The current understanding of hemostasis is focused on the cell-based model, which gives a more physiologic representation of blood clotting compared to the traditional cascade model. It consists of initiation, amplification and propagation phases. Initiation occurs when injury allows cells bearing tissue factor (Factor III) to react with Factor VII, ultimately resulting in the generation of a small amount of thrombin (Factor II). This reaction is amplified when the initial thrombin activates platelets and cleaves von Willebrand factor (vWF) from Factor VIII, allowing the former to promote platelet aggregation and adhesion to exposed subendothelial collagen. Coagulation is then propagated on the activated platelet surface, which ultimately results in generation of a large amount of thrombin, which converts fibrinogen (Factor I) to fibrin and stabilizes the aggregated platelet plug. While the cell-based model gives a better understanding of the integration of the various steps of hemostasis, the traditional model remains the most useful for daily clinical work. The traditional model divides hemostasis into primary and secondary hemostasis. Primary hemostasis refers to the interactions between the blood vessel wall, platelets and vWF.

Primary hemostatic defects may be inherited or acquired. Classically primary hemostatic defects cause petechiae, ecchymoses, and mucosal bleeding at multiple sites, and excessive and prolonged bleeding after injury, although this characterization is influenced by thrombocytopenia, which is the most common defect.

Secondary hemostasis consists of the coagulation factor cascade that ultimately result in stabilizing a platelet plug with fibrin. The coagulation factors are: I (fibrinogen), II (prothrombin), III (tissue factor or platelet phospholipid), IV (calcium), V, (there is no factor VI), VII, VIII, IX, X, XI, XII (Hageman Factor), and XIII. The factors are named more in order of discovery and naming than functional order. Bleeding due to coagulopathies may be localized or widespread. Hemarthrosis, pericardial bleeding, hemotherax, hemoabdomen and subcutaneous hematomas may occur, which are not typical of primary hemostatic defects. Excessive bleeding may also be delayed after injury, and rebleeding may occur, especially with defects in the intrinsic system. In the traditional view of hemostasis this occurs because bleeding is initially controlled by primary hemostasis, but the platelet plug is not converted into a firm clot. In the cell-based model, this occurs because the initiation phase initially controls bleeding, but the thrombin burst of the propagation phase does not occur. Depending on severity, vitamin-K antagonist poisoning may be characterized by either immediate or delayed bleeding after injury.

Disorders of blood vessels
Hereditary hemorrhagic telangiectasia is a rare disorder in humans that may cause widespread cutaneous petechial-like lesions and mucosal bleeding. It has not been reported in dogs or cats, although focal congenital telangiectasias have been reported, and Welsh Corgis may be affected by renal telangiectasia causing hematuria. Hepatic telangiectasia may occur in older dogs and cats and is asymptomatic. However, a similar condition, peliosis hepatis, is characterized by blood-filled cysts, that may rupture spontaneously and cause hemoabdomen. It has been associated with Bartonella henselae in humans and in a dog but not in cats. Acquired cutaneous telangiectasia resulted in erythema in a dog.

CUTaneous asthenia (Ehlers-Danlos syndrome), which refers to several hereditary collagen defects that cause hyperelastic skin and easy wounding, may be associated with ecchymoses, subcutaneous hematomas, and excessive bleeding in humans, but such bleeding has not been a prominent feature of the disorders in dogs and cats. Acquired vascular fragility may occur with hyperadrenocorticism in dogs, characterized by ecchymoses. Hyperadrenocorticism in cats causes easy wounding, but bleeding is usually minimal.

Vasculitis may result in focal or generalized erythema, edema, ecchymoses, and ulcers. There are numerous causes.

Presumptive diagnosis of vascular disorders relies on clinical, laboratory and imaging findings typical of the associated disorder. Definitive diagnosis is by skin biopsy or biopsy of other affected organs. Hemostasis would normally be evaluated before biopsy, and results are normal unless there is an associated abnormality (e.g. ITP and vasculitis; vasculitis, thrombocytopenia, and thrombocytopathia causing bleeding in ehrlichiosis).

Thrombocytopenia
Hereditary asymptomatic thrombocytopenia with macroplatelets occurs in Cavalier King Charles spaniels, and greyhounds often have asymptomatic mild thrombocytopenia. Symptomatic thrombocytopenia is acquired in dogs and cats. The most common mechanisms are reduced platelet production (megakaryocytic hypoplasia), increased consumption (DIC), and increased destruction (ITP, dogs >> cats), which may be due to a number of disorders, especially neoplastic, infectious, autoimmune or toxic causes. Platelet sequestration due to splenomegaly and platelet loss during marked bleeding are not common mechanisms for clinically relevant thrombocytopenia.

