Von Willebrand's Disease In Dogs

Von Willebrand's disease is the most common, mild, inherited bleeding disorder of animals, and affects many breeds of dogs.

W. Jean Dodds, DVM

Div. of Laboratories and Research
New York State Dept of Health
Empire State Plaza
Albany, NY 12201

Von Willebrand's disease (VWD) is the most common, mild, inherited bleeding disorder of people and animals. It is an autosomal trait with 2 forms of clinical and genetic expression. It can be a disease with autosomal recessive expression, in which clinically affected individuals are homozygous for the D gene and have 2 asymptomatic, heterozygous (carrier) parents; or it can be a disease with an autosomal, incompletely dominant expression (variable trance), in which both homozygotes and heterozygotes can manifest a bleeding tendency. Homozygosity is often lethal in this form of VWD.

Breeds Affected
The recessive form of VWD has been recognized in Poland-China swine, Scottish Terriers and Chesapeake Bay Retrievers. The incompletely dominant is much more common and has been recognized in 28 breeds of dogs, though virtually any breed may affected. Several Breeds have a high prevalence of the disease (15-60% gene frequency).

Clinical Signs
High morbidity and low mortality are generally associated with VWD. Typically, there is mild to severe bleeding diathesis that usually involves mucosal surfaces. Bleeding is exacerbated by physical, emotional and physiologic stress, hormonal imbalances (especially hypothyroidism), and by concomitant diseases (eg, parasitic, viral and bacterial infections). Typical clinical signs include: recurrent hematuria; epistaxis; gingival, vaginal or penile bleeding; lameness that mimics that from eosinophilic panosteitis; stillbirths or neonatal deaths ("fading pups"), with evidence of bleeding at necropsy; prolonged estrual or postpartum bleeding; hematoma formation on the surface of the body, limbs or head; excessive umbilical cord bleeding at birth; and excessive bleeding from toe nails cut too short, or after tail docking, ear cropping or dewclaw removal. Severely affected dogs may bleed to death from surgical procedures. Concomitant parvoviral infection often aggravates the bleeding tendency, which probably explains the high prevalence of severe parvoviral disease in Doberman Pinschers. About 58% of the Dobermans tested have the VWD trait.

Relationship of Hypothyroidism to VWD
Several breeds of dogs have a high prevalence of hypothyroidism the common occurrence of both VWD and hypothyroidism in some of these breeds (Dobermans, Golden Retrievers, Scotties, Corgis, Manchester Terriers) suggests a causal relationship between the synthesis and/or metabolic regulation of thyroid hormones and von Willebrand's factor (VWF) protein, which is deficient or abnormal in VWD. Hypothyroidism in people has been associated with a bleeding tendency caused by abnormal platelet function and low levels of factor VIII activity and VWF. Reduction in these abnormalities has been reported after oral thyroid supplementation. In our studies of Doberman Pinschers, there was an increased frequency and severity of bleeding episodes in animals with the VWD gene that were also hypothyroid. Clinical signs of bleeding in these dogs were lessened or controlled within 48 hours of initiating daily thyroid supplementation; VWF levels also increased. Thus, animals with thyroid dysfunction can have fluctuating levels of VWF. When these dogs are given thyroid supplementation, VWF levels can increase to within normal limits, which could preclude accurate diagnosis of their genetic status for VWD (ie, carriers of VWD might test as normal when on thyroid medication). Because of this

apparent exacerbation of the bleeding tendency in dogs with VWD and hypothyroidism, breeders and veterinarians must be aware of the increased risk and be more cautious about breeding or performing surgery on dogs with both problems.

Genetics and Recommendations to Breeders

One form of VWD is inherited as an autosomal dominant trait with variable clinical expression or, in other words, variable penetrance of the VWD gene. This type of inheritance is termed incompletely dominant. Both sexes are equally affected in VWD, unlike in hemophilia, which is an X-linked recessive trait that classically affects only males. WMIE the dominant expression of the VWD gene produces reduced levels of VWF in homozygotes with a double dose of the gene, it also does so in heterozygotes with a single-gene dosage. Clinical expression of VWD as a bleeding tendency, however, is inherited in the 2 forms mentioned at the beginning of this article. The common form is an autosomal incompletely dominant condition in which homozygosity is usually lethal, and heterozygotes can be either asymptomatic carriers or affected to a varying degree. The more rare form is an autosomal recessive disorder in which clinically affected individuals are homozygous for the trait and express a double dose of the gene, one from each heterozygous, asymptomatic parent.

The following possibilities occur when animals with the VWD gene are mated:

- If a normal dog, free of the VWD gene, is mated to one affected with or carrying the gene, about half of the litter will be affected or carriers, like the VWD parent, and the other half are normal.

