PART I

Prevalence, risks, and prognosis of pulmonary embolism and deep venous thrombosis

CHAPTER 1

Pulmonary embolism and deep venous thrombosis at autopsy

Prevalence of pulmonary embolism at autopsy

The prevalence of pulmonary embolism (PE) at autopsy varies according to the age and morbidity of the population studied. Dalen and Alpert in 1975 estimated that 15% of deaths in acute general hospitals and 25% of deaths in nursing homes or chronic hospitals were due to PE [1]. In more recent years, with more extensive use of antithrombotic prophylaxis, PE at autopsy was shown with similar prevalences among patients who died in acute care hospitals (24%) and patients who died in chronic care hospitals (22%) [2]. Outpatients, however, had a lower prevalence of PE at autopsy (5%) [2].

The prevalence of PE at autopsy of patients in general hospitals and in entire communities, with one exception, ranged from 9 to 28% and has not changed in over 60 years [2–21] (Table 1.1). One study, however, reported gross PE in 55% of patients at autopsy [10]. On average, PE at autopsy occurred in 7031 of 55,090 patients (13%) (Table 1.1, Figure 1.1).

Large or fatal PE at autopsy

Large or fatal PE in patients at autopsy in general hospitals or communities from 1939 to 2000 occurred in 2264 of 54,364 patients (4%) (range 0.3–24%) [2, 3, 8–11, 13–19, 21, 22] (Table 1.1, Figure 1.1). In most studies, the prevalence of large or fatal PE ranged from 3 to 10%. In elderly institutionalized patients, the rate of fatal PE at autopsy was within that range, 18 of 234 (8%) [23]. Data on institutionalized patients are not included in Table 1.1. A sudden increase in the rate of PE at autopsy was observed in London in 1940 due to cramped conditions in air raid shelters [22]. These rates also are not included in Table 1.1.

Small PE at autopsy

In an autopsy study that employed postmortem pulmonary arteriography as well as gross dissection and microscopic examination, gross dissection showed PE in 34 of 225 (15%) of autopsied patients [4]. Among these, PE was limited to muscular pulmonary artery branches (0.1–1 mm diameter) in 26 of 34 patients (76%) and PE was in elastic pulmonary artery branches (>1 mm diameter) in 8 of 34 patients (24%) [4]. Microscopic examination showed PE in pulmonary arterioles in 13 of 34 patients (38%) with grossly visible PE. The smallest PE that have been identified in living patients were with wedge pulmonary arteriography, which showed PE in 1–2-mm-diameter pulmonary artery branches [24] (see Chapter 71).

Fibrous bands, webs, and intimal fibrosis have been interpreted as the final state of organization of PE and these have been reported by some to indicate old PE at autopsy [7]. Meticulous dissection and microscopic examination for minute and barely visible fragments showed traces of fresh or old PE at autopsy in 52% and 64% of patients [7, 8].

Unsuspected PE at autopsy

Pulmonary embolism was unsuspected or undiagnosed antemortem in 3268 of 3876 patients in general hospitals or communities who had PE at autopsy (84%) (range 80–93%) [3, 5, 8, 11, 12, 16, 18] (Table 1.2, Figure 1.2). Remarkably, even in patients with large or fatal PE at autopsy, the majority, 1902 of 2448 (78%), were unsuspected or undiagnosed antemortem [2, 11, 12, 14–16, 18, 19, 25] (Table 1.2, Figure 1.2). In our experience, PE at autopsy caused death in 5%, contributed to death in 0.5%, and was incidental in 9.2% of 404 autopsies, and the distribution, according

Table 1.1 Prevalence of pulmonary embolism at autopsy in general hospitals and communities.

Any PE/No autopsies (%)	*Fatal or large PE/No autopsies (%)*	*Study years*	*First author, year [Ref]*
	4/242 (2)	1939	Simpson, 1940 [22]
606/4391 (14)	—	1945–1954	Coon, 1959 [3]
34/225 (15)	—	1960–1961	Smith, 1964 [4]
118/981 (12)	—	1956–1960	Uhland, 1964 [5]
17/61 (28)*	—	1951–1959	Freiman, 1965 [6]
55/263 (21)†	—	1964–1965	Morrell, 1968 [7]
567/4600 (12)	202/4600 (4)	1964–1974	Coon, 1976 [8]
—	319/1350 (24)	1976	Schwarz, 1976 [9]
280/508 (55)‡	92/508 (18)	1969–1970	Havig, 1977 [10]
216/1455 (15)	54/1455 (4)	1973–1974	Goldhaber, 1982 [11]
389/2398 (16)	—	1966–1976	Dismuke, 1984 [12]
—	105/1133 (9)	1966–1970	Dismuke, 1986 [13]
—	53/1124 (5)	1971–1975	″″
—	43/1128 (4)	1976–1980	″″
—	44/1276 (3)	1980–1984	Rubenstein, 1988 [14]
313/2388 (13)	239/2388 (10)	1979–1983	Sandler, 1989 [15]
1934/21,529 (9)	67/21,529 (0.3)	1960–1984	Karwinski, 1989 [16]
161/766 (21)	68/766 (9)	1957	Linblad, 1991 [17]
250/1117 (22)	93/1117 (8)	1964	″″
346/1412 (25)	83/1412 (6)	1975	″″
260/994 (26)	93/994 (9)	1987	″″
59/404 (15)	20/404 (5)	1985–1986	Stein, 1995 [18]
—	92/2427 (4)	1985–1989	Morgenthaler, 1995 [19]
288/3334 (9)§	—	1966–1974	Mandelli, 1997 [20]
182/1144 (16)§	—	1989–1994	″″
431/2356 (18)	178/2356 (8)	1987	Nordstrom, 1998 [2]
525/3764 (14)	221/3764 (6)	1980–2000	Pheby, 2002 [21]

*An additional 22/61 (36%) showed traces of residual pulmonary embolism (PE), fibrous bands, or webs.
†An additional 31% had had fibrous bands or intimal fibrosis indicative of old PE.
‡An additional 72 of 508 (14%) were visible only by microscopy.
§Massive and submassive PE.