Thrombocytopenia may cause spontaneous, immediate, excessive and prolonged bleeding, often at multiple sites. Clinical signs of thrombocytopenia include cutaneous bleeding (petechiae and ecchymoses), mucosal bleeding (epistaxis, petechiae, melena,
hematuria), neurologic signs (CNS bleeding) and ocular hemorrhages. The risk for bleeding is inversely proportional to platelet count and is nominally logarithmic (Table 1).

**Table 1. Severity and risk for bleeding with thrombocytopenia**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Platelet Count</th>
<th>Risk for Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>100,000–99,000/µL</td>
<td>Not increased</td>
</tr>
<tr>
<td>Grade 2</td>
<td>50,000–24,999/µL</td>
<td>Increased surgical bleeding</td>
</tr>
<tr>
<td>Grade 3</td>
<td>25,000–49,000/µL</td>
<td>Microscopic spontaneous bleeding</td>
</tr>
<tr>
<td>Grade 4</td>
<td>&lt; 25,000/µL</td>
<td>Spontaneous clinical bleeding – mild risk</td>
</tr>
<tr>
<td></td>
<td>&lt; 10,000/µL</td>
<td>Spontaneous clinical bleeding – moderate risk</td>
</tr>
<tr>
<td></td>
<td>&lt; 5,000/µL</td>
<td>Spontaneous clinical bleeding – marked risk</td>
</tr>
</tbody>
</table>

These figures are guidelines based on megakaryocytic hypoplasia. Bleeding at any platelet count is worse if there is concurrent sepsis, coagulopathy (e.g. DIC), vWD, platelet function defect, or vasculitis. Dogs with ITP and cats typically bleed less than expected at a given platelet count. Platelet counts vary with the method used and may not be directly comparable, and enumeration is more imprecise at low values. Thrombocytopenia as reported by a hematology analyzer should always be confirmed by microscopic examination of a blood smear and a platelet count should be disregarded if there is an error message. The feather edge should be examined for platelet clumps, usually a result of difficult venipuncture (and rarely induced by EDTA). The platelet count should be estimated from the red cell monolayer where about 50% of cells are touching - each platelet per oil immersion field represents 15,000–25,000/µL. Mean platelet volume and platelet distribution width are both inversely related to platelet count and usually do not help in differentiating the causes of thrombocytopenia. Similarly, platelet morphology changes are non-specific, and the diagnosis of cause is based on clinical and other laboratory findings, imaging and biopsies for neoplasia and liver disease, testing for infectious diseases, and bone marrow biopsy. Cavalier King Charles Spaniels may be affected by pathologic thrombocytopenia, in which case the clinical presentation is similar to other dogs. Plateletcrit (analogous to hematocrit) reflects platelet mass; a QBC analyzer calculates platelet number from platelet mass and thus may be the best method to confirm pathologic thrombocytopenia in this breed.

Treatment of thrombocytopenia includes addressing the primary cause, gentle handling, transfusion, thrombopoietic drugs and prothrombic drugs. Transfusion is a short-term emergency measure. Blood products include: 1) fresh whole blood, platelet-rich plasma, or fresh-frozen plasma (which contain platelet particles), 10 - 20 mL/kg; 2) 1 unit/10-30kg fresh, cryopreserved or lyophilized platelet concentrate or cryoprecipitate, where 1 canine unit refers to product derived from a 450 mL unit of whole blood; 3) platelet concentrates produced by apheresis. Transfusion should be given if critical bleeding is occurring, and prophylactic transfusion may be considered with platelet counts < 5,000–10,000/µL. Transfusions may be needed q1-3 days if severe thrombocytopenia persists. Transfusion has the greatest utility when thrombocytopenia is due to reduced production and rapid resolution is anticipated. It is less useful in DIC, and least useful, but not useless, in ITP (See SA142). Fresh whole blood is normally procured in-house. The other blood products are variably available from commercial blood banks.

**Thrombocytopenia**

Hereditary platelet function defects may be diagnosed at all ages, but often first appear when excessive bleeding occurs with loss of deciduous teeth. Platelet counts are usually normal. Defects have been identified in the Bassett hound, Landseer, Finnish Spitz, otter hound, Great Pyrenees, grey collie (associated with cyclic neutropenia), von Willebrand Disease American cocker spaniels, boxers, German shepherd dogs, and mixed-breed dogs. Chediak-Higashi syndrome is a defect in Persian cats, which also have dilute smoke-blue coat color and yellow-green irises. Hereditary platelet function defects are rare, and the most likely one encountered is perhaps Bassett hound thrombopathia.

