thrombogenesis may be initiated, i.e. the *aetiology* of DVT, is not a defined haematological issue; no components of the coagulation mechanism are involved during the inception of the pathological process.

The introduction of haematological concepts and methods into the study of venous thrombosis is of quite recent origin. No haematological publication prior to the Second World War mentioned thrombosis (for example, see Eagle's excellent review 1938), and landmark studies of DVT made little or no reference to haematology. After 1945, considerations of haematology were only gradually introduced into the study of DVT (Robb-Smith, 1955); in the third edition of the Biggs-MacFarlane monograph on haematology (Biggs & MacFarlane, 1962), thrombosis was mentioned on only six of about 350 pages of text.

Virchow's seminal work (1856, 1858, 1862) was 'thrombological' not 'haematological', though this is a verbal rather than a clinical medical specification. Investigation of the haemophilia of Queen Victoria's child was already in hand as he organised his knowledge, but that investigation was wholly unrelated to his already-active studies of thrombosis and embolism.

3. Virchow's studies of thrombosis and embolism

Virchow's objective from 1846 to 1856 was to prove that pulmonary 'phlebitis' is actually 'pulmonary embolism' arising from thrombi formed in distal veins, and thus to contradict Cruveilhier. He wrote almost nothing of note about the mechanism(s) of thrombogenesis, but made crucial observations about the morphology of venous thrombi and the sites at which they form. Acceptable accounts of the aetiology of DVT must explain those observations.

Virchow's work on thrombosis and embolism has been widely misunderstood and misrepresented during the past half century.

3.1 The status and provenance of 'Virchow's triad'

In a generally excellent review, Bovill & van der Vliet (2011) wrote: "In the mid-nineteenth century, Rudolph Virchow described, in a paper on PE, three factors that he felt contributed to thrombogenesis (32). The three factors were blood flow (stasis or impaired flow), composition of the blood (hypercoagulability), and changes in the vessel wall (endothelial activation and or damage). This triad has guided thinking about thrombogenesis for 150 years." Their reference (32) is to a secondary source (Owen, 2001). The quoted passage from Bovill & van der Vliet sums up a common but mistaken belief about Virchow's contribution to the field (e.g. Peterson, 1986; Rosendaal, 2005; Esmon, 2009; Kyrle & Eichinger, 2009; Meetoo, 2010). Virchow wrote no such thing.

In both *Thrombose und Embolie* (Virchow, 1856) and the relevant lectures in *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre* (Virchow, 1858), the focus was on pulmonary embolism, not thrombogenesis. The only passage in *Thrombose und Embolie* that vaguely resembles 'Virchow's triad' (pp. 293-4 of the Matzdorff-Bell translation) states: "*the sequence of the possible stages and consequences of blockage may be classified and studied under three headings: (1) phenomena associated with irritation of the vessel and its vicinity; (2) phenomena of blood-coagulation; and (3) phenomena of interrupted blood-flow*". But as the context makes clear, this refers to the 'blockage' of the pulmonary artery by a metastasised thrombus, not to the formation of that thrombus in a distal vein. The quoted passage from Virchow's classic appears to have been misread and mistranslated during the mid-20th century, perhaps because English-speaking readers found 19th century technical German difficult; there was no full and authoritative English translation of *Thrombose und Embolie* until 1998. Several authors have made this point (Brinkhous, 1969; Brotman *et al*., 2004; Dickson, 2004; Malone & Agutter, 2006; Bagot & Arya, 2008), but the misinterpretation persists. Some of these authors claim that although 'Virchow's triad' has no basis in what Virchow wrote, it is nevertheless useful in clinical practice (Brotman *et al*., 2004; Bagot & Arya, 2008). That may seem practical, guiding us to deal with injured veins, administer anticoagulants, and maintain a reasonably high venous blood flow rate in the lower limbs; but it is not scientifically honourable to exonerate and even legitimate an accidental and regrettable distortion of Virchow's meticulous observations to the detriment of our understanding of the aetiology of DVT.

The truth is that Virchow neither conceived nor wrote 'Virchow's triad'; the phrase first appeared in print following the historical study by Anning (1957), about a century after Virchow's seminal works were published.

3.1.1 Precedents and mutations of 'Virchow's triad'

In its original form - the statement that DVT is caused by some combination of disturbed blood flow, altered blood composition and vessel wall abnormality - 'Virchow's triad' was unexceptionable though misconceived. It afforded a general view of causation, and it is hard to imagine any contribution to the aetiology other than the three named facets. Moreover, it was one of a line of general points of view about DVT dating from the late 19th and early 20th centuries and thus belonged to an institutionalised tradition. For example, Aschoff (1924) proposed a 'tetrad': that DVT is caused by some combination of changes in the coagulability of the blood, changes in the formed elements of the blood, changes in the circulatory blood flow and changes in the vessel walls. But Virchow did not contribute to that tradition.

However, 'Virchow's triad' underwent mutations early in its history (late 1950s). 'Disturbed blood flow' came to be equated with 'venous stasis' (and to mean slow-flow rather than literally no-flow), just as 'altered blood composition' came to be interpreted as 'hypercoagulability'. It must be emphasised that Virchow never mentioned 'hypercoagulability' and furthermore explicitly rejected the 'doctrine' (*die Lehre*) that stasis has any causal role in thrombosis or embolism. 'Virchow's triad' would have bewildered him. The mutations continued and some authors, contrary to the superb studies by Welch (1887, 1899), have doubted whether vessel injury is causally significant in venous

thrombosis (Comerota *et al*., 1985; Kyrle & Eichinger, 2009); however, others such as López & Chen (2009) have recognised that events at the vessel wall precede coagulation. Moreover, retarded blood flow or 'stasis' is sometimes viewed as only a 'potentiating influence' because – so it is conjectured - it allows coagulation factors to accumulate locally (Thomas, 1988; Mammen, 1992; Hamby, 2005). Thus, increasing emphasis has been placed on the presumption of abnormally rapid blood coagulation (Thiangarajan, 2002; Bulger *et al*., 2004), i.e. on thrombophilias, fostering the misleading impression that the aetiology of DVT is to be understood within the domain of haematology rather than that of circulatory anatomy and physiology.

Interestingly, the invention of 'Virchow's triad' in the late 1950s - and the concomitant assumption that DVT is a haematological disorder - followed in the wake of the FDA's acceptance of anticoagulant therapy and prophylaxis (Cundiff *et al*., 2010). Some connection might be suspected, and was indeed suspected at the time. We have quoted the barbed comments of Pulvertaft (1947) elsewhere (Malone & Agutter, 2008). Robb-Smith (1955) wrote: "*In recent years haematologists have been forced to take an interest in the practical if not the theoretical aspects of thrombosis by the introduction of anticoagulant therapy*." Later in the same article, he observed: "*… the coagulationist, tilting his tubes with stop-watch in hand, appears to have inherited the mantle of druidical haematomancy, like the medieval physician who based his prognosis on the appearance of the buffy coat in the bleeding bowl… one has the feeling that the stock-in-trade of reagents and reactions to produce a fibrin clot is remote from a thrombus*". Robb-Smith understood the spirit of Virchow's work. (Of course, he did not use the phrase 'Virchow's triad', which would not be coined for another two years.)

3.2 Virchow's *real* triad

Although Virchow's studies during the decade 1846-56 were motivated by refutation of Cruveilhier's opinions and therefore focused on the causation of pulmonary emboli, not of thrombosis, his observations of venous thrombi were crucially important, thanks to his skilled use of the Lister microscope (invented in 1827). One of these observations was his three-part contrast between a thrombus and an *ex vivo* clot. On pp. 514-5 of the *Gesammelte Abhandlungen* (Virchow, 1862), he recognised that:

1. a thrombus, unlike a clot, has a manifestly layered structure, later called the Lines of Zahn (Zahn, 1876);
2. the fibrin content is many times denser than is found in a clot;
3. the white cell content is vastly greater.