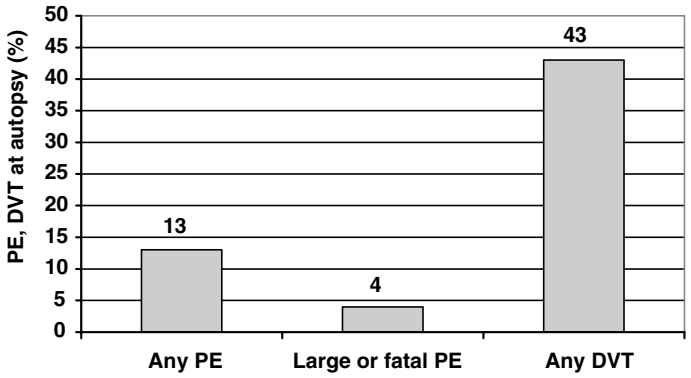

Figure 1.1 Prevalence of pulmonary embolism (PE) and deep venous thrombosis (DVT) at autopsy.

Table 1.2 Unsuspected pulmonary embolism at autopsy.

Any unsuspected or undiagnosed PE [unsuspected PE/total PE (%)]	*Unsuspected or undiagnosed minor or small PE [unsuspected small PE/total PE (%)]*	*Unsuspected or undiagnosed fatal or large PE [unsuspected large PE/total PE (%)]*	*Study years*	*First author, year [Ref]*
563/606 (93)	—	—	1945–1954	Coon, 1959 [3]
91/107 (85)	—	—	1955–1960	Uhland, 1964 [5]
514/567 (91)	—	—	1964– 1974	Coon, 1976 [8]
199/217 (92)	161/162 (99)	38/54 (70)	1973–1974	Goldhaber, 1982 [11]
310/389 (80)	219/244 (90)	91/145 (63)	1966–1976	Dismuke, 1984 [12]
—	—	30/44 (68)	1980–1984	Rubenstein, 1988 [14]
—	—	186/195 (95)	1979–1983	Sandler, 1989 [15]
1619/1934 (84)	436/484 (90)	1183/1450 (82)	1960–1984	Karwinski, 1989 [16]
52/59 (88)	36/37 (97)	14/20 (70)	1985–1986	Stein, 1995 [18]
—	—	47/92 (51)	1985–1989	Morgenthaler, 1995 [19]
—	—	189/279 (68)	1987	Nordstrom, 1998 [2]
—	—	124/169 (73)	1995–2002	Attems, 2004* [25]

*All patients ≥70 years old.
PE, pulmonary embolism.

to whether diagnosed and treated, suspected but not diagnosed or treated, or unsuspected is shown in Table 1.3 [18]. Many patients with unsuspected large or fatal PE had advanced associated disease [18]. Patients who suffer sudden and unexplained catastrophic events in the hospital are a group in whom the diagnosis might be suspected more frequently if physicians maintain a high index of suspicion [18].

Rate and sequence of organization of thromboemboli

A thrombus contains extensive regions of masses of agglutinated platelets [26]. Platelets are deposited first, followed by leukocytes, followed after a variable period of time by fibrin with trapped red cells and a few scattered leukocytes [26]. The rate of organization of thromboemboli has been assessed in rabbits [27, 28]. The following results were shown [27, 28]:

8 minutes. Thrombus covered by an eosinophilic rim of platelets. Small amounts of fibrin were interspersed among the platelets at the edge of the thrombus [28].

3 days. Thrombi contained masses of red cells, fibrin, platelets, and white cells together with a number of macrophages. Parts of the surface not in contact with the vessel wall were covered by flattened cells and in places these were buttressed by a layer of elongated cells beneath. Platelets were particularly

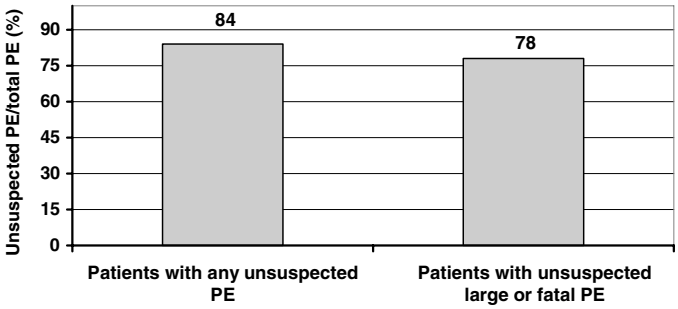

Figure 1.2 Prevalence of unsuspected pulmonary embolism (PE) at autopsy.

Table 1.3 Autopsy patients ≥18 years old ($n = 404$).

	PE caused death (%)	*PE contributed to death (%)*	*PE incidental (%)*	*PE total (%)*
Diagnosed and treated	3 (0.7)	0 (0)	1 (0.2)	4(1.0)
Suspected but not diagnosed or treated	3 (0.7)	0 (0)	0 (0)	3 (0.7)
Unsuspected	14 (3.5)	2 (0.5)	36 (8.9)	52(12.9)
Total	20 (5.0)	2 (0.5)	37 (9.2)	59 (14.6)

Modified from Stein and Henry [18] and reproduced with permission.
PE, pulmonary embolism.

Table 1.4 Deep venous thromboses; autopsies with full limb dissection.

