Review

The aetiology of deep venous thrombosis

P.C. MALONE and P.S. AGUTTER

From the 1Theoretical and Cell Biology Consultancy, Glossop, UK

Summary

Most ideas about the pathogenesis of deep venous thrombosis (DVT) are dominated by a ‘consensus model’ first articulated around 1962. This model invokes ‘Virchow’s triad’ and attributes thrombogenesis in veins to some combination of ‘hypercoagulability’, ‘stasis’ and ‘intimal injury’. This arose as a by-product of studies on the mechanisms of haemostasis and bleeding diatheses that were at best only indirectly relevant to thrombosis, and there are reasons for doubting the causal significance of ‘hypercoagulability’ and ‘stasis’ in the aetiology of DVT. Proponents of the consensus model make little reference to a substantial literature, mostly historical, that: (a) emphasizes the significance of the venous valve pockets (VVP) and blood rheology in DVT pathogenesis; and (b) describes morphological features specific to venous thrombi that a valid aetiological model must explain. This literature provides the basis for an alternative hypothesis of DVT aetiology, published some 30 years ago, which has been experimentally corroborated and is compatible with recent cell and molecular biological studies of the venous endothelium. We review this alternative hypothesis, considering its potential value for future research on DVT and embolism, and its significance for clinical practice.

Introduction

Deep venous thrombosis (DVT) is a significant and costly health-care and social problem. The average population incidence is about 0.5 per 1000 person-years, but increases markedly with age; men are at slightly greater risk than women. Moreover, DVT is a common post-operative complication, and a serious threat to the patient’s general recovery. It has become headline news in the guise of ‘traveller’s thrombosis’, which was first recognized half a century ago. Large-scale studies have shown that long flights slightly increase the risk of DVT, and the incidence increases, apparently exponentially, with travelling time. However, nearly all the ‘traveller’s thrombosis’ cases reviewed by these authors occurred in passengers with well-established DVT risk factors such as smoking, hypertension, varicose veins, cardiac dysfunctions, obesity, cancers, autoimmune diseases and inherited or acquired thrombophilias. These factors, which have been extensively discussed in the literature, contribute much more to the incidence of DVT in the general population than does ‘traveller’s thrombosis’ per se, and the condition remains most frequent in patients who require protracted bed-rest, especially after surgery involving a prolonged period of general anaesthesia.

Potentially thromboembolic DVT usually arises in one of the large deep veins of the lower limb and is associated with significant morbidity and mortality. Unlike superficial venous thrombosis, which can present painfully, DVT tends to be asymptomatic unless either (a) fractured thrombi metastasize as emboli or (b) morbid sequelae develop.
Cina et al.\textsuperscript{19} reported at least 100,000 deaths per annum from pulmonary embolism in the United States. Emboli are found in over 10\% of unselected autopsies and pulmonary embolism is fatal in as many as 0.1\% of all patients. Furthermore, recurrent venous thrombotic and thromboembolic episodes are more common than was once believed.\textsuperscript{20}

Morbidity usually begins with oedema caused by the raised venous pressure distal to a thrombus, which increases the rate of capillary filtration. Although this subsides within a few months in approximately half of all cases because of thrombolysis and recanalization,\textsuperscript{21} untreated DVT can have disabling and even lifelong consequences (collectively labelled ‘post-thrombotic syndrome’) arising from residual venous obstruction, valve incompetence, or both. Chronic venous disease, manifest for example in painful varices, is a common sequela of valvular incompetence: valves injured during thrombosis are infiltrated with white blood cells, and this alters their morphology and physical characteristics irreversibly.\textsuperscript{22} Such infiltration of the valves may have an aetiological significance that has been widely overlooked or misunderstood. We shall return to it later in this essay.

Prophylaxis against and treatment of DVT are clearly important health-care issues. Currently, clinicians rely on anticoagulants (particularly low-molecular-weight heparin) and thrombolytic agents; surgical thrombectomy and compression stockings are important approaches to treatment and prophylaxis, respectively, but are often considered alternative or supplementary measures.\textsuperscript{18,23–28} The emphasis is therefore on pharmaceutical interference with the normal haemostatic mechanism, implying a consensus haematological interpretation of the aetiology of DVT. We shall briefly explore the evolution of this consensus. We shall also explore an alternative hypothesis, first published some 30 years ago, that we believe explains the aetiology more satisfactorily.

**‘Virchow’s triad’ and the consensus model of DVT**

Peterson\textsuperscript{4} declared: ‘Virchow’s triad of stasis, vessel injury, and hypercoagulability remains a valid explanation of the pathogenesis of thrombus formation.’ Burroughs\textsuperscript{24} wrote: ‘The cause of thrombosis is often unknown but is universally ascribed to part of Virchow’s triad: stasis, hypercoagulability, and intimal injury.’ Many similar quotations can be cited, dating back to Sherry.\textsuperscript{29} Collectively, they reveal a consensus: that DVT is caused by some combination of: (i) ‘hypercoagulability’, either systemic or local;\textsuperscript{30} (ii) ‘stasis’ of the venous blood; and (iii) injury to the vein wall intima, specifically the endothelium. This aetiological scheme is attributed to Virchow.

