Thrombosis and embolism after injury

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Thrombosis is frequent in injured patients. It takes different forms, and at least one of them, deep vein thrombosis in the lower limbs, is a common cause of morbidity and death through embolic detachment. The different kinds may be

classified as follows, namely, local thrombosis, deep vein thrombosis, pulmonary microembolism, glomerular microthrombosis, allied to the Schwartzman reaction, occasional cases of arterial thrombosis, and rarely, abacterial vegetative endocarditis.

Thrombi form in flowing blood and are layered structures, unlike blood clots which form in static blood. They contain platelets, fibrin, red cells, and leucocytes, or a variable mixture, the differences depending on size, genesis, age, and venous or arterial location; but whatever the origin, the building blocks of enlarging thrombi are closely packed clumps of platelets with narrow fibrin borders (Fig. 1). Two main processes are involved, namely, coagulation and platelet aggregation. These are interlinked and local release of thrombin is probably the key factor; thrombin promotes platelet clumping at a low concentration and fibrin formation at a higher concentration. Further, the release of substances from platelets can set in motion the coagulation process.

Local Thrombosis and Haemostasis

Thrombosis is frequent as a direct response to injury. In burned skin, for example, small venous thrombi may become prominent in the subdermis and subcutaneous tissue. Generally, they consist of platelet masses, many applied to the intima (Fig. 2), strands of fibrin, red cells, and some leucocytes. Usually they become visible a day or two after burning though they probably begin earlier, during the period of burn oedema. Local inflammatory changes may be visible in the vein wall. This thrombotic or thrombophlebitic condition has to be distinguished from that of stasis in venules and capillaries of the heat-affected dermis, which is the result of gross and

Fig. 1 Platelet-fibrin 'building block' of enlarging thrombi. The pale zone is composed of closely packed platelets and is surrounded by a dark rim of fibrin. This extends into a peripheral network trapping red cells and leucocytes. PTAH $\times$ 240.

Fig. 2 Small thrombosed vein in the deep dermis of burned skin. Burn three days previously. Note the pale platelet clumps, including an extensive rim of platelets lining the intima, below and to the right. PTAH $\times$ 480.

rapid permeability of the minute vessels (Sevitt, 1949). Histologically, stasis is manifest as distended vessels packed with red cells and with little or no fibrin or platelets, at least as seen by light microscopy.

Thrombosis also occurs locally after other kinds of injury, including mechanical and electrical trauma; and direct trauma to endothelium is probably the cause after venepuncture or catheterization. An unusual form is thrombosis of the axillary or subclavian vein which is said to be due to its nipping between the clavicle and the first rib.

The process following direct trauma is similar to that found in haemostasis. In both, platelet masses accumulate on the injured intima and later fibrin forms. The event is probably triggered off by the exposure of subendothelial areas to the flowing blood. Platelets adhere to the damaged area with subsequent build up of a multi-layered mass of clumped platelets. The adhesion phenomenon is probably related to the formation of a fine film of adsorbed plasma protein as found when platelets adhere to glass, whilst the platelet clumping or aggregation is due to the exposure of basement membrane or collagen fibres. Collagen is well established as a potent aggregating substance. The adhesion and sub-

sequent clumping of platelets are the basic initial processes in the cessation of bleeding and in thrombosis of vessels injured in continuity. The process was first observed *in vivo* by Jones in 1851 who noted that the injured vessels became blocked 'by a mass composed apparently of colourless corpuscles and fibrin'. This was confirmed by Zahn (1875). The role of platelets was identified by Bizzozero (1886) and Welch (1899), who also found that platelets accumulated before leucocytes and preceded the formation of fibrin. Thus, the basic processes have been known for a hundred years or more.

Four stages may be distinguished, namely, platelet adherence, platelet aggregation, platelet degranulation, and platelet disruption or rhexis. The first and second are probably reversible, but the latter two are associated with the formation of fibrin and the transformation of the platelet plug to a mixed fibrin-red-cell-leucocyte mass and extension of the thrombus.

The fine structure can be related to biochemical processes set in motion by the clumping platelets. Electron microscopy (French, 1965; Poole, 1964) has shown that soon after injury platelets adhere to the sites of defective endothelium, at first loosely, but as they increase in number they swell and become closely packed into a mosaic and come to form obstructive masses. Parts may break off intermittently and become embolic. These are the 'white bodies' demonstrated by ciné microphotography in vessels around injured areas (Robb, 1963) and burned skin, and observed by Jones (1851) many years ago. In small veins, they probably contribute to the phenomenon of pulmonary microembolism (*vide infra*).

At this stage, the platelet membranes are intact. Interspaces about 200 Å wide separate adjoining cells, but they are occupied by an amorphous material with fine bridges between the platelet surfaces. This probably contains fibrinogen. Platelet granules and other organelles are first unaltered and fibrin is absent. This is probably a reversible stage, individual platelets having the possibility of returning to the blood stream. Then, platelet degranulation occurs, at first at the edges of the clump, and this probably sets in motion a local biochemical chain process which produces further platelet aggregation and degranulation, culminating in the formation of fibrin and the disruption of the platelets. In the degranulation process, platelet granules and mitochondria are lost, though the vesicles remain; the manner by which the granules discharge their contents is uncertain, though local fusion between the boundary membranes of platelets and granules has been found, which suggests a direct discharge to the exterior (Poole, 1964). Degranulation is believed to be the morphological expression of the platelet-release phenomenon originally described by Grette (1962), whereby adenosine diphosphate (ADP), serotonin, catecholamines, platelet factor 3 (PF3), platelet

factor 4 (PF4), and other substances are released. Adenosine diphosphate and adrenaline are now known to promote platelet aggregation, one enhancing the effect of the other. Platelet factors 3 and 4 are known to be capable of triggering the extrinsic and intrinsic coagulation mechanisms respectively, thereby releasing thrombin, and this can produce further clumping of platelets and their degranulation as well as the transformation of fibrinogen to fibrin. Notwithstanding recent studies, much of the intermediary processes is not fully understood.

