

What is VTE?

Overview

This chapter covers the basics of VTE, opening with some definitions and statistics from the literature to illustrate the size of the problem. Recurrent VTE and idiopathic VTE are discussed and the importance of prevention is highlighted. The economic burden of VTE in the United Kingdom is discussed and comparisons are made globally. The changes in our understanding of VTE are detailed in a chronological history of the condition, which places our current understanding in context.

An introduction

Venous thromboembolism (VTE) is the term used to encompass the two related conditions of deep vein thrombosis (DVT) and pulmonary embolism (PE). Venous thrombosis is the term used to describe conditions in which blood clots (thrombi) form in a vein, causing partial or complete obstruction to blood flow. The 'deep veins' of the calves, thighs and pelvis are the most common sites of thrombus formation, although clots can also form in more proximal veins and in the upper extremities. Venous thrombosis of the 'deep veins' is known as DVT.

If a piece of the blood clots breaks off and travels from its site of formation through the venous system, it is known as an 'embolus' (from the Greek *embolos*, meaning wedge or plug). If the clot is carried through the blood stream, through the chambers of the heart and into the pulmonary circulation, it can become lodged in the arteries of the lungs, where it is known as a PE. A large PE that restricts blood flow to the lungs can be fatal (Chapter 2 provides further information on the pathophysiology of the condition).

Each of the stages of VTE (i.e. calf DVT, proximal DVT, PE) may or may not be associated with clinical symptoms, depending upon the severity of the thrombosis, the adequacy of the collateral vessels (the vessels surrounding the occluded vein) and the extent of the inflammation caused by the blockage. The general health of a patient is an additional factor that can influence presentation. For example, a moderately sized PE may cause no symptoms in an otherwise healthy patient, but may result in severe symptoms or even death on a background of advanced cardiopulmonary disease (Kearon 2003). Chapters 5 and 6 delve further into the clinical presentation of the two conditions and the investigations and treatments currently used in practice.

Both symptomatic and asymptomatic VTE have been associated with fatalities and acute morbidity. A report commissioned by the House of Commons Health Committee in 2005 estimated that VTE in hospitalized patients causes up to 32000 deaths from PE per year in the United Kingdom, as well as causing significant chronic health problems due to post-thrombotic limb and venous ulceration. Approximately 100000 people in England and Wales suffer with venous leg ulcers following a DVT, which are often resistant to treatment, leading to prolonged hospitalization and discomfort to patients, costing the NHS an estimated £100–300 million each year (Bosanquet 1992; Laing 1992). The total cost of managing VTE within the NHS is thought to be £640 million each year (House of Commons Health Committee 2005).

Public awareness in the United Kingdom

The death of a 28 year-old woman from a PE after a long-haul flight from Sydney to London in Autumn 2000 provoked a media frenzy surrounding 'economy class syndrome' and 'traveller's thrombosis'. However, the risks of hospital-acquired VTE remained unpublicized – which is quite extraordinary, considering the impact the disease has on national morbidity and mortality figures. Frustrated by this lack of awareness, a group of health professionals founded Lifeblood, a thrombosis charity with the intention to increase awareness and research funds for thrombosis (Hunt 2008).

In 2004, representatives from the charity met with the House of Commons Select Committee to highlight the issues. Emphasis was given to the fact that at least 50% of the deaths attributed to VTE were related to hospital admission, yet, despite the opportunity for these patients to receive thromboprophylaxis, it was not being implemented. It was pointed out that only 20% of eligible patients were receiving prophylaxis and health care professionals appeared ignorant of the risks (Hunt 2008).

The Chief Medical Officer agreed with the issues raised and wrote to all doctors in 2005, informing them of good practice guidelines regarding VTE prevention (House of Commons Health Committee 2005). It was then that the National Institute for Clinical Excellence was commissioned to produce thromboprophylaxis guidelines for all hospitalized patients, and a VTE Expert Working Group was established to report on how best practice could be promoted and implemented (Hunt 2008).