This tripartite distinction between 'venous thrombus' and 'clot' has a better claim to be labelled 'Virchow's triad' than the stasis-hypercoagulability-injury mantra, since Virchow actually wrote it. Moreover, it encapsulates common clinical knowledge; for instance, those who have seen a thrombus extracted during a venectomy or an embolism removed at post-mortem have had the opportunity to observe the white 'tail' (the *Kopfteil* in the terminology of Aschoff, 1924).

In view of the clarity of Virchow's summary distinction, the now-commonplace tendency to treat 'venous thrombus' as synonymous with 'clot' is surprising. Perhaps we should recall

the elementary fact reported by Joseph Lister in his Croonian lecture (Lister, 1863): circulating blood has no inherent tendency to coagulate; coagulation is initiated *only* when blood makes contact with an abnormal surface, i.e. anything other than normal, uninjured vascular endothelium. Haemostasis is a part of normal physiology, initiated when blood leaks from a vessel. Venous thrombogenesis is not normal physiology; it is a pathological process entailing local blood coagulation *in situ*. A venous thrombus is a lesion, in the strict sense of an abnormal change in a tissue caused by injury or disease. Venous thrombi are in many respects *like* clots, but they are not clots, so it is not logical to infer that they are formed in the same way as clots.

3.2.1 The importance of Virchow's *real* triad

The morphological characterization of venous thrombi encapsulated in Virchow's publication is important in two respects:

First, an account of the aetiology of DVT must include a causal explanation for all three morphological features. That is the critical test of any aetiological hypothesis.

Second, Virchow's *real* triad constitutes a triple criterion for assessing experimental thrombi. Any coagulum or other structure produced in an experimental setting that does not display Lines of Zahn, dense fibrin and a white *Kopfteil* cannot be regarded as a thrombus, and the experimental model that generates such a structure cannot be considered a model for venous thrombogenesis (cf. Welch, 1887, 1899).

3.2.2 Leukocytes and venous thrombogenesis

Nowadays, notwithstanding Virchow's observations, it seems to be tacitly assumed that leukocytes have no aetiological significance and are concentrated in the *Kopfteil* of a thrombus only because they are adventitiously trapped in the fibrin mesh. But adventitious trapping cannot explain the segregated whiteness of the *Kopfteil*; erythrocytes are also adventitiously trapped by the fibrin and they outnumber leukocytes in the circulating blood by many orders of magnitude, hence the redness of the subsequent, more newly-formed, *Schwansteil* of a thrombus.

Virchow's key insight was that the leukocytes concentrated in a venous thrombus (as distinct from a clot) originate from within the blood stream, not from outside (migrating through the vessel wall) as previously supposed. *A fortiori*, they must form while the blood is *flowing*, since such an excess of leukocytes over erythrocytes can be provided only from a large volume of circulating blood. However, he was not the first investigator to recognise that white material is a primary constituent of what we now call 'venous thrombi'. Hunter (1793) wrote about the 'inflammation of the internal coats of veins', describing a lesion of the kind we now call 'venous thrombosis' as a local accumulation of 'pus'. Similarly, Cruveilhier focused on the accumulation of 'inflammatory' material, denoting the process by the term 'phlebitis' (Talbott, 1970). Unlike Hunter and Cruveilhier, who denounced the 'magnifying glasses' of their day, Virchow used the microscope, so he was able to see that the white material in a venous thrombus was not amorphous but comprised a mass of cells. Two decades later, the improved Zeiss microscope made platelets readily visible as obviously copious blood elements.

This observation inspired investigations of venous thrombi over the following seventy years. The elegant and detailed morphological studies of Welch (1887, 1899) highlighted the contributions of leukocytes as well as platelets to thrombus structure, and Aschoff (1924) declared that the causation of DVT would only be understood when the accumulation of white cells was explained: "*Along with the explanation of this marking* [the Lines of Zahn] *stands or falls the whole problem of thrombus formation, so far as consideration of the majority of cases of autochthonous thrombosis goes*".

3.2.3 Why do leukocytes accumulate at sites of venous thrombogenesis?

Hunter realised in 1793, more than 60 years before the germ theory of disease was articulated, that leukocytes swarm to sites of either tissue injury or local infection (a phenomenon more recently termed 'margination of leukocytes'). After Pasteur's work had been accepted, it was widely supposed that infections contribute to the causation of DVT; but when no consistent correlation between thrombosis and infectious agents was established, and antibiotics did not alleviate or prevent DVT, that hypothesis was abandoned during the first half of the 20th century. This aspect of history was reviewed briefly in our monograph (Malone & Agutter, 2008, chapter 7). Once again, Virchow was uncannily prescient on this topic; although unaware of the epoch-making discoveries being made in Pasteur's laboratory while he was writing *Thrombose und Embolie*, he perceptively described the accumulation of white material in thrombi as '*puriform but not purulent*' (Virchow, 1856).

For more than a century there has been experimental support for the inference that the cause of leukocyte and platelet margination at the site of venous thrombogenesis is local injury. Welch (1887, 1899) showed that experimental thrombi induced by electrical or other traumatic injury to the venous endothelium morphologically resembled autochthonous thrombi. This established the only valid way of evaluating experimental thrombi; as stated in section 3.2.1, coagula that lack the structure summarised in Virchow's *real* triad are not 'thrombi'.

The studies of Sandison (1931) and Stewart *et al*. (1974) supported Welch's conclusion: vessel injury (by whatever agency) causes the generation of thrombi indistinguishable from autochthonous ones - dominated by the accumulation of vast numbers of sequestrated/marginated white cells.

However, in most DVT cases encountered clinically and viewed microscopically, the venous endothelium appears ostensibly intact. Therefore, the key questions arising from the studies of Virchow and others (notably Welch and Aschoff) are: what causes the putative *subtle* injury to the venous endothelium that could initiate autochthonous thrombogenesis, and is a particular zone or area of venous endothelium involved?

3.2.4 A caveat

These two questions were the points of departure for the VCH hypothesis and their answers are fundamental to the VCH mechanism. However, Virchow's *real* triad does not only concern leukocyte/platelet margination at the site of thrombus formation. Its other

two microscopic facets should not be overlooked: the remarkably high density of fibrin in those parts of a thrombus that are formed first, in the *Kopfteil*; and the extraordinary morphology of the Lines of Zahn. These observations remind us that despite the importance of leukocytes in thrombogenesis, their swarming around the site coincides with, and is often preceded by, local coagulation. In the tenth lecture in *Die Cellularpathologie*, Virchow (1858) overtly attacked Cruveilhier but made this exception: *"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 a previously existing coagulum which marks the start of the process"*.

This observation indicates that the subtle endothelial injury inducing local leukocyte/platelet swarming and margination also initiates local coagulation, which may proceed rapidly. But though Virchow did not speculate about the cause or nature of that subtle injury, he did pin-point its location.

3.3 Thrombi are formed in venous valves

Virchow (1856, 1858) showed that venous thrombi are formed in the valves, including the (usually monocuspid) valves that control vein junctions, which Franklin (1937) termed 'ostial valves'. The formation of thrombi in valves was mentioned in *Thrombose und Embolie* and two thrombi arising from two ostial valves were illustrated in *Die Cellularpathologie*. It is worth recalling that even the smallest veins have valves (Phillips *et al*., 2004), which *ipso facto* are potential sites of thrombogenesis.

