

Before Editing

Chapter 6 Hemostasis and Thrombosis

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Learning Objectives

- By the end of this chapter, the student should be able to:
- Define hemostasis and describe its physiological significance.
 - Identify the sequential phases of the hemostatic response.
 - Explain the roles of vascular endothelium, platelets, and coagulation factors in achieving hemostasis.
 - Distinguish between primary and secondary hemostasis.
 - Describe the coagulation cascade, including the intrinsic, extrinsic, and common pathways.
 - Interpret laboratory tests used to assess hemostatic function.
 - Outline the mechanisms underlying Pathological Thrombosis.
 - Correlate hemostatic defects with Clinically relevant bleeding and thromboembolic disorders.

1 Introduction

Hemostasis is the physiological process by which bleeding is arrested following injury to a blood vessel. The term derives from the Greek words haima (blood) and stasis (stopping), and it encompasses a highly coordinated series of cellular and molecular events designed to maintain vascular integrity while simultaneously preserving blood fluidity within intact vessels. In the healthy individual, this balance is maintained with remarkable precision; disruption in either direction – toward excessive bleeding or pathological clot formation – can carry profound clinical consequences.

The hemostatic response involves 3 overlapping phases: vascular spasm, platelet plug formation, and blood coagulation.

These phases do not operate independently; rather, they are tightly integrated through a network of biochemical signals, feedback loops, and inhibitory mechanisms. A fourth process, fibrinolysis, subsequently dissolves the clot once tissue repair is underway, restoring normal blood flow. Together, these four processes constitute what is often referred to as the hemostatic system – a dynamic equilibrium rather than a static endpoint.

Understanding hemostasis is fundamental to the study of pathology, internal medicine, surgery, and clinical pharmacology. Disorders of hemostasis, whether inherited or acquired, are among the most commonly encountered conditions in clinical practice. These range from relatively mild conditions such as Von Willebrand disease to life-threatening emergencies including disseminated intravascular coagulation (DIC) and massive pulmonary embolism. For first-year MBBS students, a firm grasp of normal hemostatic physiology forms the essential foundation upon which the pathology of bleeding and clotting disorders will subsequently be built.

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1- Introduction

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2 Vascular Response to injury

2.1 The Role of the Endothelium

The endothelium – the single-cell-thick inner lining of all blood vessels – occupies a central position in hemostatic regulation. Under normal, undisturbed conditions, the endothelium maintains an actively antithrombotic environment. It achieves this through several mechanisms: secretion of prostacyclin (PGI₂) and nitric oxide (NO), both of which inhibit platelet activation and promote vasodilation; expression of thrombomodulin on its surface, which converts thrombin from a procoagulant to an anticoagulant molecule; and production of tissue plasminogen activator (tPA), which initiates fibrinolytic activity.

When endothelial continuity is disrupted by physical trauma, inflammation, or ischemia, these protective mechanisms are suspended and a rapid prothrombotic shift occurs. Subendothelial collagen, von Willebrand factor (vWF), and tissue factor (TF) are exposed to the circulating blood, initiating platelet adhesion and activating the coagulation cascade. This transition from antithrombotic to prothrombotic endothelial behavior is rapid, often occurring within seconds of vessel wall injury.

2.2 Vascular Spasm

The earliest and most immediate hemostatic response to vessel injury is vasospasm – a reflex constriction of the injured vessel mediated by local myogenic reflexes, autonomic nervous system activation, and the release of vasoactive substances from platelets and endothelial cells. Vasospasm serves to reduce blood flow through the damaged segment, minimizing blood loss while downstream hemostatic processes are initiated. The degree of vasospasm is proportional to the severity of the vascular injury; a completely severed vessel may remain constricted for 20–30 minutes, providing a critical window for clot formation.

In small arterioles, vasospasm alone may be sufficient to arrest bleeding permanently. In larger vessels, however, vasospasm is a temporising measure and must be followed promptly by effective platelet plug formation and coagulation.

3 Primary Hemostasis: Platelet Plug Formation

Primary hemostasis refers specifically to the formation of the platelet plug, a loose but rapidly formed barrier that temporarily seals a breach in the vascular wall. This process unfolds through three sequential steps: platelet adhesion, platelet activation, and platelet aggregation.