The expert working group recommended that all inpatients required a mandatory VTE risk assessment regarding their need for thromboprophylaxis, and that thrombosis teams should be established within hospitals to ensure that this is implemented (CMO 2007). National audits have been carried out annually by the All Party Parliamentary Thrombosis Group (APPTG) since these recommendations were made. The 2007 findings were disappointing and although 99% of trusts were aware of the guidelines, only 32% of them were undertaking a risk assessment for hospitalized patients (APPTG 2007). The Department of Health responded to this by publicizing a DVT Risk Assessment Tool in 2008 (see Appendix 1) and the follow-up audit carried out in the same year showed improvements. In 2008, 70% of acute NHS trusts declared that they were undertaking a documented VTE risk assessment in line with the recommendations of the Chief Medical Officer (APPTG 2008).

The feeling among many health professionals is that VTE is still more of a 'Cinderella issue' than it should be. The media thrive on stories concerning hospital-acquired infections, which account for about 6000 deaths each year in the United Kingdom, yet ignore hospital-acquired VTE – which causes significantly more. The charity Lifeblood have done much to increase public awareness in the United Kingdom; one such method was the institution of an annual 'National Thrombosis Week'; another was creating accessible information on the subject on the internet (Hunt 2008).

With increasing public awareness of VTE and government incentives mandating thromboprophylaxis in hospitals, it is hoped that future mortality figures attributable to VTE will be on the decline.

The scale of the problem

Determining the number of people who develop VTE each year has proved to be a challenge. Clinical symptoms are notoriously unreliable and the disease can often present 'silently', with no symptoms whatsoever (Verstraete 1997), meaning that many people may have VTE that has gone unrecognized. Conversely, a large number of cases of PE diagnosed at autopsy were included in the figures of some studies whether or not they were symptomatic, failing to take into account other pathology responsible for death and resulting in an overrepresentation in some of the data (White 2003). Despite these difficulties in determining exact incidence rates, it is clear that VTE remains a major public health problem and that concentrating on its prevention is key.

The incidence of VTE

A number of studies focusing on the epidemiology of the disease have been carried out worldwide, with the vast majority of the data being generated in the United States. A study over a 25 year period demonstrated that as many as 145 individuals per 100 000 in the general population develop symptomatic DVT and up to 69 individuals per 100 000 experience a PE (Silverstein 1998). More recent studies have suggested that the incidence of VTE is about 120 per 100 000 people per year (Heit *et al.* 2001; Cushman *et al.* 2004). The higher figures cited by Silverstein are thought to reflect the large number of cases detected at autopsy. A review of several large American studies compiled by White (2003) suggest that the incidence of first-time symptomatic VTE, standardized for age and sex in predominantly Caucasian Americans, was in the range 71–117 cases per 100 000 population. Based on this information, researchers have estimated that over 300 000 United States citizens develop a first lifetime VTE each year (Heit 2005). Furthermore, recent computer modelling suggests that more than 900 000 incident or recurrent, fatal and non-fatal VTE events occur in the United States annually, which is more than the estimated number of strokes ($n = 700\,000$) and heart attacks ($n = 865\,000$) (Heit *et al.* 2005). The incidence of VTE does not appear to have changed significantly over the last 25 years (Heit *et al.* 2006).

European studies have collected similar figures. A French study from 2001 found that new cases of DVT occur at a rate of about 87 per 100 000 of the population, with PEs occurring at a rate of 46 per 100 000 (Oger 2000). A Swedish study confirmed a DVT incidence of 117 per 100 000 (Nordstrom *et al.* 1992). Lindblad *et al.* (1991) carried out a population-based autopsy study, which showed that autopsy-

diagnosed fatal PE occurs in around 40 per 100 000 population. Using this incidence-based approach, it is estimated that VTE has an incidence of 145 per 100 000 diagnosed pre-mortem and 47 per 100 000 diagnosed at post mortem (House of Commons Health Committee 2005).