DVT n/N *(%)*	*Site (number of thrombi)*	*Site (number of patients)*	*First author, year [Ref]*
95/324 (29)		Thighs or pelvis 7 Thighs and Calves 38 Calves only 50	Rossle, 1937 [29]
100/165 (61)	Thighs 22 Calves 87 Ankle 17 Foot 71		Neumann, 1938 [30]
88/200 (44)		Thighs only 3 Thighs and Calves 28 Calves only 57	Hunter, 1945 [31]
35/130 (27)			Raeburn, 1951 [32]
32/100 (32)*		Thighs only 18 Thighs and Calves 10 Calves only 4	McLachin, 1962 [33]
149/253 (59)		Thighs only 24 Thighs and Calves 39 Calves only 86	Gibbs, 1957 [34]
13/27 (48)	IVC 1 Pelvic 1 Thigh 23 Calves 35†	Thighs only 1 Thighs and Calves 7 Calves only 5	Stein, 1967 [35]
540/1350 (40)	Pelvic 41‡ Thigh 21 Calves 74		Schwarz, 1976 [9]
161/261 (62)	IVC 8 Pelvic 31 Thigh 129 Calves 128 Foot 87		Havig, 1977 [10]

*Males >40 years old.
†Calf 11 microscopic thrombi in addition.
‡Sample of 37 patients.
DVT, deep venous thrombosis; *n*, number of patients with DVT; *N*, number of patients necropsied.

Figure 1.3 Extensive antemortem thrombus located in popliteal and calf veins. Previously unpublished figure from Stein and Evans [35].

prevalent near the thrombus–vessel wall junction. Mononuclear cells were prominent [27].

5 and 7 days. Beginnings of vascularization were apparent. Capillaries were within the thrombus mass and in cellular areas of attachment to the intima. The central area of the thrombus showed mainly debris [27].

7 days. Occluding thrombi had retracted in places and were covered by flattened cells, and showed one or more firm cellular attachments to the intima. Macrophages were conspicuous and contained lipid, fibrin, and cellular debris together with fibroblastic cells [27].

14 days. Thrombi consisted of cellular masses containing small clumps of fibrin and variable amounts of fat and fibrous tissue [27].

20 days. Some thrombi appeared as polypoid masses protruding into the lumen and containing variable amounts of fat, fibrous, and elastic tissue, and on occasion calcium, while others showed lipid within foamy cells and a fibrous tissue cap containing fibroblasts, collagen, and elastic tissue [27].

30 days. Thromboemboli were converted to eccentric fibrofatty thickenings of the intima [27].

Deep venous thrombosis at autopsy

Data on patients who had complete dissection of the lower extremities at autopsy are from prior decades, and before the general use of antithrombotic prophylaxis [10, 29–36]. Among patients at autopsy who had full limb dissection, 1213 of 2810 (43%) showed deep venous thrombosis (DVT) [10, 29–36] (Table 1.4, Figures 1.1 and 1.3).

Among 161 patients with DVT at autopsy, 7 patients had thrombi in the common iliac vein and 22 had thrombi in the external iliac vein. Each of these patients also showed DVT in the femoral vein [10]. The external iliac vein showed thrombi in 12 of 161 patients (7%) without femoral vein involvement. In 4 of these patients, the calf veins showed DVT, but not the femoral veins [10].

Deep venous thrombosis affected the veins of the calves more frequently than the veins of the thighs, and both were more frequently affected than the veins of the pelvis. The distribution of 601 thrombi found in 311 patients who had dissection of the pelvic, thigh, and calf veins was 54% in the veins of the calves, 32% in the veins of the thighs, 12% in the pelvic veins, and 1% in the inferior vena cava [10, 30, 35, 36] (Figure 1.4). The distribution of 563 thrombi among 261 necropsied patients who had dissection of the veins of the foot as well as the veins of the calf, thigh, and pelvis was 28% in the veins of the foot, 38% in the calf, 27% in the thigh, 6% in the pelvic veins, and 1% in the inferior vena cava (IVC) [10, 30] (Figure 1.5).

Among 282 necropsied patients who had complete dissection of the veins of the thighs and veins of the calves, the thrombi were located only in the veins of the calves in 54% of patients [31, 33–35] (Figure 1.6).

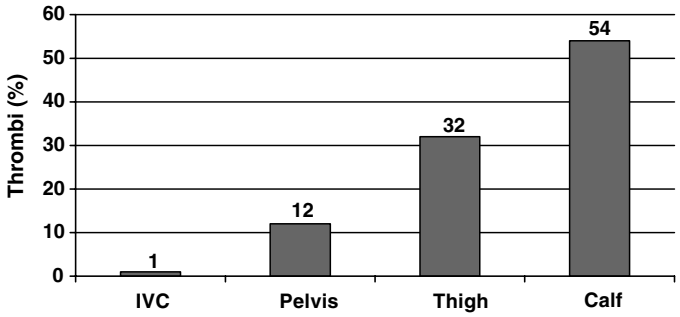

Figure 1.4 Distribution of deep venous thrombosis among patients at autopsy in whom pelvic, thigh, and calf veins were dissected.

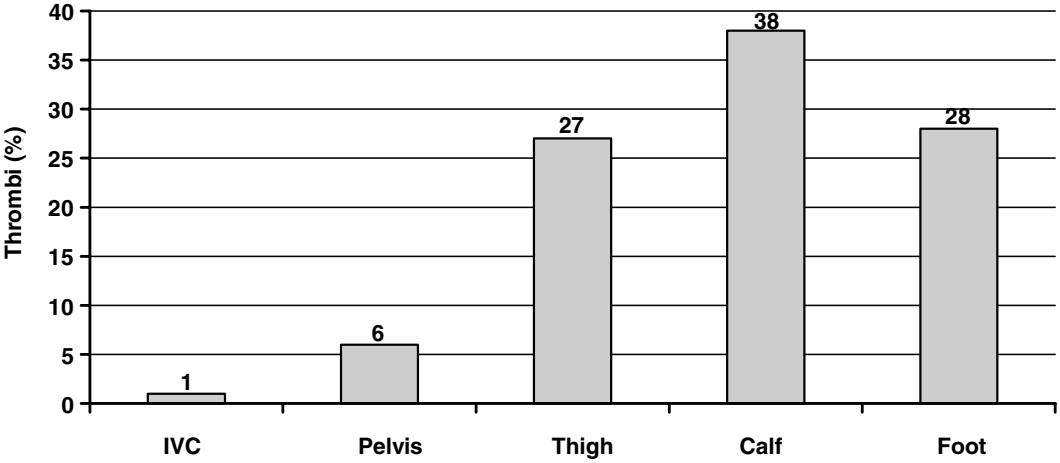

Figure 1.5 Distribution of deep venous thrombosis among patients at autopsy in whom veins of the foot as well as pelvic, thigh, and calf veins were dissected.