However, the phrase ‘Virchow’s triad’ is problematic. First, it was not used in medical textbooks or research literature before the 1950s, nearly 100 years after Virchow’s seminal publications. Indeed, we have not found it in the title or abstract of any publication before the early 1980s. Its origin is obscure. Second, Virchow was concerned not with the causes of venous thrombi but with their life-threatening effects, i.e. their metastasis as emboli. These points have been explored previously.\textsuperscript{31–35} Third, although he pioneered this field of pathology (and many others), Virchow was not the first to investigate the process now dubbed ‘DVT’. He invented the words ‘thrombus’ and ‘embolus’, but he did so to help him evaluate critically (and as far as possible, to reconcile) the divergent studies of his predecessors, notably Boerhaave,\textsuperscript{36} Hunter\textsuperscript{37} and Cruveilhier.\textsuperscript{38} He especially sought to overturn the paradigm of ‘phlebitis’ created by Cruveilhier (presaged in Hunter’s ‘inflammation of the veins’). Fourth, Virchow never wrote about ‘hypercoagulability’, nor did he imply the concept, and he explicitly dismissed the idea that ‘stasis’ is causally related to thrombosis and embolism.\textsuperscript{39,40} In other words, there is no justification in Virchow’s writings for attaching his name to the current consensus model of DVT; rather the contrary.

Some readers might question this claim. Virchow is frequently alleged to have considered ‘stasis’ thrombogenic, apparently on the basis of the following quotations from Thrombose und Emboli:\textsuperscript{39} (i) ‘...especially in that part of the cava...which is next to the obturated iliac, a layer of almost stagnating blood will develop. This situation is by all means able to initiate coagulation of the blood’; (ii) ‘If there is a general or localised reduction in blood flow, we usually see spontaneous coagulation, most frequently in those veins that have anastomoses or that form a plexus, which means that they have a certain number of superfluous ducts...’. [our italics]. However, ‘almost stagnating’ and ‘a general or localised reduction in blood flow’ do not mean ‘stationary’ or ‘static’. Moreover, quotation (i) describes the reduction of linear blood velocity as (primarily) a consequence, not a cause, of thrombus formation. (Indeed, while impaired circulation is in some sense a ‘cause’ of DVT—see below—thrombi also retard the movement blood in the vein; so thrombogenesis and impaired circulation can be regarded as cause and consequence of each other.) In Die Cellularpathologie,\textsuperscript{41} Virchow attributed ‘manifold misinterpretations’ to the
Thrombose und Embolie implied the concept of ‘hypercoagulability’ in intravascular coagulation. Indeed, he denied it, although he associated ‘reduction in blood flow’ (or, in his preferred phrase, ‘interrupted circulation’) with intravascular coagulation.

It is also occasionally claimed that Virchow implied the concept of ‘hypercoagulability’ in Thrombose und Embolie. Browse et al.\(^4\) wrote: ‘Category 3 [of ‘Virchow’s triad’]—‘changes in blood constituents’—is hypercoagulability’ [our italics]. Virchow mentioned that fibrin(ogen) concentration was a potential determinant of thromboembolism, and noted that the blood could be made ‘more adhesive’ by adding oil, paste or other substances. But this ‘increased adhesiveness’ of blood surely indicates ‘interrupted circulation’ and interaction with the endothelium rather than a ‘change in blood constituents’. As for fibrin(ogen) concentration, he obviously did not envisage a systemic increase. (If he meant local increase his prescience was remarkable, and the notion is not apparent in the remainder of his work.) Hence our assertion that Virchow neither conceived, mentioned nor implied ‘hypercoagulability’.

This discussion suggests (at least) three questions. First, if the consensus model is not after all rooted in Virchow’s work, what was its true provenance? Second, is it valid to use ‘stasis’ to denote what Virchow called ‘interrupted circulation’ or ‘reduction in flow’? Third, what are we to make of the other components of the consensus model, viz. ‘hypercoagulability’ and ‘endothelial injury’?

**Origin and character of the consensus model**

The now-familiar ‘explanation’ of DVT in terms of ‘hypercoagulability’ and ‘stasis’ seems to have become entrenched\(^4\)–\(^7\) about a decade after the clinical value of anticoagulant therapy for thrombosis had been established.\(^4\)–\(^5\) Wessler\(^4\) and Mustard et al.\(^4\)–\(^5\) wrote scholarly historical reviews of the field, but their emphasis was on biochemical and haematological studies, notably those exploring anticoagulation. This emphasis persisted in later publications. For example, Browse et al.\(^4\) remarked ‘Not until the discovery of the coagulation cascade did the modern era of thrombosis research begin’, and the monograph on DVT by Ogston\(^5\) is likewise largely haematological in content. However, in the third edition of Biggs and MacFarlane,\(^5\) which contained a detailed molecular account of the coagulation cascade as then conceived, and explained the known deficiencies in haemostasis (bleeding diatheses such as haemophilia) at length, only eight of the 360 text pages were devoted to thrombosis. These observations suggest that the remarkable success of biochemical haematology in explaining the mechanism of haemostasis and its failures in conditions such as haemophilia had led, almost as an afterthought, to an attempt to explain thrombosis in similar terms, i.e. to the consensus model; and that this attempt was encouraged, perhaps even initiated, by the clinical success of anticoagulant treatment.