The VTE Impact Assessment Group in Europe (VITAE) used an epidemiological model developed by clinical and epidemiological thrombosis specialists working across Europe and the United States to derive estimates of total VTE events. The total annual burden of VTE in the 25 EU member states (population 454 million) was estimated to be 640 000 symptomatic DVT and 383 000 PE (Department of Health 2007).

In the United Kingdom this equates to approximately 59 000 new cases of DVT and 29 500 new cases of non-fatal PE per year (House of Commons Health Committee 2005). Initial treatment of VTE is costly and patients often go on to develop serious long-term complications which inevitably add to the cost burden on health services. Most patients with VTE require more than one diagnostic test, as well as a prolonged hospital stay involving treatment with heparin and multiple blood tests to monitor progress. The Office for Healthcare Economics estimated the annual cost in the United Kingdom of treating patients with postsurgical DVT and PE in 1993 was up to £222.8 million. The total cost to the United Kingdom for the management of VTE is estimated at £640 million. In addition to this, the long-term expenditure to care for those patients with chronic complications such as venous ulcers is thought to amount to £400 million (House of Commons Health Committee 2005).

Factors influencing the figures

Age

Incidence of VTE varies considerably, depending on an individual's age. In persons 15 years old or younger there are less than five cases per 100 000 of the population annually. This figure rises exponentially with age to around 500 cases per 100 000 of the population at age 80 years (Anderson *et al.* 1991; Silverstein 1998; White 2003). As the population ages, the number of deaths each year due to PE is also predicted to grow (Heit *et al.* 2005).

Sex

The use of oral contraceptives and hormone replacement therapy have been associated with VTE in women, but published data have shown no consistent differences in the incidence of VTE between the sexes (Nordstrom *et al.* 1992). Silverstein *et al.* (1998) noted a slightly higher incidence among women during childbearing years, but a higher rate

in men after the age of 50. The overall age-adjusted incidence rate was found to be 114 per 100 000 in men and 105 per 100 000 in women, with a male:female sex ratio of 1.2:1 (Heit 2008).

Race

Race has also been shown to effect incidence rates of VTE. Compared to Caucasians, studies have shown that African-Americans have an incidence of VTE approximately 30% higher, while Asian and Native American subjects show an incidence almost 70% lower (White *et al.* 1998 and 2003; Klatsky *et al.* 2000). An explanation for the lower incidence in Asian populations has not been found, but it has been suggested that it may relate to a lower prevalence of genetic factors predisposing to VTE, such as factor V Leiden. This condition, which causes hypercoagulability and a propensity to VTE, is described further in Chapter 5; it has been shown to have a 0.5% prevalence in Asian populations compared to 5% in Caucasians (Ridker *et al.* 1997; Gregg *et al.* 1997; Angchaisuksiri *et al.* 2000).

Season

The seasonal variation of VTE has been observed in various French studies. Bounameaux *et al.* (1996) found no relation to the incidence of DVT and time of year, but a large data set ($n = 127318$) analysed by Boulay in 2001 discovered a 15% rise in VTE admissions during winter months and 15% fewer admissions during the summer. Further research is needed to confirm this finding, but it has been suggested that the figures are related to a decline in physical activity during the winter months, thus showing an inverse relationship between physical activity and the development of VTE (White 2003).

It is clear from the figures listed above that the presence of various risk factors, such as increasing age, have been shown to influence which patients develop VTE. In a community review of 1231 consecutive patients treated for VTE, 96% had at least one risk factor (Anderson *et al.* 1992) and risk appears to increase in proportion to the number of risk factors an individual has (Anderson *et al.* 2003). Specific risk factors and evidence for identifying which patients are at risk are discussed more comprehensively in Chapter 5.

Mortality rates

Estimates of mortality rates from VTE have varied widely among the studies that have been performed to date. VTE often affects patients with other concurrent diseases that reduce survival, such as cancer, which makes exact mortality figures difficult to establish. In the United States, it is estimated that 50 000–200 000 people die of PE each year

(Anderson 1995; Clagett *et al.* 1998; Dismuke *et al.* 1986; Horlander *et al.* 2003), which is thought to exceed the number of deaths due to myocardial infarction and stroke (Heit *et al.* 2005).