After degranulation the platelets become virtually empty sacs within intact membranes, but they remain distinct for a time. Later they disintegrate. Fine fibrin strands appear, first at the edges of the platelet clump where degranulation began and where the platelets are in contact with the plasma, and then around and within the haemostatic or thrombotic plug. The plug forms within a few minutes of injury, and degranulation and fibrin formation are present by 30 minutes. However, accounts differ and some workers report a quicker sequence of events. Within a few hours, fibrin considerably increases and many red cells are now present (Weiner and Spiro, 1962). By 24 hours, most platelets have disintegrated and few are recognizable in the oldest part of the thrombus, though new clumps may have appeared in adjoining areas. This is probably the explanation of the appearance in Fig. 2, where many platelets and little fibrin is present; the burn was three days old. The plug is unstable before the appearance of fibrin but becomes converted into a relatively stable thrombus by its binding by fibrin.

The sequential changes in the original thrombus nidus and its transformation into a fibrin-red cell mass indicate a dynamic process in thrombogenesis. Its lesson goes beyond that of haemostasis and points to the need for serial studies in all other forms of thrombi to decide their origin and evolution. This has special relevance to deep vein thrombi, since the nature of their nidi is uncertain.

Pulmonary Embolism and Deep Vein Thrombosis

These are common complications in injured patients, but they are also well recognized in orthopaedic, gynaecological, general surgical, and obstetric patients and certain medical subjects such as those with congestive cardiac failure. Consequently, the thrombogenic factors are likely to be common ones and not restricted to specific general or local effects of trauma, such as the release of tissue thromboplastin. The thrombotic process is abacterial and non-inflammatory, and the distinction drawn between so-called thrombophlebitis and phlebothrombosis (deep vein thrombosis) is not justified. Inflam-

matory changes in the vein wall are secondary to the thrombosis. In only a minority of cases do the thrombi produce symptoms or signs referable to the limbs, such as pain or swelling. Most cases of thrombosis are silent and this explains the frequency of unheralded embolism, that is, embolism not preceded by limb signs. For a detailed account of the subject see Hume, Sevitt, and Thomas (1970).

PULMONARY EMBOLISM

Death from embolism in patients with fractured hips or other injuries is familiar to surgeons. However, the incidence of fatal embolism is greatly underestimated clinically; some say that only 10% of fatal cases are diagnosed during life.

Dissection of the pulmonary arteries revealed major emboli in 20% of 468 patients reaching necropsy after a wide variety of injuries (Sevitt and Gallagher, 1961). This corresponded to a frequency of about 1% fatal embolism among those admitted to hospital for longer than a day or two. Embolism was relatively common in those over 50 years old and was the most frequent cause of death in the elderly injured. This picture has been improved considerably by the institution of routine oral anticoagulant prophylaxis for many groups of injured patients (Sevitt and Gallagher, 1959; Sevitt, 1962; Sevitt, 1968). Before prophylaxis, embolism was particularly common (46-60%) in elderly subjects dying with a fractured femur or tibia, was frequent in those with a fractured pelvis (27%) or spine (14%), but less common in other subjects. Even young battle casualties have a not inconsiderable risk, as fatal embolism was found in 6.2% of over 1,000 such subjects, mostly in those with lower limb injuries (Hamilton and Angevine, 1946).

The importance of age, and also duration of bed rest, for embolism was demonstrated among 250 subjects who reached necropsy after road accidents (Sevitt, 1968b). Major emboli were found in 19 subjects, but 17 were among the 60 subjects over 45 years old who lived more than four days at bed rest, an incidence in this group of 28% major embolism. This is in accord with the frequency of deep vein thrombi and its relationship to age and duration of bed rest. The group of patients with fractured hips is growing in importance because the injury is common; the number of elderly persons at risk is increasing and they have a high rate of thrombosis and embolism. Their frequency of embolism is about 20 times the overall rate found in general hospitals. The differences in the frequency of embolism in those with different injuries is only indirectly related to the nature or the location of the injury: an increasing risk of deep vein thrombosis largely depends on increasing age and duration of bed rest, and then differing rates of thrombus detachment become significant. Major embolism is also not uncommon in medical, surgical, and

other non-traumatic cases (McLachlin and Paterson, 1951; Gibbs, 1957; Roberts, 1963). Special lung studies have revealed an incidence of over 60%, evidence of repeated embolism, since the figure includes cases with recent, organizing, or old organizing emboli, or a mixture of cases (Braconier, 1967; Freiman, Suyemoto, and Wessler, 1965).

Major embolism, that is, embolism judged to have caused or contributed to death, is largely determined by the extent of blockage of the pulmonary arterial tree. At necropsy it is conveniently divided into: (1) a large bifurcation embolus, or large separate emboli blocking both hilar arteries; (2) a large embolus in one main artery with or without emboli in lobar branches, or large emboli in lobar arteries of both lungs; and (3) multiple small emboli within central and peripheral arteries of both lungs. Estimation of the significance of the emboli found is often a matter of judgment and experience based on a proper dissection of the pulmonary arterial tree, but blockage of more than half the cross-sectional arterial bed is generally accepted as potentially lethal in man. Of course, the patient's age and health, and especially the strength of the heart,

are also important in determining life or death. These must be taken into account.

Minor emboli, those judged to be subclinical or certainly non-fatal, are either one or two pieces of thrombus in a lobar artery or sublobar branch or one or a few fine calibre thrombi lodged centrally or peripherally.

The source of major and minor macro-emboli is of course thrombi in deep veins of the lower limbs: detachment and embolism represent an 'accident' in their life history. Subsequent events include lysis or disintegration of the emboli, their mural contraction and reduction to fibrous or fibrofatty (atheromatous) plaques, and organic canalization of obstructive emboli with the formation of fibro-endothelial lined channels and also bronchopulmonary anastomoses.