3.1 Platelet Adhesion

Circulating platelets do not ordinarily adhere to an intact endothelial surface. Following vascular injury, however, exposed subendothelial collagen binds to glycoprotein VI (GPVI) and glycoprotein Ia/IIa (GPIa/IIa) receptors on the platelet surface, initiating direct adhesion. In vessels experiencing high shear stress – such as arterioles and small arteries – this initial binding is insufficient on its own. Under such conditions, vWF, which is released from Weibel–Palade bodies within endothelial cells and from platelet alpha-granules, acts as a molecular bridge between subendothelial collagen and the platelet surface glycoprotein Ib–IX–V (GPIb–IX–V) complex, enabling stable adhesion despite high flow rates.

3.2 Platelet Activation

Adhesion triggers a rapid and dramatic change in platelet morphology and biochemistry. Resting platelets are small, disc-shaped, and metabolically quiescent. Upon activation, they undergo a shape change from smooth discs to spiny spheres, dramatically increasing their surface area and enabling contact with adjacent platelets and coagulation proteins. This shape change is mediated by reorganization of the actin–myosin cytoskeleton.

Activated platelets simultaneously release the contents of their intracellular granules. Alpha-granules discharge fibrinogen, vWF, factor V, P-selectin, and platelet factor 4 (PF4). Dense granules release adenosine diphosphate (ADP) and serotonin (5-HT), both of which serve as potent amplifiers of platelet

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activation, recruiting additional platelets to the site of injury. Simultaneously, activated platelets synthesize thromboxane A₂ (TXA₂) via the arachidonic acid–cyclooxygenase pathway; TXA₂ further potentiates both platelet activation and vasoconstriction.

3.3 Platelet Aggregation

The final step in platelet plug formation is aggregation – the crosslinking of adjacent activated platelets into a cohesive mass. This process is mediated primarily through the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor, which undergoes a conformational change upon platelet activation that enables it to bind fibrinogen. Fibrinogen, a bivalent molecule, simultaneously engages GPIIb/IIIa receptors on neighboring platelets, forming molecular bridges that draw platelets together.

The resulting platelet plug is effective but mechanically fragile. It is sufficient to temporarily arrest bleeding from small vessels but cannot withstand the shear forces present in medium to large arteries without reinforcement from the fibrin mesh generated by the coagulation cascade. This requirement for reinforcement underscores the importance of secondary hemostasis, which proceeds concurrently and in intimate association with platelet plug formation.

4 Secondary Hemostasis: The Coagulation Cascade

Secondary hemostasis refers to the coagulation cascade – a sequential series of enzymatic reactions in which clotting factors, most of which are serine proteases circulating in inactive (zymogen) form, are successively activated to ultimately generate thrombin and a stable fibrin clot. The cascade is traditionally divided into the extrinsic pathway, the intrinsic pathway, and the common pathway, though it is now recognized that these divisions are somewhat artificial and that extensive cross-talk exists between them in vivo.

4.1 The Extrinsic Pathway

The extrinsic pathway – also referred to as the tissue factor (TF) pathway – is the primary initiator of coagulation in vivo. It is triggered when TF, a transmembrane glycoprotein expressed constitutively by subendothelial cells including smooth muscle cells and fibroblasts, is exposed to circulating blood following vascular injury. TF forms a high-affinity complex with activated factor VII (FVIIa), a small amount of which circulates constitutively in the plasma. The TF–FVIIa complex then activates factors IX and X directly.

The extrinsic pathway is extraordinarily rapid; measurable factor Xa activity can be detected within seconds of TF exposure. However, this pathway is subject to early inhibition by tissue factor pathway inhibitor (TFPI), which forms a quaternary complex with TF, FVIIa, and FXa, effectively shutting down this initial burst of activation. Continued coagulation therefore depends on amplification through the intrinsic pathway.