It took more than a century for our modern understanding of haemostasis to evolve. This history is too complex to recount in detail here; briefly, the molecular cascade model of blood coagulation was adumbrated in papers by McFarlane\(^5\) and Owren,\(^5\) where the practice of using Roman numerals for the coagulation factors began. Developments during the earlier part of the 20th century are well described in essays by Howell\(^5\) and Eagle.\(^5\) These developments originated in the ‘classical (thrombin) hypothesis’ of Schmidt.\(^5\) The earliest proto-biochemical studies on blood coagulation, those of Buchanan,\(^5\) and methodologically presaged Schmidt’s studies. This entire body of work owed little or nothing to Virchow or his direct successors such as Zahn,\(^5\) Welch\(^6\) and Aschoff,\(^6\) and it referred only incidentally and sporadically to thrombosis and embolism. Moreover, the emphasis from Schmidt’s time onwards was not in vivo thrombogenesis but in vitro clotting and its inhibition, which was assumed to be an experimentally amenable model for haemostasis, and has since been presumed analogous to thrombosis. However, Virchow\(^4\) distinguished explicitly between the in vivo thrombus and the in vitro clot: ‘1. the structure of the thrombus is in layers [which would later be called the lines of Zahn]; 2. the fibrin content is denser; 3. the population of colourless corpuscles is denser, and to a striking degree . . .’ Some proponents of the consensus model seem to have lost sight of this distinction and use ‘clotting’, infelicitously, to denote ‘thrombogenesis’.

Because of its origin, development and inherent character, the consensus model does not explain, or seek to explain, the detailed morphological characteristics of a thrombus as described by Virchow,\(^4\) Zahn,\(^5\) Welch\(^6\) and Aschoff.\(^6\) But an ability to account for these characteristics is an important criterion for any aetiological hypothesis, as Aschoff\(^6\) has emphasized. Moreover, since the consensus model developed to maturity with no more than incidental reference to DVT, its
perspective on DVT aetiology might be inappropriate. We therefore have grounds for viewing it critically.

‘Hypercoagulability’

Thrombi are usually said to result when the ‘delicate balance of haemostatic machinery’ is disturbed. However, some published discussions of ‘hypercoagulability’ seem to entail flawed or circular reasoning. In essence: (i) thrombosis results from inappropriate blood coagulation; (ii) therefore, if thrombosis occurs, the patient’s blood must have an inappropriate tendency to coagulate, either locally or systemically; (iii) therefore, by definition, the patient has a local or systemic hypercoagulability. Such discussions are embellished by loose interpretations of Virchow (above) and by the recognition of well-defined conditions that do merit the label ‘hypercoagulability’, but this does not rescue the logic. Nor does a posteriori reasoning along the lines: ‘since anticoagulants protect against DVT and act by down-regulating the coagulation mechanism, ergo thrombosis must result from a pathological up-regulation of the coagulation mechanism, which the treatment normalizes’.

Such implicit arguments may have arisen and become entrenched when ‘hypercoagulability’ was first discussed in the literature. These early papers reflect the excitement that accompanied the new understanding of haemostasis (the molecular cascade model). Their main thrust seems to be as follows: we know that inherited ‘hypocoagulability’ disorders can prejudice haemostasis to a greater (e.g. factor VIII deficiency) or lesser (e.g. von Willebrand’s disease) extent; so could there be ‘positive’ as well as ‘negative’ disorders, completing a spectrum of coagulability from the hypo- to the hyper-, with physiological normality in the centre of the imagined continuum? By 1962, many influential workers in the field seem to have adopted this view (see the papers cited in the preceding section).

Nowadays, the word ‘hypercoagulability’ is used both specifically, to denote a condition with a defined aetiology, and non-specifically, as in the implicit reasoning we have just evaluated. To avoid this ambiguity, we shall use the accepted synonym ‘thrombophilia’ for the specific sense. A number of different hereditary (‘essential’) and acquired thrombophilias have now been described.

‘Thrombophilia essentialis’ was recognized well over a century ago. The main symptom is intermittent claudication, associated with arterial rather than venous occlusion, and bleeding times and in vitro clotting times are reduced. The syndrome can progress to thrombosis of the abdominal and pelvic vessels, rather than the lower limb veins, and potentially to haematuria and collapse. It seems to have been first described by Armand Trousseau in the late 19th century, and later, independently, by George Elgie Brown and Kaare Kristian Nygaard. The condition was long known as ‘Nygaard-Brown syndrome’ (e.g. reference 64). It is difficult to equate thrombophilia essentialis with any of the inherited thrombophilias recognized today, which have different aetiologies. Prominent examples are protein C, protein S and antithrombin III deficiencies, and factor V Leiden (in which a mutation renders activated factor V resistant to degradation by protein C). There are several recent reviews of this field.