Survival after PE is much worse than after DVT alone (Douketis *et al.* 1998) – almost a quarter die suddenly and approximately 40% die within 3 months (Heit *et al.* 1999).

Some studies have shown that this mortality rate is decreasing (Horlander *et al.* 2003; Heit *et al.* 1999), while others state that it is stable (Goldhaber 1998). The mortality rate within 3 months of a venous thromboembolic event has been documented at 15–17.5% (Goldhaber 1997; Heit *et al.* 1999; Horlander *et al.* 2003). In individuals older than 65 years of age, Siddique *et al.* (1996) reported a fatality rate after diagnosis of PE of 16.1% in African-Americans and 12.9% in Caucasians. Data collected more recently by the RIETE registry (an ongoing, international, multicentre, prospective cohort of consecutive patients presenting with symptomatic VTE confirmed by objective testing) describe a three month mortality rate from fatal PE at 1.68%, with an overall mortality rate of 8.65%, and cite PE as a cause of death in 19.4% of patients in their study (Laporte *et al.* 2008).

In the United Kingdom it has been estimated that PE may account for rates of sudden death at up to 0.40 per 1000 population (Lindblad *et al.* 1991), equating to over 24000 deaths per year. A retrospective analysis of autopsy reports carried out in the 1980s found PE as a cause of death in 10% of general hospital patients (1% of all admissions) and 83% of these patients also had DVT in the legs at autopsy (Sandler *et al.* 1989). The VTE Impact Assessment Group in Europe (VITAE) estimated VTE-related deaths in Europe to be at 480000 annually. Of these deaths, 7% had been diagnosed with VTE and treated, 34% were estimated to be sudden fatal PE and 59% followed undetected PE (Department of Health 2007). The annual population death rate from VTE was about 0.1%, which in the United Kingdom, with a population of 60 million, equates to over 60000 deaths annually (Department of Health 2007).

Although the figures may vary, researchers are consistent about the clinical predictors that put patients at risk of fatal PE, and agree that identification of high-risk patients is important to adapt treatment to the level of risk (Laporte *et al.* 2008). The major clinical factors predictive of fatal PE in studies to date are advanced age, cancer, immobilization for neurological disease, systolic arterial hypotension, underlying cardiovascular disease and chronic lung or congestive heart failure (Laporte *et al.* 2008; Heit *et al.* 1999; Goldhaber *et al.* 1999). Numerous clinical trials over the past 30 years have shown that thromboprophylaxis reduces the frequency of VTE and thus deaths from fatal PE (see Chapter 6 for more information).

Recurrent VTE

VTE is a chronic disease, with about 30% of patients developing recurrence within the next 10 years (Heit *et al.* 2000; Schulman S *et al.* 2006). Recurrence appears to be highest within the first 6–12 months since the initial event (Heit 2008), with a recurrence rate of approximately 7% at 6 months (White 2003). Factors that appear to predict recurrence include male gender, increasing patient age and body mass index, neurological disease with lower limb paresis and active cancer (Heit *et al.* 2000; McRae *et al.* 2006). ‘Idiopathic’ VTE (VTE unassociated with surgery/trauma/identifiable underlying cause) is an independent predictor for recurrence in itself and those patients with thrombophilic tendencies are also at risk (Heit 2008). A possible link has been found with recurrent VTE and those patients with a persistently increased plasma fibrin D-dimer level (Palareti *et al.* 2006) and those with residual venous thrombosis (Prandoni *et al.* 2002).

Anticoagulation is effective at preventing recurrence, but the duration of anticoagulation does not seem to affect the risk of recurrence once primary therapy for the incident event is stopped (Schulman *et al.* 2006). After stopping anticoagulation therapy, the risk of recurrence for patients with transient risk factors, e.g. recent surgery, is approximately 3% per year, whereas in patients with a continuing risk factor, e.g. malignancy or idiopathic thrombosis, the risk is at least 10% per year (Kearon 2003).