DEEP VEIN THROMBOSIS

Venous dissection studies at necropsy revealed deep vein thrombi in the lower limbs in 65% of 125 injured patients, higher (80%) in certain groups such as the elderly, dying with limb fractures after bed rest (Sevitt and Gallagher, 1961). The high frequencies are not the result of processes in moribund subjects since they were confirmed *in vivo* by venographic studies (Borgström, Greitz, van der Linden, Molin, and Rudics, 1965; Freeark, Boswick, and Fardin, 1967). Studies of medical, surgical, and other necropsies (McLachlin and Paterson, 1951; Gibbs, 1957; Roberts, 1963) also revealed a high incidence of deep vein thrombi, ranging from 36 to 60%. The relationship to advancing age and duration of bed rest or other immobility supports the old contention that venous stasis of the lower limbs is of major pathogenetic importance.

Structure and growth of thrombus

The thrombi have a laminated structure both circumferentially and longitudinally (Fig. 3). This means that the layers formed successively and that the thrombus grew by an additive process. Numerous red cells trapped in a fibrin mesh may dominate the histological picture, but foci of closely packed platelets, each fringed by fibrin and surrounded by granular leucocytes, are present in most regions (Fig. 1). The red cell masses are laminated, with seams of fibrin between them or connecting them with leucocyte and platelet zones. The platelet masses vary in size and number; they often connect with each other in a coralline fashion, and are particularly prominent in actively propagating areas and especially at the thrombus head. The individual platelets, though closely packed, do not seem to be fused; at the histological level their outlines are preserved. Electron microscopy has not been reported but the unusual pulmonary embolus reported by Levene and Levene (1957) was formed of closely approximated spherical bodies resembling platelets, though they were not well

Fig. 3 The layered structure of a deep vein thrombus. Note the thin valve cusp in the middle and the thickened vein wall below. Multiple small platelet foci with fibrin rims are present in the thrombus to the right of the cusp. Picromallory $\times 24$.

preserved. The close fringing by fibrin, often condensed and well defined, is an important feature. Similar structures form a major part of arterial and cardiac thrombi; they are found in many experimental thrombi, especially those produced by direct trauma (*vide infra*); they are also formed when flowing blood is shunted extracorporeally through a tube (Mustard, Murphy, Rowsell, and Downie, 1962), and *in vitro* by rotating a column of blood in a closed ring of plastic tubing (Chandler, 1958; Poole, 1959).

As in haemostatic plugs, the intimacy between the aggregates and the bordering fibrin is the key to thrombus growth, whilst the lamination indicates the manner of growth. The structure points to the release of a fibrin-forming substance from the clumped platelets, and a platelet-clumping substance during fibrin formation. Thrombin release could account for both (*vide infra*).

Thrombus growth is illustrated in Figure 4. At first, growth is by propagation in the direction of the venous stream through the deposition of successive layers. By this additive process, the primary microscopic valve-cusp thrombus becomes visible (Fig. 5). The addition of further layers, both longitudinally and circumferentially, increases the length and diameter of the thrombus (Fig. 6). Contraction helps to prevent venous blockage; serum is squeezed out and a relatively dry, firm, and condensed tubular structure forms. Such recent, propagating thrombi lie in the centre of the venous stream, unattached to the wall of the vein except at its point (or points) of origin where

Fig. 5 Small primary thrombus in a valve pocket in the common femoral vein.

organization and fixation to the wall begin. This explains the danger of detachment and the frequency of embolism. With further propagation, venous obstruction may occur, and this often leads to retrograde thrombosis back to the next tributary (Fig. 4). This is probably due to the diffusion of activated coagulation factors from the thrombus. Even this retrograde extension occurs in a laminar fashion.

Thus, deep vein thrombi consist of a centrally directed propagating head, an elongating body, one or two points of original attachment, and sometimes a peripheral retrograde tail. The head is not a fixed part as asserted by some, but it grows and changes as new material is deposited on its surface from the flowing blood, whilst the body is made up of the successive deposits which once formed the head.

Propagation may cease at any time, especially when venous stasis abates, and a venous flow adequate to dilute and wash away recent products of thrombosis, is restored. Later, thrombosis may recommence and then fresh coagula are deposited on organizing or even organized material. This is a common event.

Primary sites of thrombosis

The anatomy of the lower venous tree and the dynamics of a slowed venous stream decide where thrombi begin to form, especially in the horizontal position of bed rest. Thrombi may begin in the leg or thigh or both.

Macroscopically, the early manifestation is one or more small thrombi in the pockets of valve cusps (Fig. 5) or in saccules, often at vein junctions. These may be found in deep veins of the pelvis, thigh, and leg. Six main primary sites of origin have been recognized (Sevitt, 1959; Sevitt and Gallagher, 1961). These are shown in Fig. 7: (1) the iliac vein, generally the external iliac vein; (2) the common femoral vein, including the mouths of the medial and lateral circumflex

Fig. 4 Diagram illustrating the propagation of deep vein thrombi from a nidus in a valve pocket (A) and the deposition of successive layers of fibrin, platelets, etc (B and C). Retrograde extension occurs when there is venous blockage from propagation (D).

tributaries and the termination of the superficial femoral vein; (3) the termination of the deep femoral vein, often at a valve cusp guarding its ostium; (4) the popliteal vein, distal to the adductor ring and at a relatively large valve; (5) the posterior tibial veins; and (6) the intramuscular veins of the calf, particularly the soleal veins. Thrombosis at one site is independent of thrombosis elsewhere and thrombi may arise in one, two, or more of them. Their extension in the leg or thigh or both produces a variety of thrombus patterns in the lower venous tree. Thrombosis is generally bilateral though the location and dis-

Fig. 6 Deep vein thrombus in the common femoral vein taking origin from valve pockets in the superficial and deep femoral veins, and propagating centrally beyond the inguinal ligament (above). Note also the smaller independent thrombus in the deep femoral vein (right).

tribution of thrombi in the two limbs may differ. Thrombi in calf veins are probably the most frequent and earliest manifestation, and there is evidence that independent thigh vein thrombi form somewhat later in many subjects (Gibbs, 1957; Sevitt and Gallagher, 1961).