Although Virchow was the first investigator to make the critical role of valves in venous thrombosis explicit, thanks to his use of the microscope, both Hunter and Cruveilhier had probably suspected the same thing. Hunter (1793) was explicit in associating the 'inflammation' ('pus accumulation', i.e. thrombogenesis) with the 'internal coats' of veins, but he too was surprised that the structures he observed were formed in mid-lumen, not on the walls. Likewise, Cruveilhier was puzzled by the formation of 'phlebitis' in mid-lumen. Both these antecedents of Virchow held now-defunct views about what they were looking at: they believed that the 'pus' originated from outside the vessel, which made the observation of a notably centralised coagulum especially difficult to explain in contemporaneous terms. Hunter did not state explicitly that thrombi are initiated on the valves. He considered the microscope an unreliable instrument in his day and eschewed its use, and without the microscope it was/is impossible to see a valve smothered by a large thrombus. However, he was familiar with Harvey's (1628) essay on the circulation of the blood, in which the valves were described as *'eminences'* on the *'internal lining (tunicula intima)'* of the vein. Hence, we suggest, the title of Hunter's treatise (*'inflammation of the internal coats*…') suggests that he, Cruveilhier and Virchow had observed that venous thrombi are 'anchored' – and probably initiated – on/in valve pockets.

A number of detailed studies during the third quarter of the 20th century confirmed Virchow's observation that thrombi are formed in venous valves (e.g. McLachlin & Paterson, 1951; Sevitt, 1974). One of us (PCM) inherited many micrographs of venous thrombi from Simon Sevitt after his death, some of which we used to illustrate our monograph (Malone & Agutter, 2008; see especially the photographs in Fig. 10.5). All his

micrographs showed thrombi seated in the valve pockets. In some, the exact site of attachment to the endothelium is not clear because the entire pocket is filled with the thrombus, but in several images the thrombus is evidently attached to the inner (parietalis) face of the valve cusp leaflet, not to the outer (luminalis) face, and not to the vein wall. This recurrent observation played a crucial part in the formulation of the VCH hypothesis.

Bovill & van der Vliet (2011), examining the small sample of micrographs in Sevitt (1974), inferred instead that the thrombi were attached to the vein wall endothelium within the valve pocket. We shall discuss this divergence of opinion later; but it seems improbable that a thrombus perceived as 'anchored' in mid-lumen could be attached to the vein wall endothelium.

4. Valve Cusp Hypoxia: The basis of venous thrombogenesis

The foregoing background led us to articulate the VCH hypothesis and subsequently to validate it.

4.1 What severely embarrasses or kills the endothelium in a venous valve pocket?

The clue to what injures the endothelial lining of an intact, functioning, vein was suggested by Drinker (1938) and van Ottingen (1941), whose researches unexpectedly established that copious and ubiquitous thrombus-like coagula formed in the veins of the victims of carbon monoxide poisoning and were associated with endothelial alterations. Evidently, either carboxyhaemoglobinaemia or hypoxaemia could cause the endothelial injury associated with DVT. Drinker proposed this hypothesis to O'Neill (1947) who provisionally validated it, and Samuels & Webster (1952) supported the proposal. Malone & Morris (1978) showed that lesions similar to the white parts of autochthonous and experimental thrombi formed in the veins of oxygen-starved animals by the process of margination and sequestration of platelets and leukocytes. Interestingly, Samuels & Webster (1952) showed that heparin does not prevent the development of a nascent thrombus on a hypoxically injured endothelium.

In those mid-20th century papers, it was debated whether oxygen was supplied to the venous endothelium from the luminal blood or the vasa venarum. Presumably, hypoxia sufficiently severe to kill the endothelial cells and induce leukocyte swarming and phagocytosis of the debris required impaired oxygenation from both sources; it is well established that the venous endothelium can survive moderately prolonged hypoxia (Jackson *et al.*, 1988), depending on anaerobic glycolysis to provide ATP (Berna *et al.*, 2001), and surgeons procure the use of a bloodless field under a 2.5 hour tourniquet. However, hypoxia that is not so severe as to kill the cells but is sufficient to alter their phenotype can also lead to leukocyte and platelet recruitment and local coagulation. During the period 1980-2000, studies in a number of laboratories established that significant but non-fatal hypoxia in cultured venous endothelial cells induces the expression of the early growth response-1 (egr-1) gene, and this unleashes a cascade of gene-expression and phenotypic changes that would promote local coagulation and leukocyte accumulation *in vivo* (Pinsky *et al.*, 1995; Yan *et al.*, 1999a,b; Karimova & Pinsky, 2001; Ten & Pinsky, 2002).

4.1.1 The vagaries of 'venous stasis'

By the late 19th century it was clear that paralyzed patients develop DVT and PE (Malpother, 1880), and by the middle of the 20th century it was known that prolonged bed rest, e.g. in spinal injury patients, had the same consequence (Wright & Osborn, 1952; Gibbs, 1957). This association between restricted mobility and DVT was attributed to slowed venous return, i.e. reduced volume per unit time (Ochsner *et al*., 1951; Wright & Osborn, 1952). Thus, by the early 1960s, it was held to be virtually certain that 'venous stasis' contributed to the cause of DVT (Zweifach, 1963); it was imagined to promote local coagulation (Mammen, 1992). The endothelial hypoxia hypothesis (from which the VCH hypothesis was coined) directly supported this premise: if blood were to flow slowly enough to injure some part of the endothelium by hypoxaemia (even to kill that part of the tissue should flow cease altogether in an unflapped, unemptied valve pocket), local leukocyte swarming and margination, and local coagulation, would ensue through the molecular mechanisms discovered by Pinsky and his colleagues.

However, that conception seems hard to reconcile with Hewson's (1771) experiment. Hewson doubly-ligated a dog's jugular vein, and the stationary blood between the ligatures failed to coagulate after more than an hour; even after three hours, coagulation was only partial. His finding was so counter-intuitive that Lister (1863) and Baumgarten (1876) repeated it in the 19th century and Wessler (1962) in the 20th, with identical results.

Wessler's findings indicated that double ligation *did* somehow injure the vessel, directly or indirectly, because rapid coagulation followed when he introduced serum containing activated coagulation factors into the ligated portion. Importantly, however, the resulting coagula bore no morphological resemblance to autochthonous venous thrombi, so – as explained in section 3.2.1 – his world-renowned experiments were of limited relevance for understanding the aetiology of DVT.

4.1.2 Resolving the 'stasis' paradox

Wessler's studies suggested what seemed like a paradoxical conclusion: thrombi can form when blood is flowing (albeit slowly) along a vessel segment, but not when the blood is stationary. But surely the likelihood of hypoxic injury is greater when the flow rate is less, and therefore maximal when the flow rate is zero, i.e. when flow is altogether prevented by double ligation? (Oddly, Wessler scarcely mentioned valves, but as reviewed in the foregoing pages, it was already well established that valves are the sites of venous thrombogenesis.)

As Virchow (1858) remarked, "*the doctrine of stasis rests on manifold misinterpretations*". It is important to re-emphasise his inference that venous thrombi form in *flowing* blood, but not in *static* blood, and that since venous thrombogenesis is a slow process, which may evolve over hours, days or even weeks, the *rate* of blood flow may not be material factor. What matters is that the blood is always 'exchanging', however slowly; moving, rather than stationary for dangerously protracted periods.

Elegant studies on the dynamics of the valve cycle (Lurie *et al*., 2002, 2003) and the patterns of flow within valve pockets (Karino & Motomiya, 1984; Karino, 1986; Karino & Goldsmith,

1987) helped to resolve the seeming paradox. Essentially, these studies showed that when venous blood flow is *non-pulsatile (streamline)*, as when the patient's 'calf muscle pump' is inactive and there is no intermittent (*vis a tergo*) upward pressure on the soles of the feet, as in walking, a significant part of the blood within 'backwater' valve pockets is not exchanged with the luminal blood. Under such non-pulsatile flow conditions the valve does not execute its usual cycle but remains half-open/half-closed indefinitely.

Near the mouth of the valve pocket, the blood is likely to circulate in a spiral vortex, driven by the laminar flow in the vein lumen. Deep in the pocket is a secondary vortex, rotating in the opposite sense to the primary vortex and more slowly (see Fig. 1). Because the blood in this secondary vortex is never evacuated from the valve pocket while flow in the vein remains non-pulsatile, it becomes increasingly hypoxaemic. Therefore, the endothelia lining the depths of the valve pockets are progressively at risk of hypoxic injury when the venous blood flow is non-pulsatile, *irrespective of the flow rate*. This was demonstrated experimentally by Hamer *et al.* (1981), as discussed below. We concur with Schina *et al.* (1993) that non-pulsatile flow, not slow flow or 'stasis', promotes DVT.