The most clinically relevant naturally acquired platelet function defect is arguably with ehrlichiosis in dogs. Acute ehrlichiosis may cause mild-to-moderate thrombocytopenia, but bleeding characteristic of primary hemostatic defects such as epistaxis occurs at such platelet counts that would not normally cause bleeding. Platelet function defects also occur in leishmaniasis. Platelet function defects have been variably demonstrated in uremia in dogs, but the contribution to bleeding from oral and gastrointestinal ulcers, and to bleeding in hypertensive retinopathy is not known. The author encountered one dog in renal failure where bilateral hyphema was attributed to thrombocytopenia and hypertension. Platelet function defects are also common with myeloma monoclonal gammopathies, and probably contribute to the epistaxis that may be seen with this disorder. Compared to ITP, immune-mediated thrombocytopenia is rare.

Numerous drugs are reported to affect platelet function in humans, but dog and cat platelets are less sensitive. Specifically, commonly used antibiotics that affect platelet function in humans do not do so in dogs (and probably not in cats either). Although acepromazine has been reported to affect platelet function in normal dogs, this was not confirmed in recent studies. Depending on dose, NSAIDS that affect COX-1 may inhibit platelet function in dogs and cats, as does clopidogrel, and these effects are used for thromboprophylaxis.
The only routinely available platelet function test to most veterinarians is bleeding time, which should only be performed after ruling-out thrombocytopenia. Various methods have been used – the current standard test is buccal mucosal bleeding time (BMBT). The test is operator dependent. Buccal Mucosal Bleeding Time Procedure: 1) Lateral recumbency; 2) Strip of gauze around maxilla, folding up upper lip, causing moderate engorgement; 3) Position Triplett (Helena Laboratories) or Surgicutt (ITC) device gently against upper lip mucosa and push trigger. (If not available, make an incision 5 mm long x 1 mm deep with a #11 scalpel blade, but this practice is not encouraged); 4) Note start time; 5) Blot blood with blotting paper 1-3 mm below incision (do not directly touch incision); 6) Note time when bleeding stops.

Various labor-intensive platelet function tests have been used in hematology laboratories, and there is overall poor correlation with clinical bleeding. The Platelet Function Analyzer-100 (PFA-100) is simple to use and designed for point-of-care testing, but is cost-prohibitive to most practices and samples must be fresh which limits outside submissions. Plateletworks is another point-of-care test that holds promise for use in clinical practice.

**Von Willebrand disease (vWD)**

This is the most common hereditary blood disorder of dogs and has been identified in many breeds. Different genotypes and inheritance patterns have been identified and the phenotype (risk for bleeding) is variable. The clinical hallmark of the disorder in bleeders is immediate, excessive, and prolonged bleeding from oral, cutaneous and deeper wounds. Mucosal bleeding may occur, manifested by oral bleeding, hematuria, epistaxis, and excessive bleeding in estrus and post-partum, but melena is not common. Ecchymoses and occasionally hematomas may occur (presumably due to excessive bleeding post blunt trauma), but petechiae are not typical. The lower risk for severe spontaneous bleeding, petechiation and melena are features distinguishing vWD from platelet disorders. Some of these differences occur because other proteins are also involved in platelet adhesion.

Von Willebrand factor is a variable-sized glycoprotein comprised of identical subunits held together by disulfide bonds. Circulating vWF varies from dimers to multimers >38 monomers. The larger multimers are more functional. Plasma vWF concentration is measured by immunologic tests hence is reported as antigen (vWF:Ag). It is reported as a percentage of the concentration found in pooled plasma from normal dogs, which is given a value of 100%. Given that vWF:Ag is variable in normal dogs, and a dog with very mild vWF deficiency could have contributed to the plasma pool, it is easy to understand why there is a grey zone between abnormal and normal. The vWF:Ag is a quantitative measure – it does not measure vWF function, which is dependent on multimer size. However, if multimer distribution is normal, the lower the vWF:Ag the lower the vWF function and the greater the risk for bleeding. Multimer distribution may be determined in some specialty hematology laboratories by Western blot, and may also assay vWF function by collagen binding (vWF:CBA). Specialty laboratories may also offer PFA-100 testing, where vWD may increase closure time. Plasma vWF:Ag shows variation in individual animals and may be affected by other physiologic and pathologic states. For example, vWF:Ag tends to rise during gestation and exercise. These changes are most likely to affect assigning a vWD positive or negative status to dogs with values in or close to the grey zone between normal and abnormal values.