Idiopathic VTE

Idiopathic VTE is defined as thrombosis that occurs in the absence of any identifiable risk factors. Approximately 50% of patients presenting with first idiopathic or juvenile VTE have an underlying thrombophilia (Anderson *et al.* 2003). Apparent idiopathic VTE is often found to have malignancy as its underlying cause and studies have shown a 5% incidence of previously undiagnosed cancer in patients presenting with VTE (Baron *et al.* 1998). Patients with idiopathic thrombosis have a high risk of experiencing a recurrent event and indefinite-duration anticoagulation therapy is advocated in such patients (Goldhaber 2004).

A timeline of our understanding

Our understanding of venous disease has been accumulating for well over 2000 years. Advances in related areas have also contributed

towards what we know today. What follows is a chronological record of the discoveries that have provided us with a greater appreciation of venous thromboembolic disease today.

Despite its frequency today, there is little specific reference to venous thrombosis in antiquity. In artwork from ancient Egypt, Greece, Rome, Persia and South America there are representations of varicose veins and ulcers but very little suggestive of VTE.

2650–1550 BC

The first reference to peripheral venous disease was recorded in on one of the oldest preserved medical documents, the Ancient Egyptian Ebers papyrus (1550 BC) and documented the potential ‘fatal haemorrhage’ that may ensue from surgery on ‘serpentine windings’ or varicose veins. The Chinese physician Huang Ti described pathological haemostasis earlier still, in 2650 BC, writing: ‘when the blood coagulates within the foot it causes pain and chills’ – but this could of course be referring to arterial thrombosis (Dickson 2004).

460–377 BC

Hippocrates (460–377 BC) made many references to the vascular system and ulcers and was first to use the term ‘leucophlegmasia’ to describe bilateral leg oedema, most likely due to conditions such as heart failure and liver cirrhosis but possibly also due to post-thrombotic oedema (Anning 1957). He observed the magical transformation of blood from liquid into a solid and reasoned that it was due to cooling.

AD 129–200

The Greek physician Galen (AD 129–200) also recognized this phenomenon and introduced the term ‘thrombosis’, which is Greek for curdling. Galen was also first to describe the four classic symptoms of inflammation (redness, pain, heat and swelling). Early physicians from Hippocrates onwards followed the Theory of Humours, which taught that the body is made up of four ‘humours’ (blood, phlegm, black bile and yellow bile). An imbalance of these humours was thought to be the cause of all diseases, and practices of blood letting and placing hot cups on patients were done in an effort to redress this balance. Humouralism was widely practised until the late nineteenth century, when it was decisively displaced by Rudolf Virchow’s theories of cellular pathology (see Box 1.1).

Box 1.1 Rudolf Ludwig Karl Virchow

Born in October 1821 in Schivelbein, eastern Pomerania (today's Poland), as the only son of a merchant, Rudolf Virchow (Figure 1.1) is considered by many to have been the most prominent German physician of the nineteenth century (Safavi-Abbasi *et al.* 2006).

Describing him as an overachiever would be something of an understatement. Among numerous accomplishments, he pioneered the modern concept of 'cell theory' to explain the effects of disease in organisms at a cellular level, displacing the long-held belief that disease was caused by an imbalance of the four 'humours'. He recognized the blood-borne pathogenesis of syphilis and was the first to describe leukaemia (Safavi-Abbasi *et al.* 2006). His name has also become eponymous with an enlarged left supraclavicular node, 'Virchow's node', which is indicative of gastrointestinal malignancy.