Valve cusp leaflets are avascular (Franklin, 1937; Saphir & Lev, 1952a,b; Sevitt, 1974) - they have no vasa venarum. The outer (medial) endothelial surface (luminalis) is oxygenated by the blood flowing through the vein lumen, irrespective of pulsatility, but the inner, lateral endothelium (parietalis) lining the valve pocket is not (see Fig. 1). Therefore, the parietalis endothelium is at greatest risk of hypoxic injury, and potentially of necrotic cell death, when oxygen-starved during sustained non-pulsatile blood flow.

4.2 The VCH thesis of aetiology: a summary

The initial version of the VCH hypothesis was conceived in 1966 and first outlined in 1977 (Malone, 1977). Its premises were tested critically during the late 1970s and early 1980s. The full version of the validated thesis, with detailed historical and experimental support and scientific and clinical implications, was published some 20 years later (Malone & Agutter, 2006, 2008). The VCH thesis is summarised in Figs. 1-4.

Under normal (pulsatile) blood flow conditions, the venous valve pockets are emptied and refilled regularly and thus do not become hypoxaemic (Fig. 1). However, if there is sustained non-pulsatile ('streamline') venous blood flow, DVT may occur. Such flow leads to suffocating hypoxaemia in the venous valve pockets, resulting in hypoxic injury to the inner (parietalis) endothelium of the cusp leaflets (Fig. 2).

This hypoxic injury activates the pleiotropic elk-1/egr-1 pathway within the endothelial cells, which in turn activates a number of chemoattractant and procoagulant factors. When normal pulsatile blood flow is restored, even transiently, leukocytes and platelets, attracted by these factors, may swarm to the site of dead endothelial cells and initiate protective coagulant action locally (Fig. 3).

Prolongation of non-pulsatile flow for multiple hours may kill the accumulated blood cells in the unemptied valve pocket. These dead cells may then form the core of a nascent thrombus (Fig. 4). If periods of non-pulsatile and pulsatile flow continue to alternate in that abnormal sequential pattern (very protracted stasis + very brief normal flow), the ensuing

serial deposition of white cells may contribute the most distinctive morphological characteristic of a venous thrombus, the striking Lines of Zahn.

Subsequent dehiscence of the growing thrombus, with or without the necrotic endothelial layer to which it is attached, might explain why venous thrombi embolise so readily. The VCH thesis also provides an aetiological explanation for post-thrombotic syndrome and, indeed, for chronic venous insufficiency in general (Malone & Agutter, 2009).

4.3 Validation of the VCH thesis

The original VCH hypothesis led to two readily testable predictions, which were the subjects of experimental studies during the 1980s. The results of these studies were unequivocal:

1. deliberately (artificially) sustained non-pulsatile flow in human patients under anaesthesia causes extreme hypoxaemia in the valve pockets, which results in hypoxia extending to anoxia in the blood 'servicing' endothelial cells in the distal pockets;
2. sustained non-pulsatile flow alternating with brief episodes of pulsatile flow in experimental animals, also under anaesthesia, generates thrombi that are morphologically indistinguishable from autochthonous venous thrombi.

The first prediction was examined on a series of patients undergoing surgery for varicose veins (Hamer *et al.*, 1981). In accordance with standard practice, the anaesthetist maintained normal circulating PO_2 levels in these patients. However, the PO_2 in the valve pockets fell consistently, and when the oxygen electrode was brought into contact with the endothelial surface lining at the base of the pockets, there was no response. The PO_2 level in these cells had fallen to a value below the detection limit of the electrode, not only confirming the predicted hypoxaemia in the valve pocket blood during sustained non-pulsatile flow (the circulating blood being still normally oxygenated), but *a fortiori* showing that the valve cusp leaflet is effectively impermeable to oxygen.

The second prediction was tested on dogs that breathed normally after a single dose anaesthetic injection, which by paralysing all muscle-pumping other than respiratory excursions ensured that blood flow in the limbs was non-pulsatile (Hamer & Malone, 1984). When the dogs began to awaken at successive intervals, the legs exhibited 'auto-jactitation' (clonus), each spasm sufficient to pump fresh blood containing living leukocytes and platelets into the recently hypoxaemic valve pockets. X-rays of the upper thigh veins using contrast radiography then revealed the growth of thrombi, which were microscopically/ morphologically indistinguishable from autochthonous venous thrombi.

The significance of these experimental findings was acknowledged by Hume (1985), who stated that the aetiology of DVT was now elucidated. The explanation of venous thrombogenesis in terms of valve cusp hypoxia was empirically demonstrated, no longer a mere hypothesis. (Hume, a surgeon who specialised in DVT, had co-authored a major monograph on the subject with Sevitt and Thomas in 1970.)

There is a third prediction, which without the VCH thesis might seem counterintuitive: it is that thrombi may form in limb veins should *rapid* blood flow remain non-pulsatile for extended periods. This prediction could repay testing on experimental animals; a convincing experiment would be instructive, though it would be technically difficult to conduct.