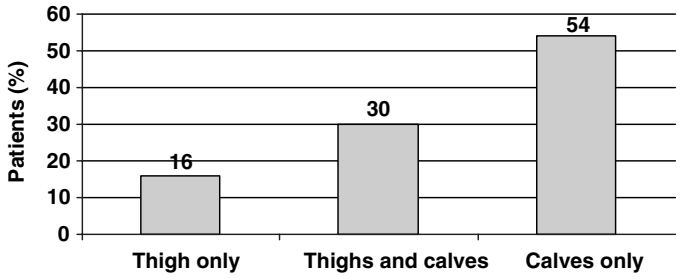

Figure 1.6 Percentage of patients at autopsy with deep venous thrombosis who had involvement of veins of thigh only, veins of thighs and calf veins, and veins of calf only.

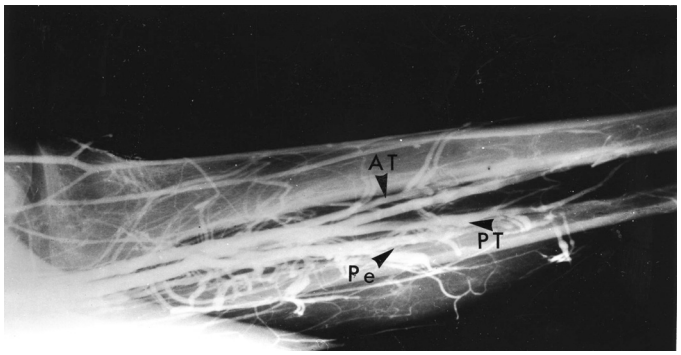

Figure 1.7 Normal postmortem venogram of calf (lateral projection) showing anterior tibial (AT), posterior tibial (PT), and peroneal (Pe) veins. The deep veins are paired. (Reproduced from Stein and Evans [35], with permission.)

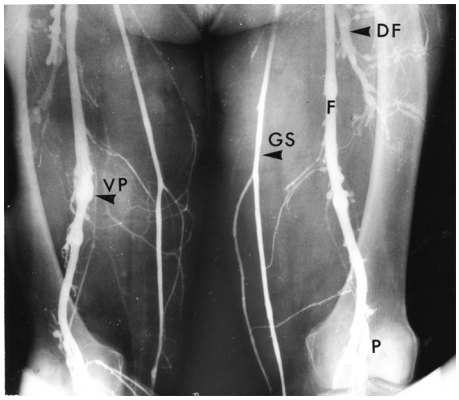

Figure 1.8 Normal postmortem venogram of the thighs (anteroposterior projection) showing the femoral (F), deep femoral (DF), greater saphenous (GS), and popliteal (P) veins. Valve pockets are shown. (Reproduced from Stein and Evans [35], with permission.)

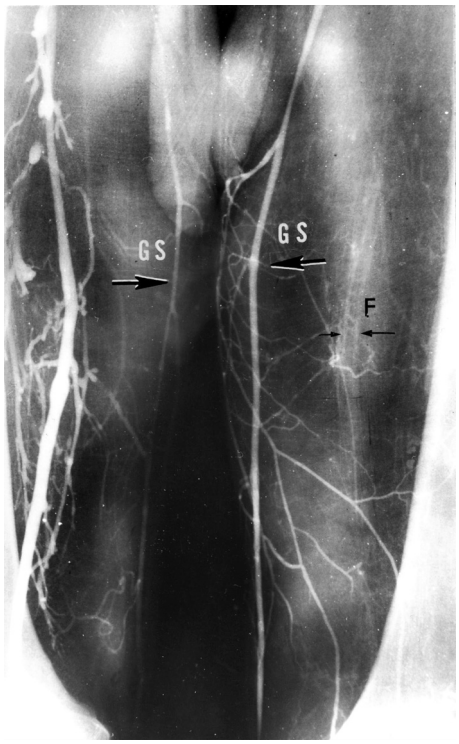

Figure 1.9 Postmortem venogram of the veins of both thighs. Extensive thrombosis of the femoral, deep femoral, and popliteal veins was found by dissection of the left thigh. The venogram of the left thigh shows absence of filling of the popliteal and deep femoral veins and only a faint outline of the femoral vein (F). The left greater saphenous vein is dilated and joined by numerous collateral vessels. The veins of the right thigh were normal. (Reproduced from Stein and Evans [35], with permission.)

Both the veins of the thighs and calves were affected in 30% of patients. Only the veins of the thighs showed DVT in 16% of patients.

Bilateral DVT was observed in 81 of 96 patients (84%) with extensive DVT at autopsy and in 26 of 65 (40%) of patients with minor DVT at autopsy [10].

Postmortem venography illustrates the extent and location of DVT at autopsy in unselected patients [35]. For comparison, normal postmortem venograms of the calf and thighs are shown (Figures 1.7 and 1.8). Postmortem venograms of DVT involving the veins of the thighs are shown in Figures 1.9 and 1.10.

