DIRECTOR'S REPORT

PERSEVERING THROUGH THICK & THIN: THE CLOTTING SYSTEM

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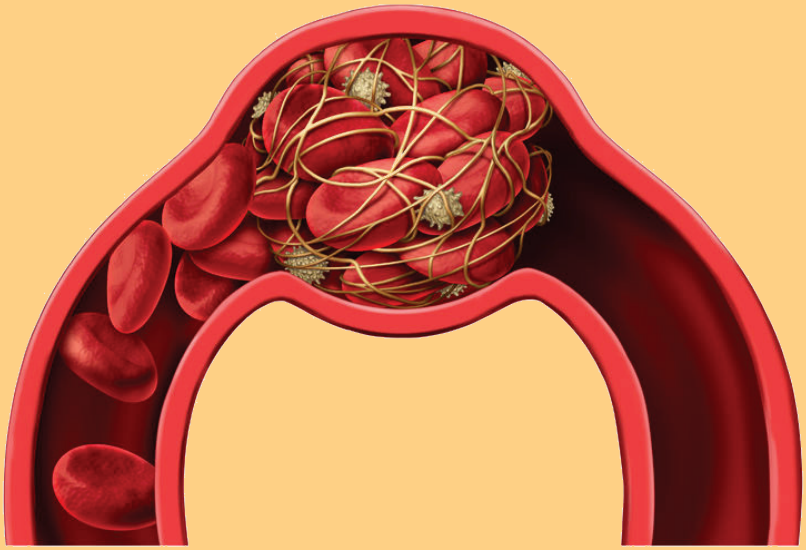

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The body's clotting (coagulation) system is a marvellously complex set of chemicals designed to stop excessive internal or external bleeding. Like many of the body's systems, it relies upon a balance between opposing factors, each of which drive the process towards a "happy medium", with the blood neither too thick nor too thin. The two major components of the clotting system required for normal function are activated by breaches in vessel wall linings, and include:

1. Clotting "factors" - clotting proteins which drive one another like dominoes along a pathway of successive enzyme activation, magnifying the initial response many-fold, and ultimately resulting in the production of a "clot" made of fibrin; and
2. Platelets – which are activated by vessel wall damage and form clots with the assistance of the clotting factors.

When these finely-tuned mechanisms go astray, clotting disorders develop, which may manifest as one of two broad tendencies:

"Thin" blood - presents with excessive bleeding and bruising due to impaired function of platelets and clotting factors. May also manifest with heavy periods or bleeding from other areas e.g. nose, rectal. It is caused by:

- * Reduced platelet numbers (called thrombocytopenia) – due to either:
- - reduced platelet production – as with vitamin deficiencies (e.g. folate, B12), bone marrow disorders (e.g. myelodysplasia) and with certain drugs (e.g. alcohol) ; or
- - increased destruction – as in immune conditions like ITP (immune thrombocytopenic purpura).

ITP is an autoimmune condition mediated by auto-antibodies directed against the platelets, tagging them for destruction in the spleen. Therapies for ITP include steroids, gamma globulin, immune suppression, and splenectomy.

Sometimes low platelets can result from excessive removal of platelets from the blood through excessive spleen activity, as when the spleen is enlarged.

- Reduced platelet function – drugs like aspirin, non-steroidal anti-inflammatories (e..g voltaren, burfen, etc) and penicillins cause platelet function impairment and secondary bruising/bleeding tendencies. Plaquenil (hydroxychloroquine) has anti-platelet effects like aspirin and, like all anti-platelet drugs, should be discontinued some days before surgery to minimise perioperative bleeding risk.
- Reduced clotting factors – when clotting factors are deficient as a result of various genetic (rarely acquired) disorders, bleeding and bruising occur.

Examples of these diseases (and their factor deficiencies) include von Willebrand's disease (von Willebrand's factor), haemophilia A (factor VIII), and haemophilia B (factor IX). Low vitamin K levels (due to malabsorption or poor intake) result in deficiencies of the so-called "vitamin-K-dependent" factors (II, VII, IX and X).

- Some disorders of coagulation (e.g. disseminated intravascular coagulation (DIC) or thrombotic thromboycopenic purrpura (TTP)) cause consumption of both clotting factors and platelets, doubly compromising clotting activity, and these "double hits" are also observed in the setting of certain medical conditions, such as liver and kidney failure.
- * Vascular fragility – as seen with corticosteroids such as prednisolone.

"Thick" blood – tendencies towards clotting are often called thrombophilias (meaning – "clot loving") or hypercoagulability states. Thrombophilias may be inherited or acquired. The inherited disorders involve an imbalance between pro-clotting and anti-clotting factors, with clotting tendencies winning out. Even if there is a definable disorder of one of the factors associated with elevated clotting risk, it is uncommon for a clot to form with only a single risk factor – rather, multiple factors are usually involved in such events. When multiple factors conspire to form clots in places such as the legs or lungs – e.g. prolonged travel, pregnancy, oestrogen pills, smoking, dehydration – then it may be possible to offer short term blood-thinning therapy (e.g. six months or so) rather than life-long treatment, if a significant clotting risk factor (e..g oestrogen therapy) can be removed. Inherited clotting conditions include factor V Leiden, prothrombin gene mutation, deficiencies of antithrombin, protein C & protein S, and elevated homocysteine levels. Acquired clotting risks can be seen in the setting of surgery, pregnancy, cancer, obesity, drugs (e.g. hormone replacement) and prolonged immobility. An autoimmune condition involving the production of antibodies which impair normal clot-fighting pathways – the antiphospholipid syndrome – is seen more commonly in the setting of other autoimmune conditions such as lupus, but can occur on its own.

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When a clot has formed, therapy to thin the blood is required. Mild clotting events affecting peripheral vessels may be managed with antiplatelet therapies like aspirin, but more serious clots involving major organs (or endangering them via embolic risk – a chance of smaller clots breaking off and travelling further to other regions) require anticoagulants. Acute therapy for significant clots often involves the use of heparin by intravenous or subcutaneous routes. Warfarin is the most established oral anticoagulant agent, and works by inhibiting vitamin-K-dependent clotting factors. Its anticlotting activity is measured by the "INR", with a reading of 1 meaning that blood is of normal thickness, and a reading of 3 meaning that the blood has been thinned three-fold. Most clotting conditions aim for a therapeutic INR of 2 – 2.5, but this varies with the disease. Warfarin therapy relies upon a stable dietary background, as bursts of extra vitamin K (as found in green leafy vegetables) will impair the blood-thinning effect; other factors, such as concomitant antibiotics and other therapies, can also cause INR levels to rise or fall, necessitating close monitoring. The NOACs (novel anticoagulant therapies, such as "Xarelto" and "Eliquis") circumvent the need for regular monitoring, with a "one-size-fits-all" dosage approach; whilst more convenient, not requiring regular monitoring, and less affected by dietary or other factors, these treatments have less evidence of usefulness in some conditions, cannot be used at extreme weight ranges, and have no available "antidote" should bleeding occur whilst on treatment.

Rudolf Virchow (1821-1902) described a "triad" of factors predisposing to venous blood clots – altered blood flow (e.g. prolonged immobility); blood vessel damage (e.g. local trauma); and altered blood constituents (i.e. clotting factors or platelets). A risk factor for clotting can be found in around 80% of patients with venous thrombosis (clots), but there is usually more than one factor at play in any clotting event. When it comes to managing factors within your control, keep active, keep hydrated, and stop to stretch and walk regularly during prolonged travel. Having read this note, you can now confidently state that "you're not a clot when it comes to clotting."

Stay safe, Glenn
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