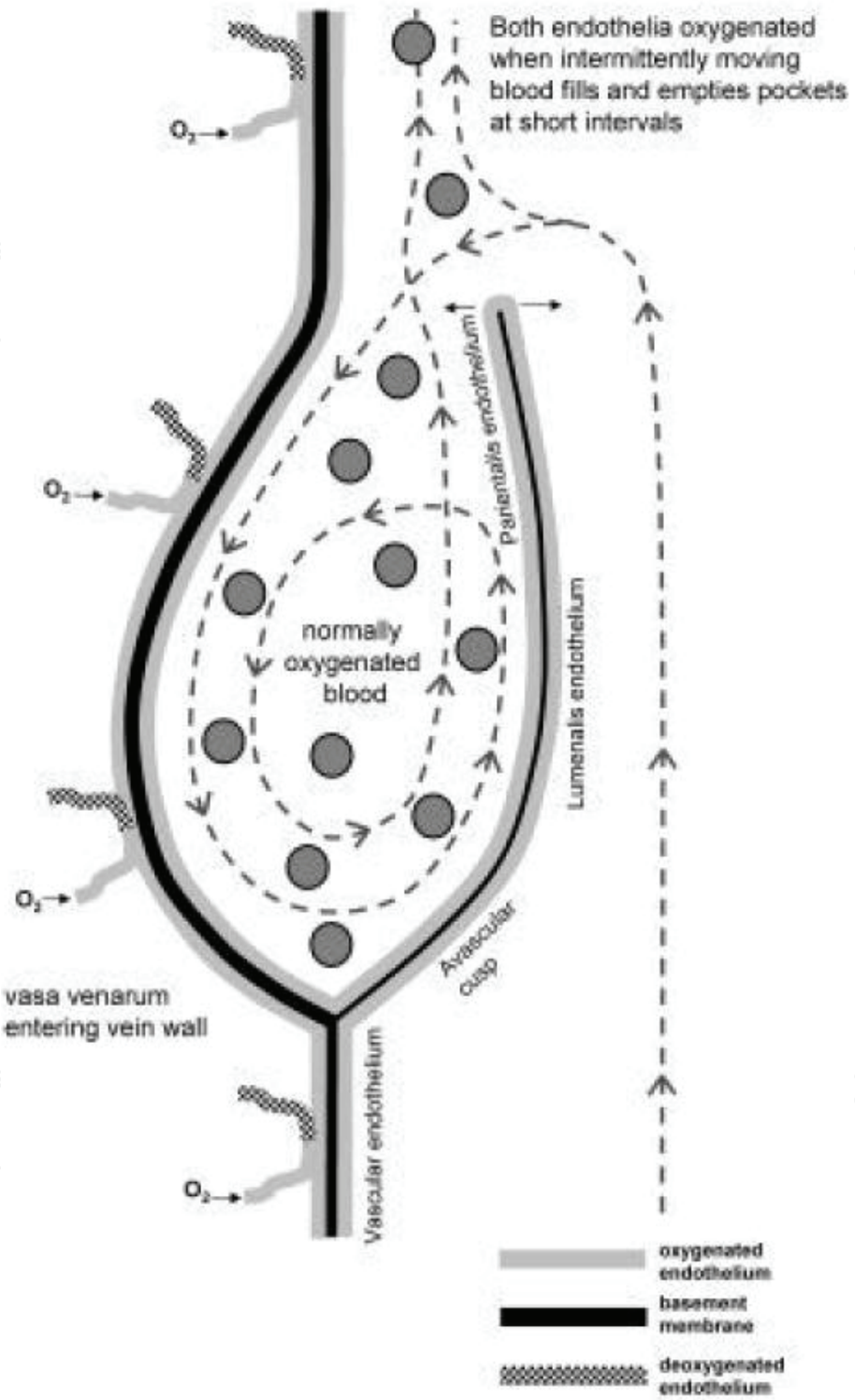

Fig. 1. Blood movements within and around a venous valve pocket during normal (pulsatile flow) conditions. The blood in the pocket exchanges regularly with the luminal blood, so valve pocket hypoxaemia does not develop and the endothelia lining the pocket remain oxygenated.

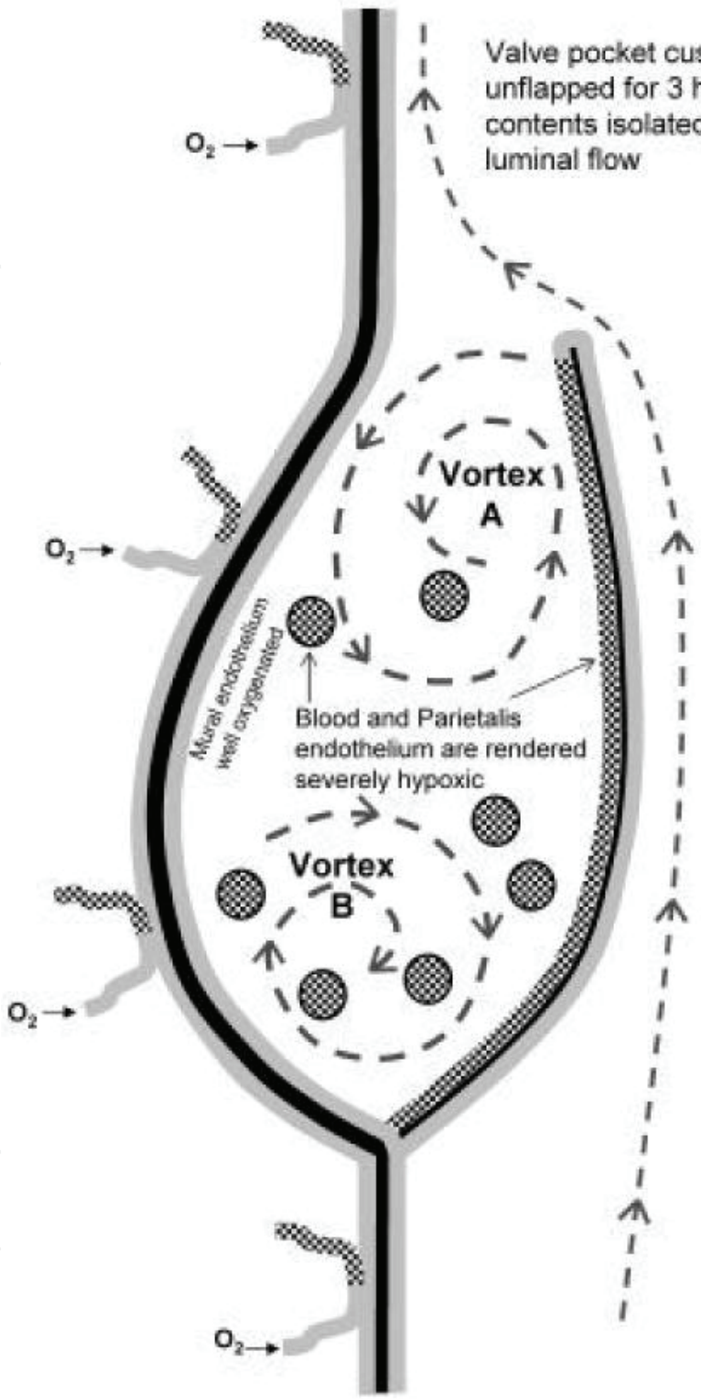

Fig. 2. When blood flow along the vein becomes non-pulsatile, irrespective of speed, the blood in the valve pocket is no longer exchanged with luminal blood, as it is under normal pulsatile flow conditions (Fig. 1). The laminar flow past the mouth of the valve pocket drives a vortex (A) in the upper part of the pocket, and this in turn drives a secondary vortex (B), rotating very slowly in the opposite sense, in the depths of the pocket. Local hypoxaemia leads to severe hypoxia, especially of the parietalis endothelium.