Virchow's 'epoch-making' paper on embolism was published in 1847, popularizing the terms 'thrombosis' and 'embolism' to describe clots or 'curds' in blood vessels. He observed: '... the

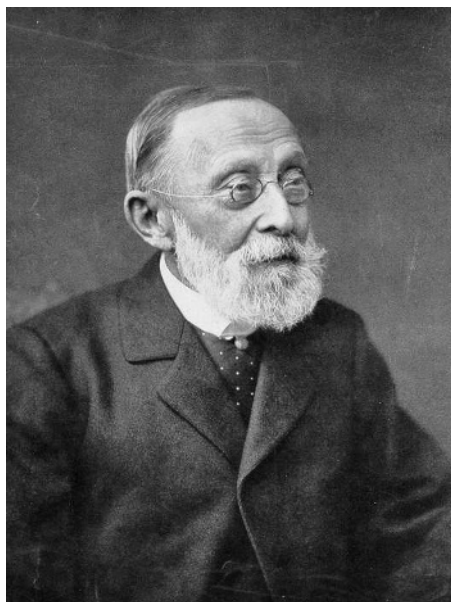


Figure 1.1 Rudolf Ludwig Karl Virchow. Courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center.

detachment of fragments from the end of the softening thrombus which are carried along by the current of blood and driven into remote vessels. This gives rise to the very frequent process on which I have bestowed the name of Embolia' (Virchow 1978).

Although Virchow's name is now eponymous with the triad of predisposing factors to VTE (irregularity of the vessel lumen, impaired blood flow and increased coagulability), the literature suggests that the three elements had been established as a cause prior to the work of Virchow and he never laid claim to these observations. The term 'Virchow's triad' did not come into use until the 1950s (Anning 1957) and its components were not fully agreed on in the literature until the 1930s (Dickson 2004). Regardless of its origins, the term still remains clinically relevant today.

Virchow acted as a political revolutionary throughout his life, upholding his belief that 'the physician is the natural advocate for the poor' (Pearce 2002). He promoted public health issues such as sewage disposal, hospital design, public hygiene and meat inspection and incidentally also discovered trichinosis (Safavi-Abbasi *et al.* 2006)

His provocative ideas were viewed with some hostility among his peers, and various medical journals refused to publish some of his work. Undeterred by this, he founded his own medical journal together with the pathologist Benno Ernst Heinrich Reinhardt. He was a keen anthropologist and contributed to the development of anthropology as a modern science. He continued to lecture, write, edit, research and serve in political bodies until his death.

Virchow died in 1902 at the age of 81, when, still active and energetic, he jumped prematurely from a moving passenger tram in Berlin. He fractured his hip and died soon afterwards in hospital. He led an immensely productive life, making monumental contributions to medical sciences. An exhaustive list of his publications and biographies can be found in Ole Daniel Enerson (<http://www.whonamedit.com/doctor.cfm/912.html>) (Safavi-Abbasi *et al.* 2006).

1271

The earliest documented case of venous thrombosis comes from an illustrated manuscript presented to the Cardinal of Bourbonnoys in the fifteenth century and outlines an account of a man suffering with classic symptoms in 1271 (Dexter *et al.* 1974). Reports that accumulated after this generally made reference to cases occurring during pregnancy or in the post-partum period (Mannucci 2002).

1452–1519

During the pioneering atmosphere of the Renaissance, dissection was accepted as a means to new discoveries (prior to this it was restricted, due to the belief that it was disrespectful to God). The anatomical drawings of Leonardo da Vinci (1452–1519) were some of the first to clearly document the structure of the venous system.

1628

Once dissection was established as a legitimate part of medical training, numerous new discoveries emerged. In 1628 William Harvey (1578–1657) overturned medical thinking by proving that blood circulates, and that the valves in veins are there to ensure unidirectional flow.

1644–1686

In 1644, Schenk first observed venous thrombosis when he described an occlusion in the inferior vena cava, and as early as 1686 the first theories on the aetiology of venous thrombosis were outlined by Richard Wiseman (1633–1714). He documented the case of a pharmacist's wife, who developed pain and swelling of her leg after a difficult labour and attributed the cause of the thrombosis to be systemic alteration in the circulating blood (pioneering the idea of 'hypercoagulability') – which he noted to be more prevalent in pregnancy and malignancy (Dickson 2004). The 'milk leg' of pregnancy was believed until the end of the eighteenth century to be due to the retention in the legs of unconsumed breast milk or commonly 'evil humours', and the French surgeon Ambroise Pare believed that leg swelling during pregnancy was due to the retention and concentration of menstrual blood (Mannucci 2002).