Thrombophilias are more prevalent among patients with DVT than in the general population. Also, the prevalence and rate of recurrence of DVT are higher in patients with thrombophilias than in others. However, the most important point for this essay is that no thrombophilia, inherited or acquired, shows a simple, regular correspondence with DVT or other pathological sequelae. This contrasts with the simple, regular and specific correspondences between haemostatic factor deficiencies and bleeding diatheses. About 30% of patients with DVT or pulmonary embolism have a diagnosable thrombophilia. It follows that about 70% do not. Moreover, it is clear from the reviews cited above that many (probably most) patients with a thrombophilia do not develop DVT. So, although thrombophilias are significant risk factors for DVT, they are not causes.

The conclusion is inevitable: thrombophilia or ‘hypercoagulability’ does not cause venous thrombosis. DVT can occur, and in the majority of cases does occur, in patients whose blood is normally coagulable.

‘Stasis’ or ‘interrupted circulation’?

If the clinical and biomedical research communities agree to use the word ‘stasis’ to denote ‘reduced linear blood velocity’ or ‘interrupted circulation’, then is the absoluteness of its standard English denotation (a complete absence of movement) relevant? Everyone in the field understands that the word carries a special, non-standard meaning in relation to thrombosis. We accept that this non-standard usage of ‘stasis’ is established in the field, but we have at least two reasons for considering it undesirable. These reasons hinge on the potential confusion between ‘stasis’ meaning...
‘no movement’ and ‘stasis’ denoting ‘slower-than-normal movement’.

In the former, normal English sense of the term, the concept of ‘blood stasis’ contradicts the basis of Harvey’s theory. Galenic theory admitted that blood flowed but necessarily considered its movement to be ‘to and fro’, implying moments or nodes of stasis at the extremities of distribution. Harvey wrote: ‘Since all things, both argument and ocular demonstration, show that the blood . . . is sent for distribution to all parts of the body, where it makes its way into the veins and porosities of the flesh, and then flows by the veins from the circumference on every side to the centre . . . it is absolutely necessary to conclude that the blood in the animal body is impelled in a circle, and is in a state of ceaseless motion’ [our italics]. In other words, motion of the blood ceases—i.e. there is stasis—only at death, unless the circulation is artificially interrupted. Harvey’s De motu cordis is commonly considered the greatest single contribution to the history of physiology. It seems inconsistent to value the work so highly, while using terminology that implicitly denies its most obvious and inseparable philosophical and scientific connotations. To presume ‘blood stasis’ in a viable mammal seems to us to imply a residual, ingrained Galenist premise, with consequences for understanding.

Second, blood stasis in the ordinary English sense of ‘stasis’ does not cause thrombosis; it prevents it. Hewson, a pupil of Hunter, disproved the Boerhaavian idea that blood solidifies locally in vivo when it is not moving. His experiment was simple and his replicates were consistent. He doubly-ligated the jugular vein of a living dog and observed that the blood remained liquid between the ligatures, where it was completely static. He wrote (p. 20): ‘From several experiments . . . I found that . . . after being at rest for 10 minutes the blood remained fluid; nay, that after being at rest for three hours and a quarter, above two thirds of it were still fluid’. On the basis of Hewson’s result, Hunter concluded that Boerhaave’s mechanistic explanation of blood coagulation was wrong. Hewson’s negative finding seemed incredible to succeeding generations, but Lister and Baumgarten each repeated Hewson’s experiment and obtained the same results. Not until several hours of stasis have elapsed does the blood even partly semi-solidify. In any case, it is well known that when death occurs by asphyxiation, e.g. by drowning, hanging or mustard-gassing, the blood remains fluid and incoagulable post-mortem. Thus, we find it confusing to use ‘stasis’ to mean ‘impaired circulation’. ‘Impaired circulation’ is indeed thrombogenic, but ‘stasis’ (blood ‘at rest’) is not.

Impaired venous return in the lower limbs is certainly important in thromboembolism, as Virchow astutely observed (see quotations above). The risk of DVT during prolonged bed rest was established in the later 19th century, and although by the 1920s it was clear that other factors must also be involved, the relevance of restricted mobility was never in doubt. Wright et al. provided experimental evidence of reduced venous blood velocity in recumbent limbs, and by the time the consensus model was fully articulated, ‘stasis’ was generally regarded as a ‘cause’ of thrombosis.