The sites of election of thrombi in the face of a slowed venous stream seem to depend on a disturbance of normal laminar blood flow at angulations, bends, tributaries, and valves. Turbulence is produced, a phenomenon similar to the eddies at the edge of a river at a bend, and the direction of flow at the periphery may even be reversed from that in the centre. Flow studies in excised vein segments (Cotton and Clark, 1965) showed that when perfusion was from below the stream eddied at the free borders of valve cusps; when Indian ink was injected into the valve pockets, it lay in a stagnant pool with little movement or diffusion into the moving perfusate. Turbulent flow produces silting of formed elements, especially platelets, and their deposition on the wall at eddy zones, as demonstrated in extracorporeal shunts (Mustard *et al.* 1962). Likely favourite sites for eddies are valve pockets, especially large ones, the dilated sinuses of the soleal veins, the termination of the posterior tibial veins when compressed by the tendinous origin of the soleus muscle, the common femoral vein near the inguinal ligament because of the multiple streams of inflow, the external iliac veins

Fig. 7 Diagram of primary sites of deep vein thrombosis. The six main sites in the thigh and calf veins are independent of each other, although thrombosis is frequent at two or more of them.

because of the acute change in flow direction, and the left limb more than the right because of compression of the left common iliac vein by the right artery. Thus venous anatomy and disturbances of flow promoted by stasis decide the primary sites of deep vein thrombosis.

Time of onset of thrombosis

A connexion between confinement to bed and venous thrombosis has been known for a long time and has received support from necropsy dissections for deep vein thrombi (Gibbs, 1957; Seviit and Gallagher, 1961; Roberts, 1963). Fresh thrombi were not found within a day of bed rest, but thereafter the frequency rose and often reached high levels among those who succumbed after a week or more of bed rest. Thus, in injured and burned patients, deep vein thrombi were seen in 19% of those who died within three days of injury, in 47% who succumbed during the next four days, and in 75 to 90% of those dying later (Seviit and Gallagher, 1961).

The absence of thrombi on the first day, their relative infrequency during the first few days, and the subsequent rise in incidence indicate that the factors giving rise to thrombi are not present or are not sufficient in the early post-traumatic period, but develop or become sufficient later. To some extent, studies *in vivo* (Flanc, Kakkar, and Clarke, 1968) in surgical cases are in conflict with necropsy findings, since many of the cases of thrombosis were detected during or soon after operation. Thrombi were diagnosed and located by limb scanning after preoperative injection of ^{125}I -labelled fibrinogen, supplemented by venography in many cases. An increased radioactivity was found in one or both legs in more than 50% of the subjects and three time patterns were recognized, namely, an early transient rise, an early sustained rise, and a late rise in radioactivity. Venograms were normal in those with a transient increase after operation and this may have been due to blood pooling in soleal sinuses or minor thrombi lysing quickly. Leaving these aside, the incidence of thrombosis confirmed by venography was 35% and half of the cases were detected on return from the operating theatre. The apparent discrepancy between this study and venous dissection at necropsy requires investigation. Perhaps the radioactive method is insufficiently selective or venous dissection is insufficiently sensitive to detect recent and perhaps minor thrombi in calf veins.

Hypothesis of pathogenesis of deep vein thrombosis

The haematological factors responsible are not specially related to injury since deep vein thrombosis is not uncommon in medical and other patients. The absence of a recognizable lesion in the intima predisposing to venous thrombosis is in contrast with those necessary for the formation of a haemostatic plug or an arterial thrombus.

Consequently, an explanation is required for the initiation of a thrombus nidus on normal intima. The selective foci of origin, especially valve pockets, depend on the production of local eddy currents promoted by a slowed venous stream, with consequent local silting of formed elements, including platelets.

Subsequent events are likely to be complex, involving platelet clumping, the platelet-release phenomenon, the failure of dilution of locally released substances, and the formation of fibrin, but the key seems to be the local generation of thrombin with its dual ability to aggregate platelets and transform fibrinogen to fibrin. The thrombin must be formed locally but cannot be washed away because of the flow disturbance. Two methods of its formation are possible, namely, (1) through thrombogenic factors brought from a distance, and (2) by local formation of thrombogenic substances. Local formation seems more likely. It can be explained through the work of Wessler and his colleagues (*see* Wessler, 1962) on the production of venous thrombi under conditions of stasis following the injection of serum into the general circulation. The serum factors found responsible were those involved in the early stage of intrinsic coagulation, namely, activated factors XII-XI or XII-XI-IX. Consequently, the carriage of activated procoagulant factors from afar could initiate the coagulation mechanism in stagnant pools such as valve pockets. This hypothesis presupposes a continual or at least intermittent activation of these procoagulant factors in the vascular system and a normal mechanism for their removal. The latter has been demonstrated, the liver and reticulo-endothelial system being largely responsible, but the former is still theoretical. The possibility is worth considering that atheromatous lesions in the lower aorta and major arteries to the lower limbs contribute to the initiation process by activating procoagulant factors in the blood flowing over them. This would help to explain the susceptibility of middle-aged and elderly subjects to deep vein thrombi, but it is not the whole explanation, since young subjects without significant atheroma may also develop deep vein thrombi.