4.2 The Intrinsic Pathway

The intrinsic pathway – or contact activation pathway – is initiated when factor XII (Hageman factor) comes into contact with negatively charged surfaces, such as subendothelial collagen or kaolin in laboratory conditions. This surface contact activates factor XII to FXIIa, which sequentially activates factor XI to FXIa. FXIa then activates factor IX to FIXa. While factor XII deficiency does not cause clinical bleeding (illustrating that this pathway has limited in vivo significance for hemostasis), deficiencies of factors XI, IX, and VIII are associated with Clinically significant bleeding disorders – hemophilia C, hemophilia B, and Hemophilia A, respectively.

Factor IXa, in combination with its cofactor factor VIII (activated by thrombin to FVIIIa), calcium ions (Ca²⁺), and phospholipid surfaces provided by activated platelets, forms the intrinsic tenase complex. This complex is the primary amplifier of coagulation, generating factor Xa in quantities far exceeding those produced by the initial extrinsic pathway activation.

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Factors Xa from both pathways converge on the common pathway. Factor Xa, together with its cofactor factor Va, Ca²⁺, and platelet phospholipids, assembles the prothrombinase complex on the platelet surface. This complex converts prothrombin (factor II) to thrombin (factor IIa) with remarkable efficiency.

Thrombin is the central effector molecule of the entire coagulation system and exerts its effects through multiple mechanisms: it converts soluble fibrinogen to insoluble fibrin monomers; activates factor XIII (to FXIIIa), which crosslinks and stabilizes the fibrin clot; activates factors V, VIII, and XI in powerful positive feedback loops; and activates platelets by cleaving protease-activated receptors (PARs) on their surface. The fibrin strands generated by thrombin polymerise spontaneously and are subsequently covalently crosslinked by FXIIIa, forming a dense, mechanically stable meshwork that reinforces the platelet plug and creates the definitive hemostatic clot.

5 Natural Anticoagulant Mechanisms

The coagulation cascade, if left unopposed, would rapidly progress to total intravascular thrombosis. The body therefore maintains several potent anticoagulant systems that confine clot formation to the site of injury and prevent its uncontrolled extension.

Box 6.1 Major Natural Anticoagulant Systems

- Antithrombin (AT): a serine protease inhibitor that neutralizes thrombin, FXa, FIXa, and other activated clotting factors; its activity is potentiated 1000-fold by heparin.
- Protein C and Protein S: thrombomodulin on the endothelial surface binds thrombin, altering its specificity; the thrombin–thrombomodulin complex then activates Protein C, which, together with its cofactor Protein S, inactivates FVa and FVIIIa.
- Tissue Factor Pathway Inhibitor (TFPI): as described above, limits the duration of extrinsic pathway activity.
- Prostacyclin (PGI₂) and Nitric Oxide: produced by endothelial cells; inhibit platelet activation and promote vasodilation.

Inherited or acquired deficiencies of these anticoagulant proteins – particularly antithrombin, Protein C, and Protein S – are recognised causes of familial thrombophilia, a condition characterised by a markedly elevated lifetime risk of venous thromboembolism. Understanding these mechanisms is therefore essential not only for comprehending normal physiology but also for the rational interpretation of thrombotic disorders encountered in clinical practice.

6 fibrinolysis

Once the hemostatic clot has fulfilled its function and tissue repair is underway, controlled dissolution of the fibrin network is necessary to restore normal vascular patency. This process, fibrinolysis, is mediated primarily by plasmin – a broad-spectrum serine protease derived from the inactive precursor plasminogen.

Plasminogen is incorporated into the fibrin clot during its formation and is subsequently activated by tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). tPA is released from endothelial cells in response to fibrin formation and has a dramatically increased catalytic efficiency when bound to fibrin, ensuring that plasmin generation is largely localised to the clot surface rather than occurring systemically. Plasmin cleaves fibrin at multiple sites, generating fibrin degradation products (FDPs), including the Clinically useful D-dimer fragment.

The fibrinolytic system is, in turn, regulated by inhibitors including plasminogen activator inhibitor-1 (PAI-1) and alpha₂-antiplasmin, which prevent premature or excessive fibrinolysis. Elevated PAI-1 levels – observed in obesity, metabolic syndrome, and type 2 diabetes mellitus – are associated with impaired fibrinolysis and a predisposition to thrombosis.