However, what does ‘impaired circulation’ really signify? We contend that reduced linear blood velocity is not the crucial factor in venous thrombogenesis. What matters far more is non-pulsatility of blood movement in the deep veins of the lower limb. In other words, we interpret ‘impaired circulation’ not (necessarily) as ‘retarded flow’, still less as ‘stasis’, but as ‘non-pulsatile flow’. We shall explain our reasoning later. For the time being, we recall that the ‘muscle pump’ is essential for maintaining pulsatile flow as well as ensuring normal venous return; prolonged immobilization of the legs retards venous return but also markedly diminishes pulsatility; so our interpretation is consistent with well-established studies such as those cited above. Moreover, Schina et al. showed that the incidence of DVT correlates with a reduced venous filling and ejection fraction. Interestingly, pulsatility and mean linear velocity are not necessarily coupled; rapid or intense muscular contraction enhances pulsatility but can actually decrease the mean linear velocity. Indeed, some circumstances seem to allow an inverse relationship between linear velocity and pulsatility. Therefore, if we are right, DVT could (hypothetically) develop when the linear blood velocity in the vein is relatively rapid, so long as pulsatility is seriously impaired. In principle at least, this is a testable prediction for future experimental study.

Endothelial injury

Like his predecessors, Virchow acknowledged that intimal injury is important in thromboembolism, but most proponents of the consensus model have marginalized or even dismissed this facet of the ‘triad’. Sevitt claimed that ‘spontaneous thrombi’ form when the endothelium appears intact and normal by light microscopy, although he had previously surmised that electron microscopy might reveal subtle changes. Comerota et al. said that the alleged role of the venous endothelium in thrombogenesis was ‘more controversial’ than
‘hypercoagulability’ and ‘stasis’, and Thomas\textsuperscript{55,86} denied that it had any such role. Even in the 1990s, Cina et al\textsuperscript{19} remarked during a discussion of embolism that ‘Mobilization of thrombi is easier in the first phases, when they do not adhere as yet to the venous wall’, implying that any association between the thrombus and the endothelium is secondary and adventitious. This seems curious, if not implausible. If haemostasis is the formation of a platelet-fibrin plug when the venous intima is injured (the subendothelium is exposed to the luminal blood), and thrombosis is ‘inappropriate haemostasis’, then it seems reasonable to postulate that thrombogenesis begins as a normal haemostatic response to endogenous endothelial injury, visible by microscopy or not. Recently, however, some researchers have shown more interest in the role of the vessel wall in thrombosis.\textsuperscript{87} Indeed, there is a burgeoning literature on the cell and molecular biology of the vascular endothelium, and particularly its pro-thrombotic responses to hypoxia.

The probable involvement of hypoxic injury to the endothelium in venous thrombogenesis was established more than half a century ago,\textsuperscript{88,89} but these forward-looking publications seem largely forgotten. The recent renewal of interest in this issue seems to have been motivated initially by research on ischaemia-reperfusion injury (IRI). This phenomenon, first described explicitly by Hearse\textsuperscript{90} in 1977, has attracted intense interest, and the field has been extensively reviewed.\textsuperscript{91,92} It primarily concerns hypoxic injury to cardiac and (to a lesser extent) arterial tissue (reperfusion with fresh blood results in pathogenic responses that can include thrombosis), but some inferences from these studies have been extrapolated to veins. In addition, some recent and molecular biological research bears directly on venous endothelial hypoxia and its consequences.

Salient publications in this field during the past decade,\textsuperscript{93–99} have shown that the endothelium controls venous tone by secreting prostanoids, EDRF, ATP and other factors, and by regulating sodium and calcium fluxes. Conversely, these secretion processes are affected by changes in local blood velocity and shear stress, and the endothelium mediates the signalling. Even more significantly, hypoxaemia (and presumably endothelial hypoxia) initiates a web of signalling pathways in the venous endothelial cells, notwithstanding their tolerance of anaerobic conditions, resulting in the attraction of leukocytes and platelets and subsequent fibrinogenesis. Details are reviewed in (e.g.) reference 99. It is now accepted that these findings are relevant to DVT, and the consensus model has been amended accordingly.

The revised consensus model can be summarized thus: impaired venous circulation (‘stasis’) causes local endothelial hypoxia, which initiates the signalling pathways that lead to platelet and leukocyte recruitment and the local production and/or activation of coagulation factors. Under conditions of continued underperfusion, and especially of ‘hypercoagulability’, this results directly in thrombogenesis.

Elucidation of the endothelial signalling pathways and their consequences has been a valuable contribution to knowledge, and endothelial hypoxia is certainly implicated in the aetiology of DVT. However, we pose two questions about this revised consensus: is any particular part of the venous endothelium implicated; and does DVT result from the response of living endothelial cells to hypoxia, as alleged, or from the response of living blood cells to dead (necrotic) endothelium? Our answers to these questions might not accord with the consensus view.

The venous valve pockets: morphology, rheology and role in thrombogenesis

Necropsy and other studies show that thrombi arise in veins that are richest in valves (especially those of the lower limb) and usually involve the venous valve pockets (VVP).\textsuperscript{82,100,101} In the early 1950s, it was shown (for the first time since Virchow) that venous thrombi form in the VVP.\textsuperscript{102–104} Sevitt\textsuperscript{82,105} observed that thrombi are initiated as microscopic nidi in the depths of VVP adjacent to the cusps, and the main constituents of these nidi are leukocytes, platelets and fibrin (i.e. they are ‘white thrombi’).