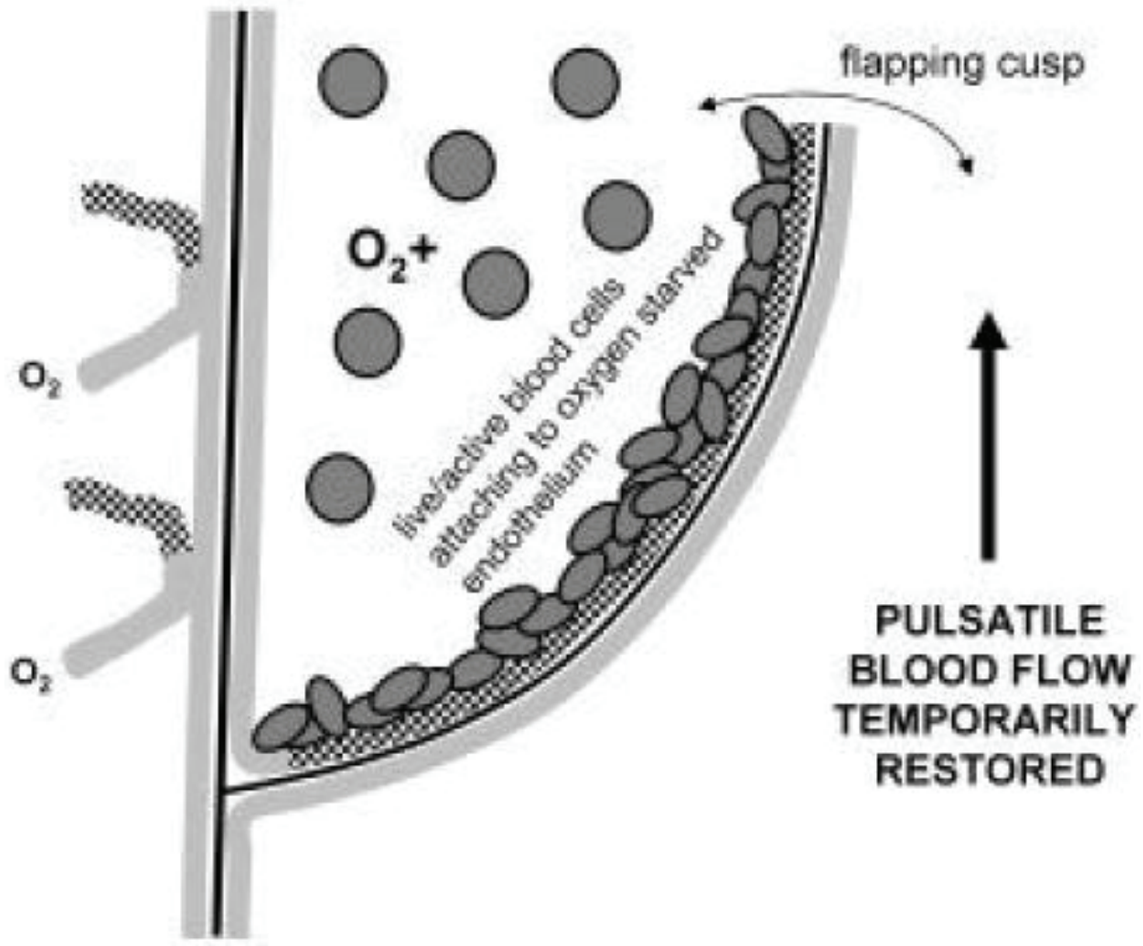

Fig. 3. Each single pulsation by the muscle pump will evacuate 'dead blood' from all affected valve pockets after prolonged periods of hypoxaemia and replace it with fresh blood containing living, active white cells including platelets. In this diagrammatic illustration, these fresh cells are shown in juxtaposition with the parietalis endothelium; our evidence and the historical literature (Aschoff, 1924; Saphir & Lev, 1952a; Sevitt, 1974) indicate that leukocytes swarm on to the severely embarrassed or possibly dead/ necrotic cell layer, forming the white core of the thrombus *Kopfteil*. Because the valve leaflet projects into the centre of the vein, the *Kopfteil* may have seemed to its first observers to be 'in the centre of the afflicted vein'. It may be conjectured that the vein wall endothelial cells deep in the valve pocket also become sufficiently hypoxic for the egr-1 pathway to be activated, notwithstanding any possible oxygenation via the vasa venarum. This is assumed by Bovill & van der Vleet (2011), who propose that coagulation is initiated on the vein wall endothelium, not the valve cusp parietalis, a speculation that will be discussed further in section 5.

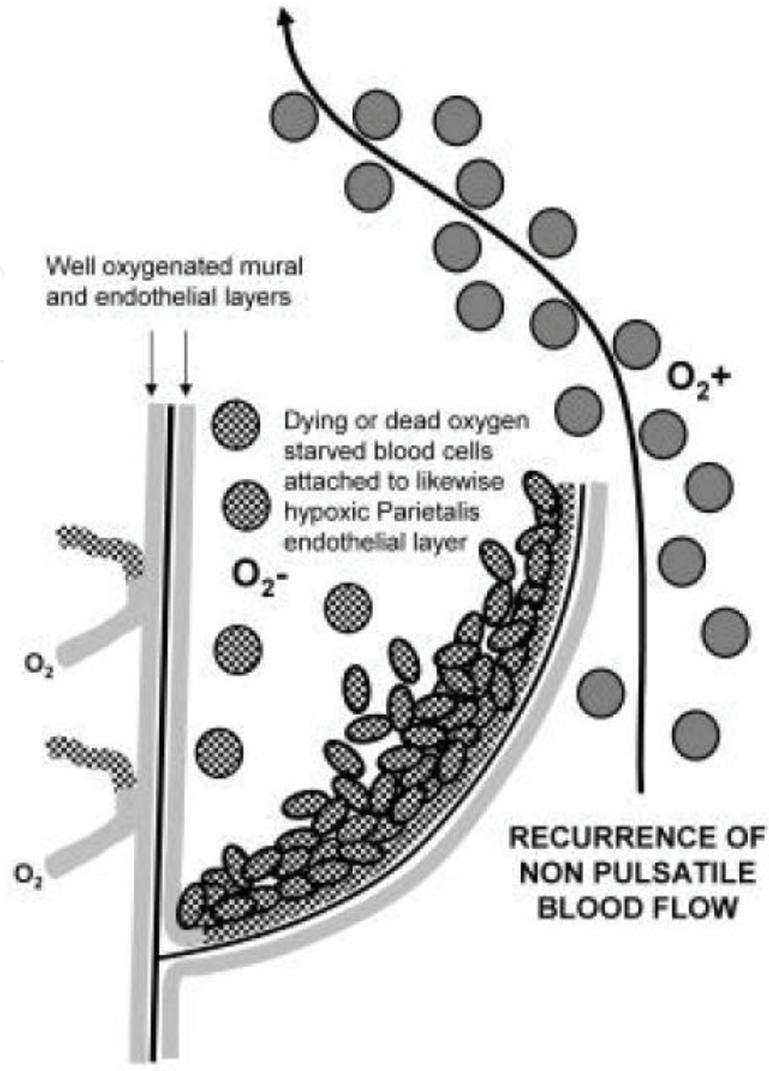

Fig. 4. When sustained non-pulsatile flow resumes after a pulsatile episode, any white cells that have swarmed over the necrotic parietalis endothelium die likewise as a result of valve pocket hypoxaemia. Meanwhile, coagulation can continue. With further episodes of pulsatile flow, the process will be repeated, generating successive layerings of dead cells interspersed with fibrin, accounting for the Lines of Zahn morphology. The necrotic parietalis is fragile and is liable to dehisce (see illustrations in Malone & Agutter, 2008, chapter 10), particularly when the nascent thrombus outgrows the valve pocket and protrudes into the vein lumen, where it is subjected to tension by the flowing blood after the resumption of pulsatility. This may explain the tendency of venous thrombi to embolise.

5. Extending the VCH thesis of aetiology

5.1 Accounting for Virchow's *real* triad

As previously elaborated (Malone & Agutter, 2006, 2008), the VCH explains leukocyte accumulation and the white *Kopfteil*, it accounts for most of the known risk factors such as

the effect of ageing (cf. Saphir & Lev, 1952b; Van Langevelde *et al*., 2010), and it is consistent with the readiness of venous thrombi to embolise. However, though it is consistent with them, some might reserve judgment as to whether it accounts fully and explicitly for (1) the high density of the fibrin around the *Kopfteil* and (2) the Lines of Zahn. These observations need further clarification.

The dense fibrin in nascent thrombi was likewise described by Sevitt (1974). Bovill & van der Vliet (2011) pointed out that it is consistent with tissue factor (TF)-induced coagulation, but they suggested that coagulation is initiated on the vein wall not the parietalis endothelium of the valve pocket. That suggestion would have to be experimentally verified and corroborated before it could be regarded as fact rather than conjecture. Its plausibility depends on the commonly held belief that TF is the primary physiological trigger for coagulation (e.g. Hoffman & Monroe, 2001); also, TF is one of the many targets of activation by egr-1 (Mechtcheriakova *et al*., 1999) so it is expected that valve pocket hypoxaemia will activate it. Primary involvement of TF in coagulation during venous thrombogenesis could explain why anticoagulants are allegedly more effective for prophylaxis than are platelet inhibitors.

A possible difficulty with this explanation for the high fibrin density is that heparin does not inhibit the initiation of thrombi on hypoxic venous endothelium (Samuels & Webster, 1952), and heparin is known to inhibit TF directly and by activating tissue factor promoting inhibitor (e.g. Lupu *et al*., 1999; Ettalaie *et al*., 2011). Alternative explanations should therefore be considered. For instance, the inception and growth of a venous thrombus are slow processes, characterised by the serial margination of successive layers of platelets and leukocytes on the hypoxia-induced lesion of the valve pocket endothelium as blood continues to circulate past the site. This results in a much denser crowding of platelets (as well as leukocytes) than is likely in a haemostatic plug or during the coagulation of shed blood, and densely crowded platelets will generate a dense fibrin mesh.

No matter whether coagulation is TF-induced by the luminal endothelial cells of the valve pocket, as Bovill & van der Vliet speculate, or whether the crowded platelets on and around the injured/ necrotic parietalis endothelium spin out the dense fibrin, logical extension of the VCH thesis provides an explanation for that facet of Virchow's *real* triad. As for the Lines of Zahn, the serial deposition described earlier is the critical factor; but the slow secondary vortex in the depths of the valve pocket (Karino, 1986) will also contribute by weaving the leukocyte/platelet-rich and dense fibrin layers around each other.

Thus, the extended VCH mechanism accounts for all three aspects of Virchow's *real* triad.