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7 Laboratory Assessment of Hemostasis

Clinical evaluation of the hemostatic system relies on a panel of standardized laboratory investigations. An understanding of the principles and interpretive limitations of these tests is fundamental to clinical medicine.

7.1 Bleeding Time

The bleeding time (BT), traditionally measured using the Ivy or Duke methods, assesses primary hemostasis – specifically platelet function and vascular integrity. A standardized skin incision is made and the time to cessation of bleeding is recorded. Normal values for the Ivy method are typically 2–9 minutes. The BT is prolonged in thrombocytopenia, platelet function disorders (e.g., Glanzmann thrombasthenia, Bernard–Soulier syndrome), and von Willebrand disease. However, due to its poor reproducibility and limited sensitivity, the BT has been largely supplanted by newer platelet function analyzers in many centers.

7.2 Prothrombin Time and International Normalized Ratio

The Prothrombin Time (PT) measures the integrity of the extrinsic and common pathways (factors VII, X, V, II, and fibrinogen). It is performed by adding thromboplastin (a TF–phospholipid mixture) and calcium to citrated plasma and recording the time to clot formation. The normal PT is approximately 11–13 seconds.

Because thromboplastin reagents vary between laboratories, the PT is standardised to an International Normalized Ratio (INR) for clinical use, particularly for monitoring warfarin anticoagulation therapy. A therapeutic INR range for most indications is 2.0–3.0. The PT/INR is the first-line test for evaluating extrinsic pathway function and is markedly elevated in liver disease, vitamin K deficiency, and warfarin overdose.

7.3 Activated Partial Thromboplastin Time

The activated partial thromboplastin time (aPTT) assesses the intrinsic and common pathways (factors XII, XI, IX, VIII, X, V, II, and fibrinogen). It is performed by activating citrated plasma with a contact activator (e.g., kaolin or ellagic acid) in the presence of phospholipid and calcium. The normal aPTT is approximately 25–35 seconds.

The aPTT is prolonged in hemophilia A and B, heparin therapy, lupus anticoagulant, and deficiencies of factors XI and XII. Notably, factor XII deficiency prolongs the aPTT significantly but is not associated with clinical bleeding, reflecting the limited in vivo role of the contact activation pathway in hemostasis.

7.4 Platelet Count and Other Tests

A full blood count (FBC) provides the platelet count, the normal range of which is 150,000–400,000 per μL ($150\text{--}400 \times 10^9/\text{L}$). Thrombocytopenia is defined as a platelet count of less than $150 \times 10^9/\text{L}$ and is classified as mild ($100\text{--}150 \times 10^9/\text{L}$), moderate ($50\text{--}100 \times 10^9/\text{L}$), or severe (less than $50 \times 10^9/\text{L}$). Spontaneous bleeding typically does not occur until the count falls below approximately $20 \times 10^9/\text{L}$.

Additional specialized tests include thrombin time (TT), fibrinogen assay (Clauss method), D-dimer assay, mixing studies (to distinguish factor deficiency from inhibitor), and platelet aggregation studies using various agonists.

8 Pathological Thrombosis

Whereas physiological hemostasis is a protective response to vascular injury, pathological thrombosis represents the inappropriate formation of a thrombus within an uninjured or minimally injured vessel. The conceptual framework for understanding thrombosis was established in the 19th century by the German

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pathologist Rudolf Virchow, who proposed that three factors predispose to intravascular clot formation – a triad that continues to bear his name.

Box 6.2 Virchow's Triad

- Endothelial injury or dysfunction: damage to or activation of the endothelium exposes subendothelial matrix components and promotes a prothrombotic surface; encountered in atherosclerosis, hypertension, inflammation, and trauma.
- Abnormal blood flow (stasis or turbulence): stasis, as occurs in venous insufficiency, prolonged immobility, or atrial fibrillation, disrupts the laminar flow pattern that normally keeps platelets away from the endothelium and allows coagulation factors to accumulate; turbulence, as seen downstream of atherosclerotic plaques, causes endothelial injury.
- Hypercoagulability (thrombophilia): an imbalance of the hemostatic system favouring coagulation, whether due to inherited defects (e.g. Factor V Leiden mutation, prothrombin G20210A mutation, antithrombin deficiency) or acquired states (e.g., malignancy, pregnancy, oral contraceptive use, antiphospholipid syndrome).