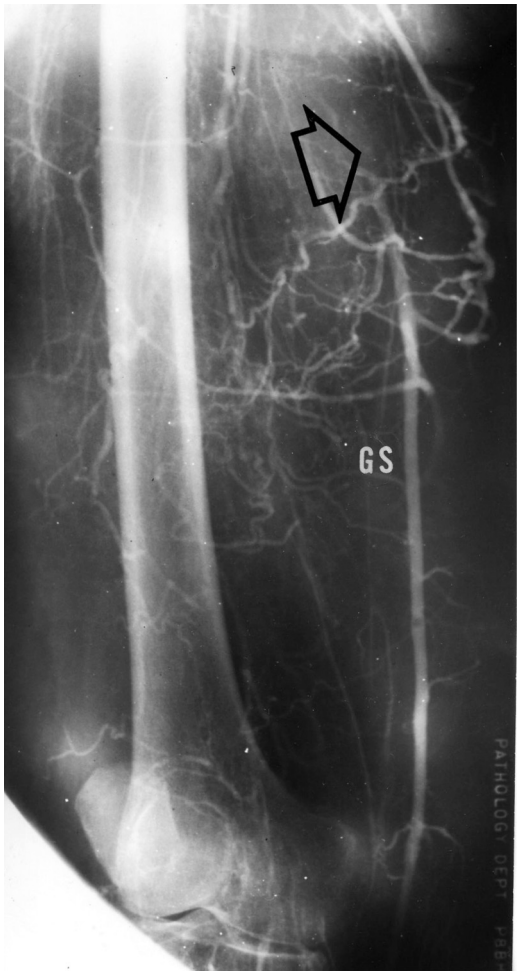

Figure 1.10 Postmortem venogram of right thigh. The femoral vein has not filled with contrast material because of a completely occluding thrombus. The greater saphenous (GS) vein is distended. Collateral vessels formed at the site of an occluding thrombus in the greater saphenous vein (arrow). (Reproduced from Stein and Evans [35], with permission.)

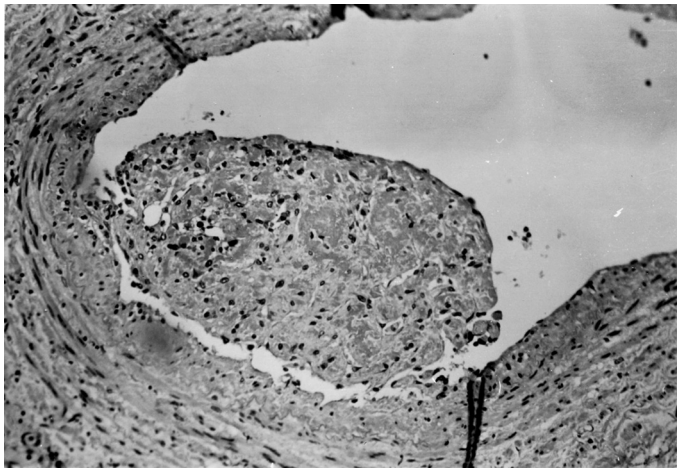

Figure 1.11 Organized thrombus in anterior tibial vein (same patient as Figure 1.12). This thrombus is older than the thrombus in the femoral vein, and there is no phlebitis here. Hematoxylin and eosin ×40. (Previously unpublished figure from Stein and Evans [35].)

Forward thrombosis versus retrograde thrombosis

In every case that we examined in which the veins of the thigh and the calf showed DVT in continuity, the thrombi in the calf were older than those in the thigh [35] (Figures 1.11 and 1.12). This supports the concept that forward thrombosis is more common than retrograde thrombosis.

Collateral veins around occlusions

Clinically unsuspected DVT at autopsy was often extensive, causing collateral circulation around occlusions and dilatation of collateral veins [35] (Figures 1.10 and 1.13).

Thrombophlebitis and phlebothrombosis

The terms "thrombophlebitis" and "phlebothrombosis" in prior years were used to distinguish between DVT associated with inflammation (thrombophlebitis) and DVT not associated with inflammation (phlebopthrombosis). These are outdated terms. Histological investigations have not supported a distinction between the clinical diagnoses of thrombophlebitis and phlebothrombosis. Thrombosis of the veins of the lower extremities usually occurs without inflammation [35] (Figures 1.11 and 1.14–1.16). Inflammation of the walls of the veins, when it occurs (Figure 1.12), is usually secondary to the thrombosis [35]. No clear evidence indicates that inflammation

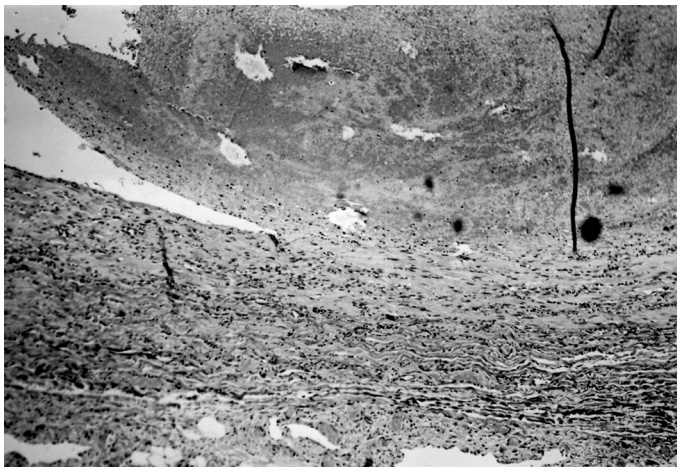

Figure 1.12 Thrombus attached to femoral vein (same patient as Figure 1.11). Lymphocytic infiltrate is shown throughout the wall of the vein. The patient had signs and symptoms of deep venous thrombosis. Hematoxylin and eosin ×13. (Previously unpublished figure from Stein and Evans [35].)