Canine vWD is classified as Type 1, 2 or 3 based on plasma vWF concentration and multimer size. Type 1 is characterized by variably low vWF concentration, but normal multimer distribution, resulting in mild-to-moderate bleeding tendency. It is the most common form affecting many breeds, including Doberman Pinschers. Type 2 vWD is characterized by variably low vWF concentration, as well as reduction in larger multimers, resulting in moderate-to-severe bleeding tendency. Type 2vWD affects German shorthaired Pointers and German Wirehaired Pointers. Type 3 vWD disease is characterized by complete absence of vWF resulting in a severe bleeding tendency. Type 3 vWD has been identified in Chesapeake Bay Retrievers, Scottish Terriers, Shetland sheepdogs, Dutch Kooikers and sporadically in other breeds. Generally a single type of vWD is seen in a given breed, although there are exceptions – for example both Type 1 and 3 vWD have been seen in Shetland sheepdogs.

Diagnostic testing may be with intent to: 1) identify etiology in a dog presented for clinical bleeding; 2) screen for risk for bleeding prior to surgery; or 3) screen for a known genetic mutation prior to breeding. In a dog with abnormal bleeding due to vWD, the likely hemostatic results will be prolonged BMBT, normal platelet count, normal ACT, normal to slightly prolonged APTT, normal PT, normal fibrinogen/TT (see SA141), and decreased vWF:Ag and vWF:CBA. In an emergency situation with limited testing resources, prolonged BMBT, normal platelet estimate, and normal whole blood clotting time or ACT in a dog with signs of a primary hemostatic defect will have a high positive predictive value for vWD. Assuming a normal BMBT of 2 - 4 minutes, dogs with Type 1 vWD have BMBT > 5-6 min, and dogs with Type 2 and 3 vWD have BMBT > 12 min.

With respect to screening a dog for risk of hemorrhage before surgery, neither BMBT nor vWF:Ag can be used to directly predict risk. This probably reflects, at least in part, operator variation in BMBT, surgical procedures, and judgment of excessive bleeding. Predicting hemorrhage is most difficult for dogs with mild-to-moderate Type 1 vWD. Dogs have been judged to be bleeding excessively with normal BMBT, and dogs with low vWF:Ag and prolonged BMBT have also been judged to not have excessive bleeding. However, this does not mean the tests are useless. Overall the longer the BMBT and the lower the vWF:Ag, the more likely there is to be excessive bleeding and these tests will be abnormal in dogs with moderate-to-severe vWD, i.e. dogs that are at increased risk for bleeding. Genetic testing for a number of vWD genotypes is also commercially available (VetGen). A finding of an abnormal
genotype will not predict risk for bleeding in Type 1 vWD. A dog with a normal genotype would not have abnormal bleeding due to vWD. However, no laboratory test for any disorder has a 100% positive or negative predictive value. Given the simplicity of performing a BMBT and measuring vWF:Ag, if there is enough concern to perform a genetic test, then, pending further data correlating genotype and phenotype, consistency of the result with other tests for vWD is recommended.

Testing for vWD genotype and removing positive dogs from a breeding program has proven to be a valuable tool to reduce prevalence of the disorder in a breed. Measurement of vWF:Ag is not sufficiently sensitive for screening as some carriers will fall in the grey zone between normal and abnormal. However, data correlating genotype and phenotype are not complete, and measurement of vWF:Ag in dogs that have had a genetic test is encouraged.

Prophylactic treatment or treatment of a bleeding episode includes desmopressin and transfusion. Desmopressin is given at a dose of 1 µg/kg SC 30 min before surgery to raise plasma vWF concentration. This has resulted in improved vWF function, decreased BMBT and PFA-100 closure times in dogs with Type 1 vWD. Transfusion of vWF may be given via fresh whole blood (10 – 20 mL/kg), fresh-frozen plasma (10 mL/kg), fresh platelet-rich plasma (10 mL/kg) or cryoprecipitate (1 unit/10 kg). Fresh whole blood or fresh-frozen plasma are the most readily available products. Canine vWF is labile, but studies at the author’s institution have shown it is stable in plasma at room temperature for 24 hours, so deterioration during transfusion is not a concern. Transfusions may need to be repeated every 6 – 12 hours to maintain adequate vWF concentrations. Repetitive transfusions with fresh whole blood may create volume overload and polycythemia. Although of unproven additional benefit, at the author’s institution donors are given desmopressin to boost vWF levels in fresh-frozen plasma and cryoprecipitate.

Acquired von Willebrand Syndrome is a well-documented but rare disorder in humans. It may be a complication of autoimmunity, hematologic neoplasia, hypothyroidism, and increased shear forces with cardiovascular implants. The disorder has been reported as a complication of angiostrongylosis in a dog. It has not been documented as a complication of hypothyroidism in dogs. Mitral valve insufficiency may cause a lowering of vWF concentration and function, but not to the point of causing a bleeding tendency.

References & suggested reading