5.2 Cross-talk between leukocyte recruitment and coagulation

The molecular changes in endothelial cells subjected to valve pocket hypoxaemia were discussed in chapter 12 of Malone & Agutter (2008) and by Bovill & van der Vliet (2011). The generation of reactive oxygen species (ROS) in the hypoxic endothelium is of particular interest because ROS promote both neutrophil recruitment (Millar *et al*., 2007) and the activation of TF (Banfi *et al*., 2009), as well as activating egr-1. This involvement of ROS could support the proposal that a vegan diet has prophylactic value against DVT and VTE (Cundiff *et al*., 2010), since vegan diets are allegedly rich in antioxidants, though a statistically sound test of this proposal would involve a very large patient cohort. Bovill & van der Vliet note that other hypoxia-related transcription factors such as hypoxia-inducible

factor-1 are potential targets for ROS in the affected endothelium, though the relevance of this to venous thrombogenesis is uncertain.

In examining the molecular cross-talk between leukocyte recruitment and coagulation during venous thrombogenesis, it is important to distinguish early events from developments associated with the growth of a 'mature' thrombus. For example, TF-bearing microvesicles derived from either monocytes or vein wall pericytes seem to be prominent during the development of thrombi, but are almost certainly not involved during the initiation of venous thrombosis (Bovill & van der Vliet, 2011). More importantly from the practical, clinical standpoint, anticoagulants stop the growth of a thrombus but they do not prevent its initiation. It is therefore not surprising that the decline in incidence of DVT/VTE and post-thrombotic syndrome in hospital patients has been only marginal, notwithstanding recent advances in anticoagulant treatment (Kahn & Ginsberg, 2004; Heit, 2005).

5.3 Why is DVT not even more common than it is?

The evidence reviewed in section 4 testifies to the correctness of the VCH thesis, but the imaginative reader might raise this question. Sustained non-pulsatile flow in the deep limb veins with short episodes of pulsatile flow are quite common in the daily lives of some humans, and is certainly common among carnivores, which sleep and remain immobile for many hours per day. In this context, the proposal of Brooks *et al.* (2009) that the valve pocket endothelia are more resistant than the luminal endothelium to the induction of coagulation could be of interest.

These authors proposed, on the basis of preliminary evidence, that the levels of von Willebrand factor (vWF), thrombomodulin (TM) and endothelial protein C receptor (EPCR) change with depth in the valve pocket, so that the endothelial cells express less of the procoagulant (vWF) and more of the anticoagulant (TM and EPCR) factors. Trotman *et al.* (2011) pursued this hypothesis and found that the level of vWF did indeed decrease with depth in the pocket, but so did the level of EPCR; the TM level showed no significant change. There was extensive inter-individual variation in all three of these proteins, so the patterns were not entirely clear, but the hypothesis advanced by these authors could in principle help to explain 'why DVT is not even more common than it is'. In principle, The Brooks *et al.* proposal could be tested critically by a study on a large experimental animal group. The incidence of thrombogenesis under conditions similar to those used by Hamer & Malone (1984) could be correlated with the expression of vWF (and perhaps TM and EPCR), as assessed e.g. by immunostaining in the valve pocket endothelia after the end of the experiment. However, the most important factor in thrombogenesis is without doubt the duration of the valve pocket hypoxaemia.

6. Implications of the VCH mechanism for prophylaxis

6.1 The balance between anticoagulant and mechanical prophylaxis should be reconsidered

Anticoagulants do not prevent the initiation of DVT (section 5.2), in particular the recruitment and margination of leukocytes and platelets to the injured parietalis endothelium, but they prevent the growth of already-formed venous thrombi to clinically significant size. Whether they inhibit the putative local effects of TF (see above) is debatable.

From the point of view of patient care, this is not a crucial issue; what is important is to prevent the potential morbidity and mortality associated with DVT, specifically VTE and post-thrombotic syndrome. Therefore, preventing thrombus growth is 'useful'. Nevertheless, it seems inherently more satisfactory to prevent the initiation of thrombosis rather than just thrombus growth. That entails a reconsideration of mechanical rather than anticoagulant prophylaxis.

However, current approaches to mechanical prophylaxis are unlikely to achieve the objective of preventing the initiation of thrombogenesis. The NICE website sums up the conventional explanation for the effects of intermittent pneumatic compression, though with a curious use of the word 'theory': "*The theory behind mechanical approaches to thromboprophylaxis is that they increase mean blood flow velocity in leg veins, reducing venous stasis*" (National Institute for Clinical Excellence, 2011). It would be valid to presume that an 'adequate' mean venous blood flow velocity maintains our existence and lives, since an 'inadequate' flow velocity would ultimately be incompatible with life; nevertheless, the 'theory' invoked above in support of intermittent pneumatic compression is not consistent with our experimental proof that *pulsatile* flow maintenance is the true thromboprophylactic. The assumption that venous flow velocity has any significance in thrombogenesis is unproven, and according to the VCH thesis it is likely to be false.

This widespread misunderstanding about the significance of venous return blood flow velocity may explain why mechanical prophylaxis has remained adjunctive to anticoagulant treatment. Thus, Khoury *et al.* (2011) describe mechanical prophylaxis as 'inappropriate' or 'inadequate' unless anticoagulation is contraindicated (because of a serious bleeding risk), and authoritative sources such as Demtali *et al.* (2007), Geerts *et al*. (2008) and Sliwka & Fang (2010) strongly support the use of anticoagulant "*and to a lesser degree mechanical*" forms of prophylaxis (the quoted phrase is from Sliwka & Fang, 2010). Similarly, we recall that "*Chemoprophylaxis is recommended for medical patients at moderate to high risk of venous thromboembolism (VTE) and is now a requirement of the Joint Commission on Accreditation of Healthcare Organizations*" (Rothberg *et al*., 2010). Moreover, a very large international survey by Kakkar *et al.* (2010) revealed that "*Anticoagulant therapy was much more frequently used than mechanical devices such as compression stockings or intermittent pneumatic compression, even in patients at increased risk of bleeding*".

However, the truth – revealed explicitly by modern medical/surgical practice - is that anticoagulants and mechanical prophylaxis work hand in hand. Physicians might be more inclined to emphasise pharmacological approaches and surgeons to emphasise mechanical ones, but the difference is not absolute and the methods need not be considered mutually exclusive. Since prompt ambulation of post-operative surgical patients has also become routine in recent decades (Cundiff *et al*., 2010), this form of mechanical prophylaxis, which ensures pulsatile return blood flow in the legs, has long been valued in reducing the incidence of post-surgical DVT/VTE alongside anticoagulants; yet it might not have been recognised universally as a form of 'mechanical prophylaxis'.

The VCH thesis does not lead to an argument against anticoagulant prophylaxis. However, long-term anticoagulant use is associated with fatal or disabling bleeding (Cundiff *et al*., 2010; Cundiff, 2011) and Cochrane reviews make clear that the evidence supporting anticoagulant prophylaxis should be monitored constantly (Cundiff, 2011), and that such prophylaxis against VTE may hypothetically be contraindicated. In a sense, giving a patient

anticoagulants 'in case' he/she develops DVT might be seen as akin to dosing such patient with chemotherapeutic drugs 'in case' he/she develops a cancer.

That is an extreme view. Nevertheless, the balance between the anticoagulant and mechanical approaches to prophylaxis needs to be re-evaluated in the light of the VCH thesis, since they seem likely in time to perfect a more impartial 'cross-party' view of the aetiology of DVT and of patient management.