1800

Harvey's demonstration of blood circulation led scientists Hunter, Baillie and Hewson to abandon the theory of retention of humours and adopt the concept that venous thrombosis was due to the closure of veins by blood clots. They proposed that slow blood flow was a likely cause of this and that the thrombus formed because of a 'coagulable lymph' in plasma (the substance that was later called fibrinogen; Hunter 1793; Baillie 1793; Hewson 1846). In 1800, Hull wrote the first literature review on venous thrombosis, for the first time calling it 'phlegmasia dolens', and surmised that the coagulation of 'lymph' was due to inflammation (Mannucci 2002).

1800–1860s

The risk factors for VTE were recognised at the turn of the nineteenth century. Ferrier (1810) noted that medical illness, particularly if associated with prolonged immobilization, was a risk factor and that the condition also occurred during debilitating infections such as typhus. Hodgson (1815) noted that injury to a vein might cause thrombosis and Hutchinsonson (1829) described a case of ‘phlegmasia dolens’ in a patient who had sustained a blow to the shin from a piece of timber (Anning 1957). Surgery was first recognized as a risk factor by Spencer Wells in 1866.

Towards the end of the nineteenth century, the pathologists Virchow and Rokitansky conducted autopsy studies on fatal cases of post-partum thrombosis and concluded, independently of one another, the famous three factors of ‘Virchow’s triad’ [(vessel wall damage; decreased venous blood flow; and changes in blood leading to an increased tendency to clot formation (hypercoagulability)] as being the cause of venous thrombosis. In 1846, Virchow recognized the association between venous thrombosis in the legs and pulmonary embolism.

1860s–1900s

The components of Virchow’s triad were well investigated over the next century, and with this research came new treatments. In Virchow’s era, treatments had progressed from the blood letting of the Middle Ages to bed-rest and leeches. Surgical intervention to remove the thrombosed veins was advocated in the 1860s, then in 1884 it was discovered that leeches have anticoagulant properties (Dickson 2004). Following on from this, heparin was discovered as an anticoagulant in 1916, but was not introduced into clinical practice until the 1930s. Murray (1947) recognized its use in the prevention of PE in surgical patients. In the late 1940s the coumarins were introduced into the treatment of VTE, and De Takats (1950) suggested that the injection of a low-dose heparin would prevent DVT.

Our methods of detection improved in the 1930s, when venography was introduced to visualize the veins (Barber 1932) – a method that remains the ‘gold standard’ for detection but has been widely replaced today by the less invasive ultrasound.

1950 onwards

The 1950s were established as the era of thrombolysis, stemming from Astrup’s finding of a substance in the tissues that was capable of

activating the proteolytic enzymes in blood (Astrup 1951). This led to the discovery that streptokinase could dissolve intravascular thrombi (Johnson *et al.* 1952).

Our knowledge of genetic predisposition to clotting improved in the late twentieth century with the recognition of protein C and protein S deficiencies in the 1980s (Griffin *et al.* 1981; Comp *et al.* 1984). The 'factor V Leiden' mutation was discovered in the early 1990s (Bertina *et al.* 1994); this mutation leads to a hypercoagulable state and has since been found to be present in around 20% of patients who present with a first episode of VTE (Koster *et al.* 1993).

Conclusion

VTE is a significant problem in the United Kingdom today and our understanding of it continues to grow year by year as further research is completed. Although much has been discovered since Virchow, the value of a clinical diagnosis of VTE remains unchanged. History taking can identify risk factors but examination rarely gives us a definitive diagnosis. Today, detection of the problem is based on assessment of clinical risk and the judicious use of the investigations and treatment we now have available to us.

It is hoped that the chapters that follow will provide a comprehensive summary of VTE that can be read as a whole or as a reference point, enabling health professionals to consider VTE risk factors in their patients to provide them with up to date and effective care.

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