An alternative or supplementary mechanism is the local initiation of platelet aggregation through the local release of ADP from red cells or leucocytes silted by eddies into valve pockets. Thrombin generation might then follow through platelet degranulation and the release of thromboplastin PF3 with consequent activation of the extrinsic clotting mechanism. Against the involvement of this pathway are the reports of venous thromboembolism in patients with congenital deficiency of factor VII. Further, against this mechanism also are the experiments (Stuart and Thomas, 1967) which failed to produce venous thrombi under conditions of stasis after injecting large doses of ADP, and also the un-

certainly concerning the increased availability of platelet factor 3 induced by ADP action. On the other hand, release of PF4 may be involved, since *inter alia* it can precipitate fibrinogen and produce evidence of intravascular coagulation when given *in vivo*.

The final outcome is determined by the balance between thrombogenic and fibrinolytic mechanisms. Favouring thrombosis is the demonstration (Nilsson, 1968) that little fibrinolytic activity develops in the veins of the leg after the production of stasis, and that in injured subjects there is a relatively prolonged period of inhibited fibrinolysis following the early transient activation (Innes and Sevitt, 1964). In favourable circumstances, the thrombus nidus, once formed, is stabilized or strengthened by fibrin through further release of thrombin, and growth occurs through the deposition on the nidus of successive and alternative layers of aggregated platelets and fibrin (Fig. 4). Soon this becomes the propagating head. The original nidus is transformed into a structure containing much fibrin, many red cells, and few, if any, platelet clumps. This explains the mixed histological structure of many small valve-

pocket thrombi and the absence or infrequency of platelet collections near the valve-pocket apex (Fig. 8a) and in others the presence of platelet clumps in this zone (Fig. 8b). In this process and subsequent growth, thrombus contraction and local release of serum containing thrombin probably play an important role, although this is likely to be potentiated by the chain reaction involving the release of platelet-aggregating substances (ADP and adrenaline) and coagulation activators (PF3 and PF4) from clumped degranulating platelets. A fuller account of this postulated mechanism is given elsewhere (Hume *et al*, 1970).

Pulmonary Microembolism

Microscopic lung thrombi have been known for many years although, until recently, they have received less attention than large thromboemboli. Morphologically, two kinds can be broadly distinguished (Eeles and Sevitt, 1967), namely, (1) arterial microthrombi (micro-arterial) found in lung vessels about 0.25 to 1.00 mm in diameter

Fig. 8a Histology from a femoral valve pocket thrombus. A fibrin-red cell condensed structure, adherent to the intima at the apex of the pocket. Valve cusp on the left. No platelet clumps visible histologically. Picromallory $\times 40$.

Fig. 8b Apex of another femoral valve pocket thrombus. Valve cusp is above and to the left, and the vein wall is below. This shows several elongated oval pale foci of clumped platelets surrounded by narrow dark rims of fibrin, as well as many red cells. Picromallory $\times 120$.

(Fig. 9), and (2) capillary-arteriolar microthrombi (capillary microthrombi) mostly in vessels 20 to 100 μ in diameter (Figs. 10a and b). Repeated attacks of microembolism are now believed to be an important cause of pulmonary hypertension of insidious onset.

ARTERIAL MICROTHROMBI

Most arterial microthrombi are structurally like macroscopic emboli; they contain many red cells and a variable mixture of fibrin, platelets, and leucocytes (Fig. 9). Some are seen in the process of organization or already organized. They were found in the lungs of 12.4% of injured patients and 21.2% of burned subjects, usually one or two per section histologically (Eeles and Sevvit, 1967). Like macroscopic emboli, they occur in many subjects other than the injured. For example, Brenner (1935) found them in the lungs of 19 out of 100 unselected necropsies. Macroscopic thromboemboli are also present in some patients. In injured patients, the incidence is related to age and survival time: arterial microthrombi were uncommon in those with short survival, but their frequency rose as survival time increased (Fig. 11, bottom), and was highest (20 to 30%) in those over 40 years old who survived, mostly at bed rest, for longer than a week. Large emboli were also seen in some cases, and dissection of the

Fig. 9 Recent arterial microthrombus in a lung. H & E $\times$ 9.

Fig. 10a Capillary microthrombi in the lung. H & E. $\times$ 75.

Fig. 10b Lung capillary microthrombus showing a mixed fibrin-granular (platelet) structure. H & E $\times$ 400.

lower limb veins revealed deep vein thrombi as a potential source of lung thrombi in nearly every subject. Clearly, these arterial microthrombi are the microscopic counterpart of large thromboemboli: they originate as deep vein thrombi, become detached and carried to the lungs.

The condition is more complicated in many burned subjects. Many later-appearing thrombi can be explained by deep vein thrombosis, but the early appearance after burning of arterial microthrombi in many severely burned patients (and in some injured subjects) cannot be explained on this basis. The thrombi in them may represent the process of capillary microthrombosis (*vide infra*) occurring in larger vessels, or an additional embolic source of thrombi such as small thrombosed veins in burned skin or an injured area.

CAPILLARY MICROTHROMBI IN THE LUNGS
These generally have a different appearance from arterial microthrombi (Figs. 10a and b). They present with an eosinophilic condensed fibrillary or granular structure, some like aggregated platelets, others with a mixed fibrin-platelet structure, and some largely fibrinous in appearance. The majority are found in thin-walled

interstitial vessels, some clearly in muscular arteries and others in alveolar capillaries. Some are mural, but others are occlusive.

Microthrombi have been known for many years in burned subjects (Hayem, 1889; Pack, 1926; Sevitt, 1957), and are found in patients dying after severe injury (Eeles and Sevitt, 1967). They have also been described in the lungs of animals after experimental haemorrhage (Crowell and Read, 1955; Turpini and Stefanini, 1959; Robb, 1963; Hardaway, 1968), after various shock-like states in animals and man (Blaisdell, Lim, Amberg, Choy, Hall, and Thomas, 1966; Goodman, Lim, Blaisdell, Hall, and Thomas, 1968), and in rabbits after endotoxin shock (Thomas, 1964). Electron microscopy of the lungs of shocked dogs has confirmed that the microthrombi, in their early stage, consist mainly of platelet plugs (Goodman *et al*, 1968), and there is experimental evidence that they are formed outside the lung, that is, they are microemboli from the venous circulation.