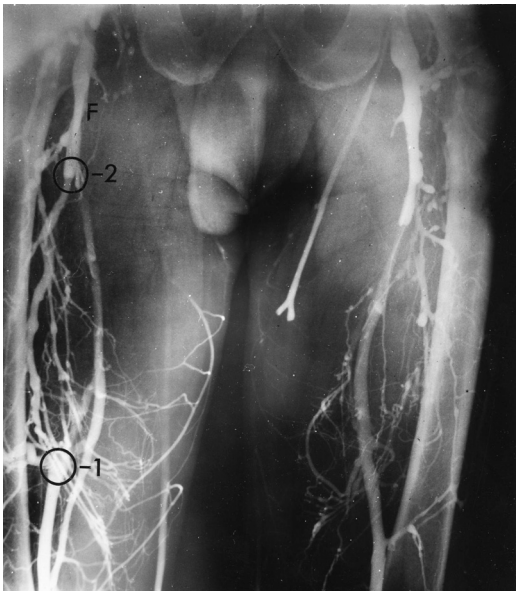

Figure 1.13 Postmortem venogram of the thighs. There is definite radiographic evidence of occlusion of the femoral vein between points 1 and 2. There is no filling of the femoral vein (F) between these points. Dilated and tortuous collaterals pass around the site of occlusion. No thrombus was found on dissection of the veins of the thigh of this patient, presumably because dissection was carried out along the collateral vessels in this area rather than the femoral vein. (This apparent femoral vein occlusion was not included among the positive cases reported in Stein and Evans [35].)

of the veins prevents embolization, or that embolization is more frequent in those patients with thrombi not associated with venous inflammation. The distinction between "thrombophlebitis" and "phlebothrombosis" is of no clinical consequence [35]. A thrombus can induce inflammation in the underlying wall of the vein, and this inflammation in some patients is extensive enough to produce pain, tenderness, swelling, and fever compatible with the clinical diagnosis of thrombophlebitis [36]. However, the underlying pathogenic mechanism is primary thrombosis and not primary phlebitis [36].

The following historical background explains the evolution of these outdated diagnostic terms. John Hunter, after studying infected venesections in human beings and in horses, attributed the thrombosis to phlebitis [37]. Virchow, however, observed that the cellular reaction in the wall of the vein usually does not occur until after the thrombus has been laid down [38]. Welch [39], in studying DVT in patients with infectious diseases such as typhoid fever, found an inflammatory lesion beneath the endothelium in which he could not demonstrate any organisms. He termed this "toxic endophlebitis" and attributed some instances of DVT to inflammation of the veins. Subsequently, patients were described who had clinical evidence of thrombosed leg veins and also had clinical signs of inflammation (warmth, redness, tenderness). A diagnosis of thrombophlebitis was made. In view of Welch's observations, it was concluded that the primary event was inflammation of the wall of the vein. In contrast, asymptomatic patients were later described who had thrombosis of

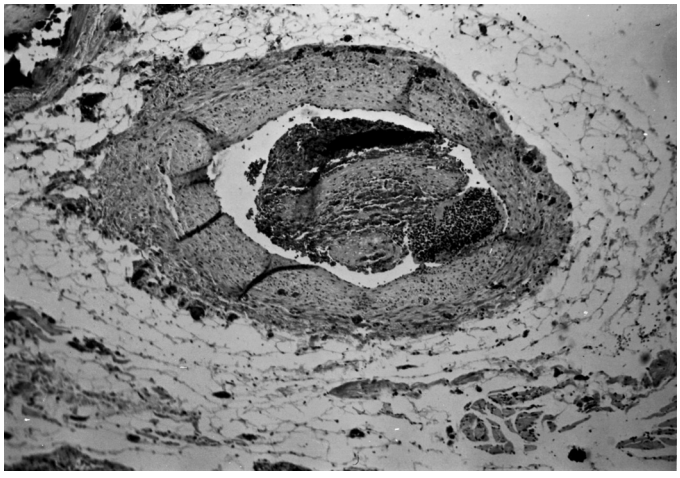

Figure 1.14 Recent thrombus attached in vein of soleal plexus. Hematoxylin and eosin ×16. (Previously unpublished figure from Stein and Evans [35].)

Figure 1.15 Fresh unattached thrombus in fomoral vein. Lines of Zahn distinguish this from postmortem clot. Hematoxylin and eosin ×4. (Previously unpublished figure from Stein and Evans [35].)

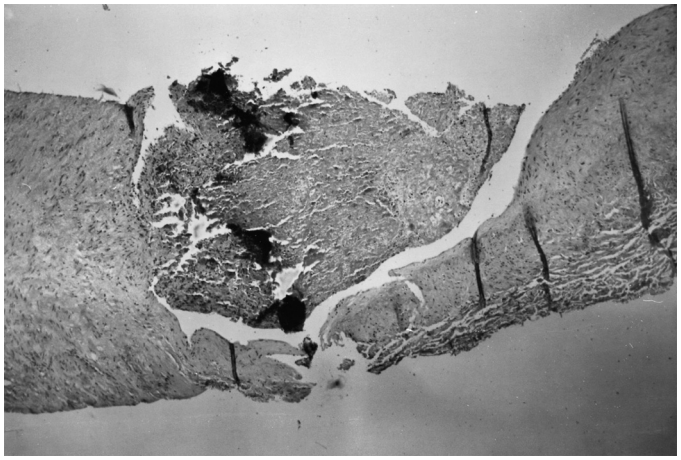

Figure 1.16 Photomicrograph showing thrombus originating in valve pocket of a posterior tibial vein. The well-organized fibrous point of attachment is capped by a fresh red cell, platelet, and fibrin clot. There is no inflammation of the vein. Hematoxylin and eosin ×4. (Previously unpublished figure from Stein and Evans [35].)