8.1 Arterial Versus Venous Thrombosis

The pathophysiology and composition of thrombi differ depending on whether they form in the arterial or venous circulation. Arterial thrombi form predominantly under conditions of high shear stress and are typically initiated by rupture or erosion of an atherosclerotic plaque, which exposes TF and subendothelial collagen to blood. Arterial thrombi are therefore rich in platelets – often described as “white thrombi” – and their formation is relatively independent of the coagulation cascade (which is why antiplatelet agents such as aspirin and clopidogrel are the mainstay of arterial thromboprophylaxis).

Venous thrombi, by contrast, form primarily under conditions of stasis and are driven largely by the coagulation cascade rather than platelet activation. They are characterised by a fibrin-rich structure interspersed with erythrocytes, giving them a deep-red appearance – hence “red thrombi.” Their formation is relatively platelet-independent, which explains why anticoagulants (heparin, low-molecular-weight heparin, and direct oral anticoagulants) rather than antiplatelet agents are used for venous thromboembolism prevention and treatment.

8.2 Consequences of Thrombosis

Depending on their location and size, thrombi may cause: (1) local vascular occlusion, resulting in ischemia and infarction of the supplied tissue; (2) embolization, in which a fragment of the thrombus detaches and travels distally to occlude a remote vessel; (3) organization and recanalization, in which the thrombus is gradually replaced by fibrous tissue and small new channels form through it; or (4) lysis, in which the thrombus is dissolved by endogenous or exogenous fibrinolytic activity.

Pulmonary embolism (PE), arising from deep vein thrombosis (DVT) in the lower limbs or pelvis, represents the most Clinically urgent manifestation of venous thromboembolism and is a leading cause of preventable in-hospital mortality. Arterial thrombosis underlies the pathogenesis of myocardial infarction, ischemic stroke, and peripheral arterial occlusive disease.

9 Clinical Correlation

9.1 Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a complex, acquired syndrome in which systemic activation of coagulation leads to the generation of intravascular fibrin, microvascular thrombosis, organ ischemia, and simultaneous consumption of clotting factors and platelets – culminating paradoxically in a severe bleeding tendency. DIC is not a primary disease but always occurs secondary to an underlying condition, most commonly sepsis (particularly gram-negative bacteraemia), obstetric complications (e.g., abruptio placentae, amniotic fluid embolism), malignancy, trauma, and incompatible blood transfusion.

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pathologist Rudolf Virchow, who proposed that three factors predispose to intravascular clot formation – a triad that continues to bear his name.

Box 6.2 Virchow's Triad

- Endothelial injury or dysfunction: ~~damage~~ damage to or activation of the endothelium exposes subendothelial matrix components and promotes a prothrombotic surface; encountered in atherosclerosis, hypertension, inflammation, and trauma.
- Abnormal blood flow (stasis or turbulence): ~~stasis~~stasis, as occurs in venous insufficiency, prolonged immobility, or atrial fibrillation, disrupts the laminar flow pattern that normally keeps platelets away from the endothelium and allows coagulation factors to accumulate; turbulence, as seen downstream of atherosclerotic plaques, causes endothelial injury.
- Hypercoagulability (thrombophilia): ~~an~~an imbalance of the hemostatic system favouring coagulation, whether due to inherited defects (e.g., Factor V Leiden mutation, prothrombin G20210A mutation, ~~antithrombin~~AT deficiency) or acquired states (e.g., malignancy, pregnancy, oral contraceptive use, antiphospholipid syndrome).

8.1 Arterial Versus Venous Thrombosis

The pathophysiology and composition of thrombi differ depending on whether they form in the arterial or venous circulation. Arterial thrombi form predominantly under conditions of high shear stress and are typically initiated by rupture or erosion of an atherosclerotic plaque, which exposes TF and subendothelial collagen to blood. Arterial thrombi are therefore rich in platelets – often described as “white thrombi” – and their formation is relatively independent of the coagulation cascade (which is why antiplatelet agents such as aspirin and clopidogrel are the mainstay of arterial thromboprophylaxis).