Necropsy studies (Eeles and Sevitt, 1967) showed capillary microemboli in the lungs of 25.4% of injured patients. This was a minimal estimate since only unequivocal evidence of thrombosis before death was accepted. Thrombi were most frequent in those with severe injury or haemorrhage. Of course, transfused blood might have played a part either through platelet debris (Jenevein and Weiss, 1964) or by activation of procoagulant factors from storage in glass. However, microthrombi were also found in those without blood loss or transfusion, which indicates that tissue damage is also important. When related to survival period, thrombi were already quite common within three hours of injury, became more frequent and numerous during the next day or two, being found in 60% of subjects dying between 12 and 48 hours after injury, and thereafter declined (Fig. 11, top). This was in contrast to the later appearance of arterial microthrombi in the lungs of the same subjects (*vide supra*). The early flood of thrombi must be related to a phase of microthrombogenesis and the ebb to subsequent thrombolysis. Embolism from the venous circulation is the likely explanation, and the slower stream of the venous flow compared with the arterial is probably important in their formation.

Pathogenesis of capillary microemboli

The appearance after injury of capillary microthrombi in the lungs seems related to aggregation of platelets and activation of blood coagulation in the venous circulation. However, primary and secondary processes are somewhat blurred at present and a number of problems are not settled. Quickened blood clotting after severe haemorrhage was first recognized by William Hewson in 1772, though it was not invariable. Speeded clotting by haemorrhage and adrenaline was studied in a series of classical papers by Cannon

Fig. 11 Frequency related to survival time after injury of capillary-arteriolar (capillary) and arterial microthrombi in the lungs of a series of injured subjects. Note the early dominance of capillary microthrombi and the later appearance of arterial microthrombi.

and his colleagues (Cannon and Gray, 1914; Cannon and Mendenhall, 1914; Gray and Lunt, 1914). This phase of hypercoagulability is now known to be an important initial component of the complex coagulative and fibrinolytic responses to injury, haemorrhage, operation, and other noxious stimuli (Warren, Amdur, Belko, and Baker, 1950; Smith, Hartwick, and Regan, 1957; Turpini and Stefanini, 1959; Bergentz and Nilsson, 1961; Arturson and Wallenius, 1964; Innes and Sevvitt, 1964; Attar, Kirby, Masaitis, Mansberger, and Cowley, 1966; Rutherford, West, and Hardaway, 1966; Leandroer, 1968; Leandroer, Bergentz, and Nilsson, 1968). Early activation of the coagulation mechanism occurs, since severe haemorrhage shortened the prolonged clotting time induced by intravenous heparin, peptone, and protamine (Shafiroff, Doubilet, Siffert, and Co Tui, 1943), and accelerated intrinsic thromboplastin generation (Turpini and Stefanini, 1959). A thrombotic accelerator, possibly thrombin, appears transiently in the blood.

Serial studies on injured patients by Innes and Sevvitt (1964) demonstrated a phase of speeded clotting and activated fibrinolysis dominating the first few hours after severe trauma, soon followed by slower clotting and reduced fibrinolysis (Fig. 12). The main fibrinolytic changes have been confirmed (Borowiecki and Sharp, 1969), and the reduced fibrinolytic activity seems due both to depletion of plasminogen and the appearance of an inhibitor. These changes are associated with a reduction in various plasma clotting factors, including prothrombin, factors V and VII, and of platelets, which indicates their consumption during acute thrombogenesis. Experimentally, the changes can be prevented by prior treatment of the animals with heparin. This is important, because it indicates that their disappearance is through consumption and not to active fibrinolysis, though that is also present for a time. Of special interest is the fall in blood platelets beginning soon after trauma and continuing for one to three days, when the lowest counts are found; after this the platelet count rises steadily to levels of thrombocytosis during the next one to three weeks (Fig. 13). The falling platelet count may be accompanied by a moderate fall in plasma fibrinogen concentration. Low fibrinogen levels may occasionally occur, but they are unusual and transient.

The continued pulmonary microthrombosis during the first two days is in accord with the falling level of platelets which in turn, can be explained by *in-vivo* clumping, consumption, and disruption during microthrombogenesis. Thus, the major period of microthrombogenesis, when capillary microthrombi are most frequent, is manifest in the blood as a period of hypo-coagulability characterized by a fall in platelets, various plasma clotting factors, and often a prolonged coagulation time. A reduced pro-

thrombin consumption after clotting and the acquisition of antiheparin properties by the plasma are also present (Innes and Sevvitt, 1964), and the latter is consistent with the appearance of platelet factor 4 in the blood (*vide infra*). Later, the fibrinogen and factor VIII levels of the plasma rise, the former often reaching high levels two to four weeks after trauma.

The trigger mechanism responsible for setting off the coagulation and fibrinolytic sequences are probably neurohumoral or humoral in origin, involving sympathetic overactivity and adrenaline secretion. How these act is unknown, though venous endothelium is a known source of plasminogen activator.

Whatever the trigger mechanism, it is likely that the early activation of coagulation and platelet clumping set up a temporary chain reaction through the appearance of intermediary coagulation products and factors released from platelets, a process with similarities to that postulated in the origin of deep vein thrombi. The findings of Brinkhous and Penick (1955) indicate that the intrinsic system of coagulation is activated, and that its activation is necessary for the development

Fig. 12 Serial platelet counts, prothrombin time, clotting time and diluted-blood fibrinolysis time in a patient during the first 24 hours after severe injury. The horizontal lines represent limits of normality. Note the early transient phase of speeded clotting and fibrinolysis, the early fall in the platelet count, and the slightly prolonged prothrombin time.