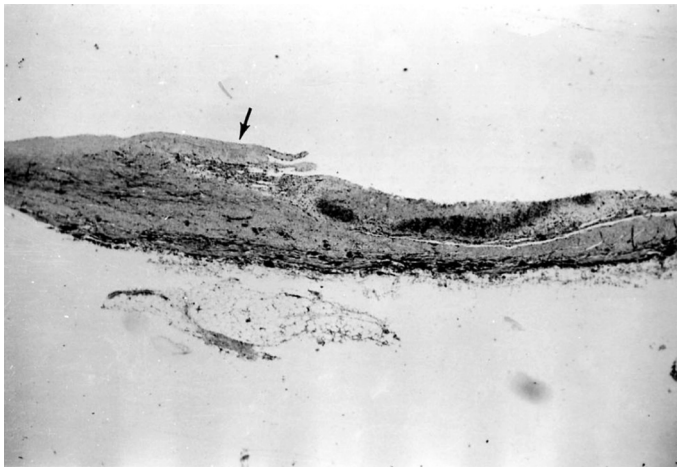

Figure 1.17 Thrombus attached to valve pocket in femoral vein and propagating along the vein. Venous valve is shown (arrow). Hematoxylin and eosin ×10. (Previously unpublished figure from Stein and Evans [35].)

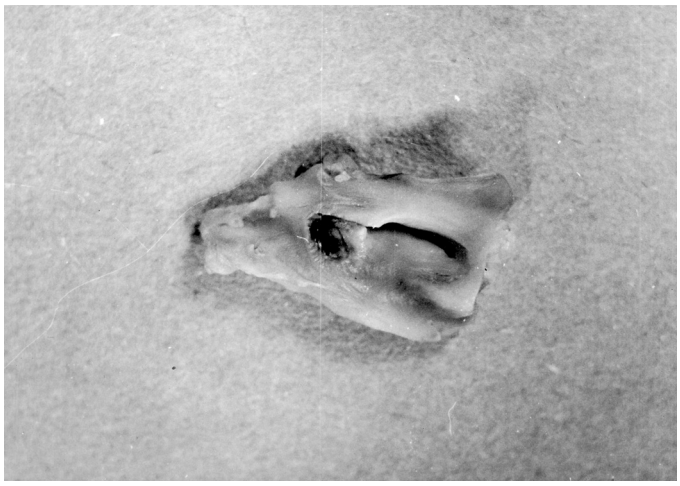

Figure 1.18 Section of left posterior tibial vein. An antemortem thrombus, 0.2 cm in largest dimension, is located within a valve pocket. (Previously unpublished figure from Stein and Evans [35].)

the lower extremities that resulted in PE [40]. These patients, because of the lack of leg signs, were said to have phlebothrombosis. Although there are situations in which phlebitis is primary and thrombosis is secondary (such as mechanical and chemical injury) [36], these are rarely compared with the incidence of thrombosis without inflammation [31, 36].

In patients with DVT at autopsy, fresh components of the thrombus as well as older components were shown, indicating that the thrombosis was continuing [35] (Figure 1.16). None of the patients were diagnosed antemortem as having DVT. A patient with clinical signs and symptoms of DVT showed lymphocytic infiltration in the media of the veins (Figure 1.12). The inflammation occurred not only at the sites of attachment of the thrombus, but also where the thrombus was apposed to the endothelium without being attached, suggesting that the thrombus induced the inflammation.

Valve pockets as site of origin of DVT

The valve pockets were a frequent site of origin of thrombi (Figures 1.16–1.18). Thrombi located in valve pockets consisted of organized fibrous points of attachment capped by fresh fibrin and red cell clot [35] (Figure 1.16). Dilated veins and enlarged valve pockets were frequently seen (Figure 1.19). There was no correlation of either of these abnormalities with the presence of thrombosis [35].

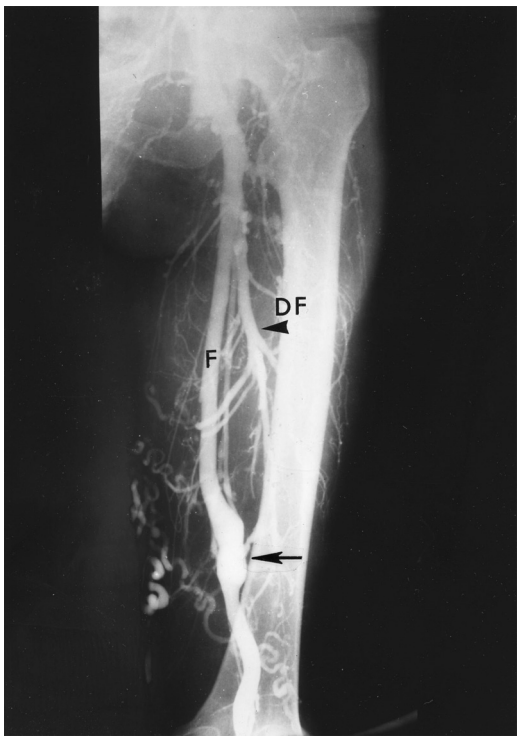

Figure 1.19 Postmortem venogram showing dilated valve pocket in femoral (F) vein of left thigh (arrow). The deep femoral vein (DF) is also shown. (Reproduced from Stein and Evans [35], with permission.)