Remarkably, this almost-invariable site of initiation of thrombogenesis has been disregarded by most subsequent investigators. One possible reason is that very few studies of venous valve architecture and function have been conducted since the time of Fabricius and Harvey. Much of our knowledge of valve morphology and pathology derives from papers by Franklin\textsuperscript{106} and Saphir and Lev.\textsuperscript{107,108} These accounts show that the vein wall is particularly thin at the valve sinus, rendering it more distensible. The valve cusps, in contrast, are stiff. Each cusp comprises a collagen-elastin network continuous with the subendothelium of the intima, covered in a single endothelial cell layer, but it is avascular. Cusps contain very few smooth muscle fibres, and these few are close to the vein wall attachments. The cusp is at its thinnest at the end,
where the distal (luminalis) and proximal (parietalis) surfaces meet.

Saphir and Lev\textsuperscript{107} found that ‘inflammatory damage’ to the vein valves is common. The cusps can become necrotic, e.g., after endocarditis or other heart diseases, and such necrosis is potentially thrombogenic. Leukocytes cluster around the damaged cusp. Nohe et al.\textsuperscript{109} showed that leukocyte adhesion is enhanced at low shear rates, and is associated with tissue factor expression by the endothelium, and Nicolaides\textsuperscript{22} reported leukocyte infiltration of the valves in chronic venous disease (see earlier discussion). The venous valves in the lower extremities can be completely obliterated by this infiltration, and prosthetic valves have been designed to treat victims.\textsuperscript{110} Leukocyte infiltration of injured cusps provides a plausible mechanism for the formation of Sevitt’s proto-thrombotic nidi.

Saphir and Lev\textsuperscript{108} found that with increased age, the cup parietalis acquired higher collagen and lower elastin contents. Valve sinuses from older individuals had less connective tissue and muscle, and more fat deposits. These changes, like leukocyte accumulation, could make the cusp less flexible and valve function less efficient, suggesting a possible connection with the increased incidence of DVT with age.

Von Recklinghausen\textsuperscript{111} observed that flow patterns in VVP are unlike those in the mainstream, and considered the implications for local tissue oxygenation, but his seminal idea was not pursued for several decades. Gibbs\textsuperscript{100} suggested that when linear blood velocity is low, eddy currents and turbulence are set up around the VVP. Karino\textsuperscript{112} showed that large stable paired vortices are established in canine saphenous VVP under normal physiological conditions. These vortices are located symmetrically about the plane bisecting the valve leaflets. Cells entering the VVP from the mainstream describe spiral orbits of gradually decreasing diameter, remaining in the pocket for a considerable time before they rejoin the mainstream. There is a smaller secondary vortex deep in each VVP, which seems to be driven by the primary vortex and rotates in the opposite sense at very low velocity. The implications include the following:\textsuperscript{113} abnormalities of valve function or blood flow characteristics (such as non-pulsatility) will perturb these flow patterns and seriously prolong the retention of blood, and the cells it contains, within the VVP. Blood behaves as a Maxwell fluid at low linear velocities, so cells including leukocytes and platelets are likely to accumulate in the secondary vortex regions.\textsuperscript{114}

Lurie et al.\textsuperscript{115,116} described a four-phase valve cycle: (i) an opening phase (about 0.25–0.30 s) during which the cusps move from the closed state towards, but not touching, the sinus walls,\textsuperscript{106} (ii) an equilibrium phase (about 0.6–0.7 s) during which the leading edges of the cusps remain suspended in the mainstream and oscillate with amplitudes of 0.1–1.6 mm; (iii) a closing phase (about 0.35–0.45 s) during which the cusps move in synchrony to the centre of the vein lumen; and (iv) a closed phase (about 0.4–0.5 s). During the equilibrium phase, flow separation occurs at the leading edges of the cusps, reattaching at the wall of the sinus; part of the flow is directed into the sinus pocket and a vortex develops,\textsuperscript{112} creating a pressure difference across the cusp that dilates the sinus and is instrumental in initiating the closing phase. Thus, the venous valve is a pressure-operated rather than a flow-driven device. Most importantly, the valve cycle is essential for ensuring the pulsatility of venous blood movement under normal physiological conditions. Clearly, pathogenic changes in the valve incident on ageing or on leukocyte accumulation will prejudice the efficiency of the valve cycle and \textit{ipso facto} the pulsatility of flow, and (as argued above) cause prolonged or indefinite retention of blood cells within the VVP.

**Implications for a model of the aetiology of DVT**

Hume, Sevitt and Thomas\textsuperscript{117} tried to accommodate the consensus model to the formation of venous thrombi in VVP. Their hypothesis suggested that ‘stasis’ consists in the prolonged sequestration of blood in VVP or similar sites when local circulatory conditions do not permit efficient exchange, and that ‘local hypercoagulability’ ensues in these sites. Notwithstanding the eminence of the authors, this hypothesis was tacitly disregarded by subsequent workers. Perhaps its fundamental difficulty lay in the attempt to amalgamate the misleading concept of ‘hypercoagulability as cause’ with the established fact that thrombi originate almost solely in VVP.