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Laboratory features of DIC include a prolonged PT and aPTT, thrombocytopenia, hypofibrinogenaemia, and elevated D-dimer and fibrin degradation products. Management is directed at treating the underlying cause, supportive therapy with fresh frozen plasma (FFP), cryoprecipitate, and platelet transfusions may be required in actively bleeding patients.

9.2 Hemophilia A

Hemophilia A is an X-linked recessive disorder caused by a deficiency or dysfunction of factor VIII. It affects approximately 1 in 5,000 male births and is characterised by recurrent episodes of spontaneous and post-traumatic bleeding, particularly into joints (hemarthroses) and muscles. Severity is classified according to residual factor VIII activity: severe (< 1%), moderate (1–5%), and mild (5–40%).

Management has been revolutionised by the availability of recombinant factor VIII concentrates and, more recently, by emicizumab – a bispecific monoclonal antibody that mimics the cofactor function of factor VIII and can be administered subcutaneously.

9.3 Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening immune-mediated adverse drug reaction in which antibodies directed against the heparin–platelet factor 4 (PF4) complex activate platelets, paradoxically generating a prothrombotic state despite the reduction in platelet count. HIT typically develops 5–10 days after initiation of heparin therapy and should be suspected whenever the platelet count falls by greater than 50% from baseline in a patient receiving heparin. Management requires immediate cessation of all heparin products and substitution with a non-heparin anticoagulant such as argatroban or fondaparinux.

10 Key Points

- Hemostasis involves vascular spasm, platelet plug formation (primary hemostasis), coagulation (secondary hemostasis), and fibrinolysis.
- The endothelium maintains antithrombotic tone through PGI₂, NO, thrombomodulin, and tPA; injury converts it to a prothrombotic surface.
- Platelet adhesion (via vWF–GPIb and collagen–GPVI), activation (shape change, granule release, TXA₂ synthesis), and aggregation (GPIIb/IIIa–fibrinogen bridges) constitute primary hemostasis.
- The coagulation cascade amplifies the initial TF–FVIIa signal through intrinsic Tenase and prothrombinase complexes to generate thrombin, which converts fibrinogen to crosslinked fibrin.
- Natural anticoagulants – antithrombin, the Protein C–Protein S system, and TFPI – confine clot formation to the injury site.
- Fibrinolysis, mediated by plasmin generated from plasminogen via tPA, dissolves the clot once healing is established.
- The PT/INR assesses the extrinsic and common pathways; the aPTT assesses the intrinsic and common pathways; the bleeding time assesses primary hemostasis.
- Virchow's triad (endothelial injury, stasis/turbulence, hypercoagulability) underpins the pathogenesis of pathological thrombosis.
- Arterial thrombi are platelet-rich (white); venous thrombi are fibrin-rich and erythrocyte-rich (red).
- DIC, hemophilia A, and heparin-induced thrombocytopenia are Clinically important hemostatic disorders with distinct pathophysiological mechanisms.

11 Summary

Hemostasis is an elegantly orchestrated physiological process that preserves vascular integrity while preventing uncontrolled thrombosis. The response to vascular injury proceeds through a sequence of tightly integrated events: reflex vasospasm reduces blood flow through the damaged segment; platelet adhesion, activation, and aggregation form a primary platelet plug; and the coagulation cascade – initiated by the TF–FVIIa complex and amplified through the intrinsic tenase and prothrombinase

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A thorough understanding of these mechanisms equips the medical student to interpret abnormal laboratory findings, recognise the pathophysiological basis of bleeding and clotting disorders, and appreciate the pharmacological rationale for the antiplatelet agents, anticoagulants, and thrombolytics encountered in clinical medicine. The disorders described in the clinical correlation section – DIC, hemophilia A, and HIT – illustrate the clinical consequences that arise when the hemostatic balance is disrupted, whether by systemic insult, genetic defect, or iatrogenic intervention.

Mastery of the content presented in this chapter will provide the student with a conceptual framework that will be revisited and expanded upon throughout the preclinical and clinical years of the MBBS programme.

End of Chapter 6. Proceed to Chapter 7: Inflammation and Tissue Repair.

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