References

1 Dalen JE, Alpert JS. Natural history of pulmonary embolism. *Prog Cardiovas Dis* 1975; **17**: 259–270.
2 Nordstrom M, Lindblad B. Autopsy-verified venous thromboembolism within a defined urban population—the city of Malmo, Sweden. *Acta Path Microbiol Immunol Scand* 1998; **106**: 378–384.
3 Coon WW, Coller FA. Clinicopathologic correlation in thromboembolism. *Surg Gynecol Obstet* 1959; **109**: 259–269.
4 Smith GT, Dammin GJ, Dexter L. Postmortem arteriographic studies of the human lung in pulmonary embolization. *JAMA* 1964; **188**: 143–151.
5 Uhland H, Goldberg LM. Pulmonary embolism: a commonly missed clinical entity. *Dis Chest* 1964; **45**: 533–536.
6 Freiman DG, Suyemoto J, Wessler S. Frequency of pulmonary thromboembolism in man. *N Engl J Med* 1965; **272**: 1278–1280.
7 Morrell MT, Dunnill MS. The post-mortem incidence of pulmonary embolism in a hospital population. *Br J Surg* 1968; **55**: 347–352.
8 Coon WW. The spectrum of pulmonary embolism: twenty years later. *Arch Surg* 1976; **111**: 398–402.
9 Schwarz N, Feigl W, Neuwirth E, Holzner JH. Venous thromboses and pulmonary emboli in autopsy material. *Wien Klin Wochenschr* 1976; **88**: 423–428.
10 Havig O. Deep venous thrombosis and pulmonary embolism. Chapters 2, 4: Pulmonary thromboembolism. *Acta Chir Scand* 1977; **478**(suppl): 4–11, 24–37.
11 Goldhaber SZ, Hennekens CH, Evans DA, Newton EC, Godleski JJ. Factors associated with correct antemortem diagnosis of major pulmonary embolism. *Am J Med* 1982; **73**: 822–826.
12 Dismuke SE, VanderZwaag R. Accuracy and epidemiological implications of the death certificate diagnosis of pulmonary embolism. *J Chronic Dis* 1984; **37**: 67–73.
13 Dismuke SE, Wagner EH . Pulmonary embolism as a cause of death. The changing mortality in hospitalized patients. *JAMA* 1986; **255**: 2039–2042.
14 Rubenstein I, Murray D, Hoffstein V. Fatal pulmonary emboli in hospitalized patients—an autopsy study. *Arch Int Med* 1988; **148**: 1425–1426.
15 Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis? *J R Soc Med* 1989; **82**: 203–205.
16 Karwinski B, Svendsen E. Comparison of clinical and post-mortem diagnosis of pulmonary embolism. *J Clin Pathol* 1989; **42**: 135–139.
17 Lindblad B, Sternby NH, Bergqvist D. Incidence of venous thromboembolism verified by necropsy over 30 years. *BMJ* 1991; **302**: 709–711.
18 Stein PD, Henry JW. Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. *Chest* 1995; **108**: 978–981.
19 Morgenthaler TI, Ryu JH. Clinical characteristics of fatal pulmonary embolism in a referral hospital. *Mayo Clin Proc* 1995; **70**: 417–424.
20 Mandelli V, Schmid C, Zogno C, Morpurgo M. "False negatives" and "false positives" in acute pulmonary embolism: a clinical–postmortem comparison. *Cardiologia* 1997; **42**: 205–210.
21 Pheby DF, Codling BW. Pulmonary embolism at autopsy in a normal population: implications for air travel fatalities. *Aviat Space Environ Med* 2002; **73**: 1208–1214.
22 Simpson K. Shelter deaths from pulmonary embolism. *Lancet* 1940; **2**: 744.
23 Gross JS, Neufeld RR, Libow LS, Gerber I, Rodstein M. Autopsy study of the elderly institutionalized patient. Review of 234 autopsies. *Arch Intern Med* 1988; **148**: 173–176.
24 Stein PD. Wedge arteriography for the identification of pulmonary emboli in small vessels. *Am Heart J* 1971; **82**: 618–623.
25 Attems J, Arbes S, Bohm G, Bohmer F, Lintner F. The clinical diagnostic accuracy rate regarding the immediate cause of death in a hospitalized geriatric population; an autopsy study of 1594 patients. *Wien Med Wochenschr* 2004; **154**; 159–162.
26 Poole JC, French JE, Cliff WJ. The early stages of thrombosis. *J Clin Pathol* 1963; **16**: 523–528.
27 Still WJ. An electron microscopic study of the organization of experimental thromboemboli in the rabbit. *Lab Invest* 1966; **15**: 1492–1507.
28 Thomas DP, Gurewich V, Ashford TP. Platelet adherence to thromboemboli in relation to the pathogenesis and treatment of pulmonary embolism. *N Engl J Med* 1966; **274**: 953–956.
29 Rossle R. Uber die Bedeutung und die entstehung der wadenvenenthrombosen. *Virchow Arch Path Anat* 1937; **300**: 180–189.
30 Neumann R. Ursprungszentren und entwicklungsformen der bein-thrombose. *Virchow Arch Path Anat* 1938; **301**: 708–735.
31 Hunter WC, Krygier JJ, Kennedy JC, Sneeden VD. Etiology and prevention of thrombosis of the deep leg veins: a study of 400 cases. *Surgery* 1945; **17**: 178–190.
32 Raeburn C. The natural history of venous thrombosis. *BMJ* 1951; **2**: 517–520.
33 McLachlin J, Richards T, Paterson JC. An evaluation of clinical signs in the diagnosis of venous thrombosis. *Arch Surg* 1962; **85**: 738–744.
34 Gibbs NM. Venous thrombosis of the lower limbs with particular reference to bed-rest. *Br J Surg* 1957; **45**: 209–236.

35 Stein PD, Evans H. An autopsy study of leg vein thrombosis. *Circulation* 1967; **35**: 671–681.
36 Allen EV, Barker NW, Hines EA, Jr. *Peripheral Vascular Diseases*. WB Saunders, Philadelphia, 1962: 559–569.
37 Hunter J. Observation on the inflammation of the internal coats of veins. *Trans Soc Imp Med Chir Knowl* 1793; **1**: 18. Quoted by Stein and Evans in Reference [35].
38 Virchow R. *Cellular Pathology as Based Upon Physiological and Pathological Histology*. J. & A. Churchill, Ltd., London, 1860: 197–203. Quoted from Gibbs NM in Reference [34].
39 Welch WH. Thrombosis. In: Allbutt TC, ed. *A System of Medicine*, Vol. 6. Macmillan, New York, 1899: 180.
40 Homans J. Thrombosis of the deep veins of the lower leg causing pulmonary embolism. *New Engl J Med* 1934; **211**: 993.