Nevertheless, the work reviewed in the previous two sections allows us to specify criteria for an adequate model of DVT aetiology. Such a model must: (i) explain, through rheological, morphological and other considerations, why thrombi are initiated in VVP; (ii) relate the initiation of protothrombogenic nidi to recognized pathological changes in the valve cusp leaflets; (iii) account for the known morphological features of a venous thrombus (the predominance of white cells in the part of the thrombus first formed, and the lines of Zahn); and (iv) give reasons for the marked tendency of venous thrombi to embolize when the muscle pump becomes active again after immobility, or...
even when the linear blood velocity remains low. A satisfactory aetiological hypothesis must also make specific, experimentally testable predictions, provide a new understanding of therapeutic and prophylactic measures, connect as much as possible with the existing literature and suggest future lines of research.

Such a hypothesis was developed during the 1960s and published in its full form a decade later.\textsuperscript{118} the ischaemic-hypoxic hypothesis.

**The ischaemic-hypoxic hypothesis (IHH)**

According to the IHH, the sequence of events that can potentially lead to deep venous thrombogenesis and subsequent embolism is as follows. Either the muscle pump in the lower limbs ceases to operate efficiently because of prolonged sitting, sleeping, paresis, neuroleptic drug ingestion, sustained general anaesthesia or other cause, or there is significant hypovolaemia. For any (combination) of these reasons, blood movement through the deep leg veins becomes largely non-pulsatile, though the linear blood velocity through the vein lumen might or might not be significantly decreased. This non-pulsatility precludes exchange of blood between the vein lumen and the VVP (as the aforementioned rheological studies indicate). The available oxygen in the VVP is consumed by the endothelial cells lining the pocket and by the trapped blood cells, and is not replaced, because the blood remains unexchanged for considerably longer than would normally be the case. The resulting local hypoxaemia affects the endothelial cells of the parietalis aspect of the valve cusp, and platelets react to their now-dead predecessors from the VVP and replaced, and fresh leukocytes and platelets adhere to the necrotic endothelium. When pulsatile flow is yet again restored, perhaps four or more hours after the start of the process, the previous series of events is repeated: the oxygen-depleted blood is evacuated from the VVP and replaced, and fresh leukocytes and platelets react to their now-dead predecessors on the parietalis. Since the initial layer of a thrombus is apparently fibrin-free,\textsuperscript{62} fibrinogenesis might begin (as part of normal haemostasis) at this second stage of thrombus formation. In consequence, the trapped blood in the VVP coagulates, forming an incipient thrombus tenuously anchored to the parietalis aspect of the valve cusp.

This seriously impairs valve function, as we mentioned earlier when we cited Nicolaides.\textsuperscript{22} In particular, the valve cycle will no longer operate efficiently, and local pulsatility of flow will be further prejudiced as a result,\textsuperscript{113} aggravating the development of pathology. However, these changes are not yet life-threatening, although they might result in significant morbidity. Only when the semi-solidified blood mass containing dead leukocytes and platelets expands beyond the confines of the VVP and comes into contact with the blood passing through the vein lumen does the incipient thrombus begin to grow. The platelets and leukocytes in the luminal blood react to the expanding mass as to dead tissue, and they coat it in a new living cell layer. Further fibrinogenesis ensues and the vein becomes partially and progressively occluded. As a result, the linear blood velocity in the lumen is decreased, oxygen consumption by the trapped cells results in lumenal hypoxaemia and further cell death, and an irrepressible cycle of thrombus growth has been initiated. The cyclical progression of events in this process is responsible for the ‘layered’ appearance of a venous thrombus in section: the lines of Zahn. The radial size of the thrombus is obviously limited by the diameter of the vein, but there is no such constraint on its length. Thus, venous thrombi can grow to lengths of 30–50 cm. As more and more of the width of the vein is occupied by the growing thrombus, the local circulation is further impaired, and more blood cells (now including erythrocytes as well as leukocytes and platelets) become entrapped in the semi-solidified mass. The ‘tail’ of the thrombus, the part...
first formed, is therefore predominantly white, while the more recently-formed ‘head’ is predominantly red.

Notwithstanding the consequent reduction in linear velocity, the passing blood stream tugs constantly on this ‘frond’ of growing thrombus and in time is likely to break the weak, narrow anchor to the necrotic parietalis endothelium. This tendency is aggravated if the venous return rate is increased, say by renewed activity of the leg muscles. The result is ‘metastasis’ of the thrombus: an embolism.

Validation of the IHH; clinical implications

This hypothesis satisfactorily explains the formation of pro-thrombotic nidi in VVP, relates the process to valve pathology, accounts for the morphological features of venous thrombi and shows why embolism of large thrombi is commonplace. Therefore, it meets the four criteria specified earlier. Without experimental corroboration of its predictions, however, it would be no more than an interesting speculation.