Fig. 13 Serial platelet counts in a series of injured subjects. The count falls on the day of injury and continues to fall for one to three days occasionally almost reaching thrombocytopenic levels. Then the count rises, often reaching levels of thrombocytosis during the next week or two.

ment of thrombocytopenia. After severe freezing of the skin in dogs, the factor VIII level and platelet count fell, but the platelet count remained normal in haemophilic dogs similarly treated. Platelet factor 4 may be an important intermediary in the chain reaction: it is rapidly released during platelet aggregation *in vivo* (Niewiarowski, Lipiński, Farbiszewski, and Poplawski, 1968; Niewiarowski, Poplawski, Lipiński, and Farbiszewski, 1968); when infused into rabbits, clotting time rapidly shortens, the blood platelet count falls and other effects suggestive of clotting activation and intravascular platelet aggregation are found (Farbiszewski, Lipiński, Niewiarowski, and Poplawski, 1968). Certainly, release of PF4 explains the appearance of anti-heparin activity in plasma found during the first hours after injury (Innes and Sevitt, 1964), and probably also the heparin resistance of plasma postoperatively and in subjects with thrombosis or embolism.

The explosive chain reaction is brought to an

end presumably by protective and inhibitory mechanisms. These include the removal of activated clotting factors by the liver and reticulo-endothelial system, the action of antithrombin and other inhibitors.

Significance and importance of capillary micro-emboli

Some workers (Pack, 1926; Wartman, 1962) have postulated that these are of obstructive importance in burns, and it has also been suggested that they are responsible for the rise in pulmonary artery pressure in some injured subjects (Hardaway, 1968). Blaisdell *et al* (1966) claimed they were responsible for acute cardio-respiratory disturbance and early death in some subjects after emergency operations on the aorta. Humoral-mediated effects are possible. Thomas, Stein, and their coworkers (Thomas, 1964; Stein, Tanabe, Khan, and Thomas, 1965; Thomas, Tanabe, Khan, and Stein, 1965) found bronchoconstriction after experimental lung embolism and related this to the release of serotonin from platelets; lung vasoconstriction was also possible. Consequently, embolization of microthrombi to the lungs after injury and burns might account for certain early respiratory effects, such as polypnoea after extensive burning (Sevitt, 1957), and contribute to certain ventilation-perfusion anomalies in injured subjects.

A breakdown in the homeostatic balance between hypercoagulability and microthrombosis on the one hand and thrombolysis on the other, has been postulated to explain 'irreversible shock' in dogs bled to severe hypotension and then unable to respond beneficially to subsequent re-infusion of blood. Thrombi in various organs including the lungs were said to be responsible (Crowell and Read, 1955; Turpini and Stefanini, 1959; Hardaway, 1962) and heparin and 'fibrinolysin' were said to be beneficial. Heparin therapy prevented the appearance of microthrombi after experimental shock (Robb, 1963; Goodman *et al*, 1968), prolonged the survival time of lethally burned dogs (Elrod, McCleery, and Ball, 1951; Johansson, 1961), and increased the survival rate in severely bled animals after return of the blood (Crowell and Read, 1955; Hardaway, 1962). However, others found that there was little protection offered by heparin in haemorrhagic shock or that it even increased the mortality (Smith, Grace, and Hussey, 1958; Schumer and Lee, 1964).

Glomerular Microthrombosis

Necropsy studies (Sevitt, 1956; Innes and Sevitt, 1964) have shown that glomerular microthrombi develop in some burned and injured patients. In burned subjects, the condition was known to Wertheim in 1867, but had been largely neglected,

They were seen (Sevitt, 1956) in 9.3% of 86 burned patients studied for renal failure and tubular necrosis; and in another study (Innes and Sevitt, 1964), in 5.3% of those with burns and in 3.8% of injured cases. They present as eosinophilic, oval or elongated condensed masses often taking the shape of or distending glomerular capillaries (Fig. 14). They stain prominently for fibrin in Mallory and PTAH preparations and are PAS-positive. Platelets are difficult to distinguish by light microscopy, though their presence may be transitory, preceding fibrin deposition, as has been claimed for glomerular thrombi in the Schwartzman reaction. The condition is minor in the majority of injured subjects affected, when less than 2% of glomeruli are involved, but it tends to be more extensive in most burned subjects when 10 to 20% of glomeruli or more contain thrombi. Even in such cases, few capillaries per glomerulus are affected but an occasional glomerulus is packed with thrombi. Presumably most of these cases are subclinical. In burned subjects, the frequency seems to be associated with short survival and the development of tubular necrosis and was particularly frequent among the elderly who died with tubular necrosis during the second day after burning (Sevitt, 1956). The thrombi are probably temporary since they are uncommon in patients surviving longer.

Occasionally, an injured or burned patient is found with many thrombi affecting the great majority of glomeruli: then tubular necrosis and renal haemorrhages may be present. Figure 15 shows the 'flea-bitten' haemorrhagic appearance

of the kidneys in such a case, a rare phenomenon. Such cases could be responsible for an unusual form of acute posttraumatic uraemia. Of course, glomerular microthrombosis is absent in most of those dying with renal failure.

Glomerular microthrombi may occur in subjects with or without lung microthrombi, and the condition is certainly much less frequent than pulmonary microthrombosis. Small thrombi are absent or scarce in other organs: this does not support an embolic origin so that the glomerular thrombi are probably formed locally within the kidney. Though an association with glomerular fat embolism has been suggested, the conditions are only occasionally related; when they are associated, fat emboli are numerous but microthrombi are few.