6.2 Mechanical prophylaxis: a rational approach

The simple objective of mechanical prophylaxis is to ensure that blood in the valve pockets is exchanged at regular intervals (Malone & Agutter, 2008). Modern surgical prophylaxis could readily be improved if the VCH principle were added to the classical objective: 'regular' (i.e. regular intermittent) pulsation need not necessarily mean '*as frequent as is current practice*'. In chapter 9 of our monograph we calculated that valve pocket hypoxaemia does not become dangerous (i.e. potentially injurious) until non-pulsatile flow has persisted for 1.5-3 hours, an estimate consistent with the empirical data (Hamer *et al.*, 1981). Less frequent, i.e. *relatively infrequent*, artificial pulses (perhaps once per hour, though that would need experiential confirmation) would preclude thrombogenesis, and would be more comfortable for patients than what must seem incessant limb compression at short intervals, day and night.

For patients confined to prolonged bed-rest, insensible, automatic alternate end-to-end Trendelenberg/ anti-Trendelenberg tilting of the bed, through a 5-10 degree angle, every hour or so, should be prophylactic by emptying the valve pockets in the upper and lower parts of the body by gravity, allowing them to refill passively with fresh venous blood at relatively short intervals (as above) and preventing unsuspected but potentially fatal hypoxaemia in unmoved pockets.

6.3 Testing the proposals for rational mechanical prophylaxis

Preferably, these proposals would require further animal testing before clinical deployment. Perhaps the original experimental design created and used by Hamer & Malone (1984) would suffice as a basis.

Three matched groups of anaesthetised animals would be required initially, each to be subjected to prolonged non-pulsatile blood flow in the leg veins, with brief alternating pulsatile episodes: (a) controls, untreated; (b) given standard anticoagulant prophylaxis; (c) given mechanical prophylaxis by one or other of the methods proposed in section 6.2. At the end of the experiment, valves from deep limb veins would be examined microscopically. The VCH prediction would be that group (a) will show the formation of quasi-autochthonous thrombi; group (b) might show incipient thrombi on the parietalis endothelia; and group (c) will show normal endothelia with no incipient thrombi.

Positive results might suggest that a randomised controlled clinical trial of one or both of the approaches outlined in section 6.2 should be undertaken. At the same time, this experimental set-up could provide a means for testing the efficacy of anticoagulants in absolute terms; for the past 50 years, anticoagulant prophylaxis has been evaluated only by statistical evidence, without the use of such a 'measuring rod'.

6.4 Application of rational mechanical prophylactic measures

In the absence of contrary evidence, there is a *prima facie* case for using the measures described in section 6.2 throughout the period of bed rest for all acute medical patients and for surgical patients with limited mobility. That would be in line with the recommendations of NICE in the UK, of similar bodies in other European countries, and of the Joint Commission on Accreditation of Healthcare Organizations in the USA (see earlier discussion), except that anticoagulants would be given a less central role in prophylaxis. (There would be little or no need for any such measures in ambulant patients.)

One area that might need more or less radical reconsideration is surgery involving general anaesthesia. However, we emphasise that our comments here are conjectural and would require detailed evaluation before they were considered for practical application. Also, they relate to a potential risk associated only with very prolonged anaesthesia, involving sustained muscle relaxation, not to surgical operations in general.

It is self-evident that relaxant anaesthesia is inherently thrombogenic. For short operations, this is unlikely to matter greatly; but for longer operations (say over 100 minutes) during which the patient is totally motionless, there is a major risk that undetectable prothrombogenic nidi will form in valve pockets. The muscular paralysis induced during anaesthesia will therefore cause thrombosis in every case unless the duration of the resultant streamline (non-pulsatile) blood flow in all veins of the body is constantly kept in mind. If the unconscious patient's veins are not squeezed, e.g. by mechanical movement of limbs, then valve pocket hypoxaemia cannot be avoided. In reality, of course, the risk depends on how quickly the patient recovers from the effects of the muscle relaxant so that the skeletal muscles of the limbs start to contract again. It would seem ideal for the state of total muscle paralysis to last only ½ to ¾ of an hour, after which the anaesthetist would have to administer another dose of curare, but that is speculation; confirmation from practice and experience would be essential before such proposals were applied.

All anaesthetists are acutely aware of the respiratory support (sustained oxygen supply) needed for safe anaesthesia, but they are far less likely to be concerned about the restoration of pulsatile blood flow in the patient's legs/ abdomen. Appropriate practice must relate to the acceptability of temporary recovery of patient motion to the surgeon, and of course the delicacy of the operation and the disturbance likely from any change in anaesthetic practice.

Besides monitoring relaxant anaesthesia, the practice of end-to-end Trendelenburg/anti-Trendenburg tilting discussed in section 6.2 could be re-employed. However, the number of degrees elevation and reduction would be only 2 x 5% to and fro in 'horizontal patient' operations. Operations performed e.g. in sitting positions would require different manoeuvres appropriate to the particular patient posture. The objective in all cases would be to limit drugged-immobility to a specific duration that must be established by experience (after an initial informed guess based on e.g. the evidence from Hamer *et al.*, 1981).

7. Conclusions

The currently prevailing beliefs about the aetiology of DVT arose from the assumption, fostered by the ascent of haematology after the Second World War, that venous thrombogenesis is primarily (or exclusively) a matter of *in situ* blood coagulation. This view became associated with a misreading of Virchow's work that gave rise to 'Virchow's triad';

an ironic association, since a key aspect of Virchow's work on venous thrombi was his three-part distinction between thrombus and clot and his demonstration that a DVT is formed when leukocytes as well as platelets swarm to the site of injury, the venous valve cusp. As a result, mainstream research in the DVT field since 1962 has taken on an increasingly haematological character, which has entailed a tacit dismissal of the important discoveries made prior to the mid-20th century, not least those of Virchow. The valve cusp hypoxia (VCH) thesis is founded on the recognition of these discoveries and on our knowledge of vascular physiology, particularly the dynamics of blood flow in venous valve pockets. It was advanced as a hypothesis in 1977 and was corroborated and validated by critical experiments during the 1980s.

In clinical terms, the VCH thesis adds nothing to accepted standards of treatment for actual, manifest thromboembolism other than to augment the rational basis for mechanical prophylaxis and to suggest reconsideration of prolonged muscle relaxant use during surgery, a potential 'silent killer'. Mechanical prophylaxis should be based not on altering the venous blood flow velocity, which is almost certainly irrelevant to thrombogenesis, but to ensuring that flow is always pulsatile. The pulses need not be frequent: once per hour will suffice to ensure that valve pocket hypoxaemia does not become seriously injurious to the endothelia, and should therefore preclude the formation of thrombi, though optimal timing can only be established on the basis of experience. The key point is to ensure that the valve pockets are emptied and refilled regularly with fresh venous blood. On the other hand, the VCH thesis indicates that anticoagulants do not prevent the initiation of deep venous thrombosis, though they restrict or retard the growth of thrombi that have already formed.

The approaches to mechanical prophylaxis inferred from VCH are testable on experimental animals. Such tests should certainly be conducted before a randomised controlled clinical trial is initiated. We encourage colleagues throughout the world to undertake these experiments – and, subject to the results, clinical trials – since only by consistent findings from different laboratories and clinical establishments can a consensus be obtained that would make rational mechanical prophylaxis the standard of care for patients at risk for DVT/ VTE.

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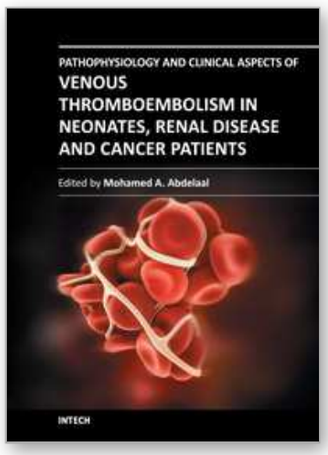

Pathophysiology and Clinical Aspects of Venous Thromboembolism in Neonates, Renal Disease and Cancer Patients

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Venous Thromboembolism remains a major health challenge in many countries because of the morbidity and mortality it inflicts, mainly in hospitalized patients. This book, with contributions from distinguished experts in the field, depicts some hot aspects on aetilogics of VTE, the disease burden in neonates, renal disease and cancer patients as well as issues relevant to prophylaxis and the concept of VTE as patient injury content.

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