Malone and Morris showed that when the veins of experimental animals were starved of oxygen by either hypokinetic or anaemic means, lesions similar to the white parts of naturally-occurring thrombi were formed. No such lesions appeared in animals subjected to arterial (i.e. atmospheric) hypoxia. Hamer et al. found that blood in VVP rapidly became hypoxic during streamline flow at low velocity, but attained a PO2 indistinguishable from that of the luminal blood when pulsatile flow recurred. Therefore, pulsatile flow is essential for ensuring that the valve cusp endothelium within the pocket receives an adequate oxygen supply. Significantly, early thrombi only developed on the valve cusps after two or more hours of non-pulsatile flow, supporting the claim that prolonged VVP hypoxaemia is instrumental in thrombogenesis.

However, the IHH predicts that venous thrombi histologically indistinguishable from those seen clinically should be induced in experimental animals by alternately rendering the limb veins hypoxaemic and then allowing them to be reperfused with fresh blood. This critical prediction was experimentally confirmed by Hamer and Malone. Hyoxaemia alone apparently produced no DVT; only when the VVP were reperfused by restored pulsatile flow were examples of experimental thrombogenesis produced. Two important features of this study were: (i) the veins were not traumatized in any way except by hypoxaemia; and (ii) the experimental thrombi were morphologically indistinguishable from autochthonous ones.

These results placed the IHH on a sound scientific footing, though further experiments (e.g. investigation of rapid but non-pulsatile blood movement along leg veins, as mentioned earlier) remain desirable. More importantly for clinical medicine, the hypothesis has significant practical implications. First, it emphasizes the need to avoid (e.g.) the parietic effects of alcohol during long-haul flights. Second, it unequivocally supports the prophylactic value of intermittent leg vein compression during prolonged periods of immobility. Third, it has surgical relevance. For instance, a very simple suggestion would be that surgical procedures are undertaken in 1–2 degrees of alternating Trendelenburg (head down/feet up) and anti-Trendelburg tilt, to ensure that VVP are always empty, or emptied at approximately hourly intervals. Moreover, it justifies the maintenance of normal blood volume during surgery, since even relatively minor blood loss can increase the risk of venous hypoxaemia and DVT. Therefore, although it implies no need for radical changes in clinical practice (according to the IHH, conventional anticoagulant treatment does not prevent the underlying cause of DVT, i.e. VVP hypoxaemia and ensuing valve cusp pathology and leukocyte infiltration, but may prevent the development of thrombi from or during these pathogenic changes by impairing the normal phagocytic functions of blood cells), we believe that it merits the attention of clinical practitioners.

Reception of the IHH and future prospects

Hume immediately recognized the significance of the Hamer and Malone study, and the validation of the major premises and predictions of the IHH, but there have been few citations of the work since then. One reason might be the perceived mismatch with the consensus ‘stasis and hypercoagulability’ model, which retained its hegemony. But this was not the only factor. Fortuitously, the publication of the hypothesis virtually coincided with the first description of IRI. IRI was already a major field of investigation by the time the IHH was experimentally validated, and at first glance it might appear to have rendered the IHH redundant, since it seems almost identical. Of course, this is not the case: for instance, valve pocket hypoxaemia and non-pulsatile flow are not issues in IRI. However, the supposition might have sufficed to deflect interest from the IHH per se.
Another, related reason that we might suggest for marginalization of the IHH is the recent glut of publications on the venous endothelium and its response to hypoxia. The 1977–84 proposal that ‘hypoxia’ is somehow related to DVT could have interested cell and molecular biologists, but explanation of DVT by reference to VVPs and blood rheology, rather than in terms of intracellular activities, may have vitiated the attractiveness of the IHH to many researchers. Yet the recent literature on venous endothelial hypoxia can be seen as ‘fleshing out’ the IHH by detailing relevant cellular and molecular processes, perhaps developing the model in ways that would combine the pathophysiological (Vichowian) and mechanistic (biochemical) traditions productively. Unfortunately, scarcely any of the modern literature mentions the parietalis aspect of the valve cusps, which is histologically and (by implication) physiologically distinctive. For example, none of the hypoxic responses of the venous endothelium that involve smooth muscle activation or alteration in dynamics of the vasa venorum can be relevant to the parietalis endothelium, which has only a collage-nous, non-muscular, non-vascularized base.

Moreover, the contemporary literature concerns the response of living endothelial cells to hypoxia. However, when proto-thrombotic nidi are believed to form on the valve leaflets, the relevant endothelial cells are most likely dead; so we probably witness a normal proto-haemostatic response to a necrotic or injured intima. This assessment is speculative and may be mistaken. Given the renowned tolerance of endothelial cells to oxygen lack, parietalis cells may not be dead after two or more hours of sustained hypoxaemia but merely ‘crying for help’, in which case some details of the signalling pathways referred to above could be relevant—so long as they occur in the parietalis.

We would urge researchers in this field to direct their attention to the valve cusp endothelia, rather than to the venous endothelium as a whole. Taking into account that valve cusps are not perfused by capillaries, and the open question of whether parietalis cells remain viable after sustained hypoxaemia, the mechanism by which proto-thrombotic nidi form in the VVP should now be elucidated using the approaches developed in the recent literature, in which case further progress in our understanding of the aetiology of DVT is assured.

References