PATHOGENESIS

The origin and mechanism of glomerular microthrombosis is obscure. Acute coagulative changes may be involved and the possibility that the thrombi are preceded by platelets must be taken into account. Also worthy of consideration is the possibility that the substance reacting for fibrin in the glomerular capillaries is the result of para-coagulation of fibrinogen rather than true clotting. This non-enzymatic process is a property of platelet factor 4 which might be involved. The independence of glomerular microthrombosis from that in the lungs or other organs points to coagulative or other changes localized to the renal blood flow.

Glomerular microthrombosis is a central feature

Fig. 14 Glomerular microthrombosis in an injured patient. PTAH $\times 75$.

Fig. 15 'Flea-bitten' haemorrhagic kidneys from a young man who died a day after a severe head injury. (Many microthrombi were present in most glomeruli, and also extensive tubular necrosis and haemorrhagic tubular areas.)

of the generalized Shwartzman reaction precipitated by two properly spaced injections of bacterial endotoxin or other procedure, and its appearance after injury or burning might represent this mysterious state in man. Glomerular thrombosis in burned patients who died from septicaemia due to *Serratia marcescens* (Graber, Tumbusch, Rudnicki, and Vogel, 1960), or other bacteria including *Ps. pyocyanea* (Innes and Sevit, 1964), could be accounted for by precipitation of the Shwartzman phenomenon by bacterial endotoxin. However, neither bacteria nor their toxins are essential for this reaction, which can be provoked in pregnant animals by a special diet. Consequently, the possibility arises that injury itself might trigger off the phenomenon in particular subjects. This would explain its appearance within a day of trauma in occasional subjects, though it would not explain why they and others, are susceptible. Perhaps, some people are already sensitized by previous infection or otherwise 'prepared' in some way, and trauma sets in motion endocrine, coagulative, or other changes which precipitate the reaction.

Arterial Thrombosis

Fortunately this is an unusual phenomenon in the absence of direct trauma. Nevertheless, a number of unequivocal cases involving large or important vessels have been reported (Sevitt, 1966). These include acute cases of extensive recent coronary artery thrombosis with recent myocardial infarction in a young woman with large burns (Cole, 1963) and of fresh coronary artery thrombi in an extensively burned young soldier (Stevens, 1965). In these patients atheroma was minimal. Other cases in the literature are referred to by Cole (1963). Coronary artery thrombosis has also been found at necropsy in occasional burned or injured patients (Sevitt, 1966). Most of them were middle-aged or elderly and had atheromatous disease of the affected vessel and elsewhere. Consequently, other explanations, that the thrombosis was coincidental or preceded the injury, and perhaps even caused the accident, was plausible. This is much less likely in the young people, and since they indicate that the phenomenon was precipitated by burning or other trauma, the possibility or even probability, cannot be excluded in those with coronary atheroma. A unique case of intravascular clotting in a previously healthy child with a small burn was referred to by Wilson, Macgregor, and Stewart (1938): thrombosis was found in the intracranial venous sinuses and Rolandic veins, and also in the arteries of the lower limbs from the lower abdominal aorta downwards. Other burned subjects, developing thrombosis of cerebral veins and venous sinuses, have been reported (Sevitt, 1957), and lateral sinus thrombosis is occasionally found in injured subjects

without head trauma. Furthermore, infarction of the kidney related to thrombosis of a renal artery branch is seen occasionally in patients without direct trauma to the organ (Fig. 16). These findings are unusual and their explanation is difficult. In those developing arterial thrombi, the post-traumatic hypercoagulable phase may have involved the arterial circulation, which ordinarily seems to escape from microthrombogenesis. In such cases, the arterial thrombosis might be considered as one kind of breakdown in the homeostatic balance between posttraumatic hypercoagulability, thrombosis, and fibrinolysis.

Abacterial Vegetative Endocarditis

This is the most uncommon form of posttraumatic thrombosis but it is found in occasional cases.

CASE

A 23-year-old male was admitted with a fractured pelvis and a minor cerebral contusion. Two days later, he became pyrexial with laboured, rapid breathing and chest pain. Fat embolism was suspected but was not confirmed at necropsy.

Fig. 16 Recent white infarct at upper pole of kidney related to thrombosis of a renal artery branch. Injured patient, but no trauma to the infarcted kidney.

Tracheostomy and artificial ventilation with oxygen were carried out because of a low arterial pO_2 . He remained cyanosed; pO_2 remained low. Radiological lung opacities developed. Cardiac arrest occurred twice and he died seven days after injury.

Necropsy confirmed the fractured pelvis and cerebral contusion. Also present were a severe interstitial pneumonitis with hyaline membrane formation, probably related to the oxygen therapy; thrombosis in a lateral sinus, in femoral and iliac veins, and multiple small pulmonary emboli; acute gastric and duodenal ulcers; and a central area of necrosis in the anterior pituitary gland, probably related to cerebral contusion. The heart weighed 312 g; a few epicardial petechiae and streaks of subendocardial haemorrhage over the anterior papillary muscle were present. Both the mitral and tricuspid valves showed recent vegetative endocarditis with numbers of pale, firm irregular crumbling vegetations lightly attached to the contact points of the cusps (Fig. 17). They were more numerous and larger in the mitral valve, measuring up to 1 cm long. Culture grew a few atypical *Bact. coli*, regarded as a contaminant. Myocardium and coronary vessels were natural. Histology of the vegetations showed that they were formed of fused platelet eosinophilic masses embedded in a fibrin network; no organisms were seen.

The pathogenesis of this lesion is unknown. It is well recognized in uninjured patients under several names, including non-bacterial thrombotic endocarditis, cachetic endocarditis, endocarditis simplex, and degenerative verrucal endocardiosis. It is distinct from the atypical verrucous endocarditis (Libman-Sacks) which is associated with acute disseminated lupus erythematosus. Factors considered to play a role are allergy, vitamin C

deficiency, haemodynamic trauma to valves, and preexisting valvular deformity. None of these seem to have been involved in the present case.

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Fig. 17 Vegetative endocarditis involving the mitral cusps (see text).

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