- If 2 affected animals or 2 carriers are mated, three-quarters of the puppies have the VWD gene. One quarter of the litter is severely affected (perhaps fatally at birth), one-half will be affected or carriers like the parents, and the remaining one quarter is normal.

- The more severely affected the parent, the more likely that it will produce severely affected bleeder puppies.' Thus, a VWD carrier, which is clinically normal but transmits the VVAFD gene (trait) to some of its progeny, is least likely to produce a clinically affected bleeder pup, provided the mate was VWD free. Mating 2 carriers of VWD, however, doubles the VWD gene, and puppies that get a double dose (one gene from each parent) are more severely affected than either parent. This is obviously an undesirable situation.

The following recommendations are offered to reduce the prevalence of VWD in a population. Blood tests for VWD animals that are related to those bloodlines known to have the problem, as well as other top-producing or winning foundation stock. Pedigrees can be sent to us (New York State Dept of Health) for evaluation of whether the animals or bloodlines are closely, distantly or not related to those of known affected families. Ideally, affected animals and carriers of VWD should not be bred. However, it may not be feasible for a breeder to eliminate these dogs as breeders, especially if they are desirable for other reasons. Therefore, if breeding affected animals is necessary to preserve important bloodlines or type the following should be considered:

- Breed asymptomatic carriers to normals and blood test the pups. Half of the litter should be normal and the other half carriers. This is the best alternative to preserve bloodlines.

- Mate 2 asymptomatic carriers only with caution and blood test the pups. Remember that only one fourth of the litter will be normal and another one fourth more severely affected than either parent.

- Breed mildly or moderately affected animals only if essential to the breed and only to normals. Be sure to blood test the pups, since half of the litter should be normal, and the other half will be affected like the parent. We do not advise this type of mating

- Do not mate 2 affected animals.

- Never breed a severely, clinically affected animal.

Laboratory Diagnosis

Diagnostic tests for canine VVM are similar to those used for human VWD.1 Specialized VWF assays are required because VWD is expressed in the blood by a deficiency or abnormality of one or more proteins of the factor VIII complex. Screening coagulation tests (APTT, PT and TCT) are non-diagnostic. A brief explanation of the factor VIII complex is given below to facilitate understanding of the tests used to diagnose VWD

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Dogs clinically affected with VWD also have prolonged bleeding times, abnormal platelet retention in *vitro,* and variable factor VIII coagulant activity levels (normal to moderately reduced). Definitive diagnosis is by finding reduced or no levels of FVIIIR:AG and/or the platelet-related assays of VWF (ristocetincofactor). A practical way to distinguish between asymptomatic heterozygotes and heterozygotes clinically affected with VWD (both have reduced levels of FVIIIR:AG) is to determine the cuticle bleeding time. This test is performed by placing the dog in lateral recumbency and cutting one or more toe nails too short with a standard, guillotine-type (Resco) nail clipper. With the foot undisturbed, the bleeding should cease within 5 minutes in normal dogs. Dogs with hemostatic defects, such as VWD or platelet dysfunction, have prolonged initial bleeding times (some never stop bleeding and must be cauterized) or begin bleeding again after initial clotting. A convenient way to perform this test is as a presurgical screen once the animal is anesthetized and the surgical site is being prepared. Clinical experience with this technique as a presurgical screen has been useful in identifying dogs that may bleed excessively at surgery.

Genetic Screening for VWD

Screening for genetic defects has been used successfully in people for many years and more recently has been applied to animals. In the mid-1960's, veterinarians began screening dog populations for inherited eye diseases and hip dysplasia. Eventually, organizations were developed to register animals free of the major hereditary conditions known to affect purebred dogs. In New Zealand and Australia, mass screening of cattle for mannosidosis has been used effectively since the mid-1970's to control this devastating disease.' The common practice of line-breeding and inbreeding purebred dogs facilitates both the transmission and recognition of all types of genetic defects. Also, because companion animals live in close daily contact with their owners, illnesses are more likely to be noticed and treated.

The screening program developed in our laboratory for inherited bleeding disorders of purebred dogs evolved from an ongoing consultation and referral practice in veterinary hematology. The number of dogs screened for VWD by blood testing has increased steadily from the inception of our program in 1976 through 1980. Since 1980, the number has stabilized; this reflects implementation of planned matings between normal and carrier stock to eliminate the gene once heterozygotes have been identified.

In developing an accurate test to detect heterozygotes, we found, as in bovine mannosidosis, a skewed distribution between normal and abnormal populations, with a small but defined area of overlap.' Despite this overlap, we have developed an effective program to identify heterozygotes and to gradually eliminate them from the breeding population. Data in support of this conclusion have shown a significant decrease in the overall prevalence of VWD in Scottish Terrriers, Golden Retrievers and Miniature Schnauzers. The prevalence of VWD has been reduced in Scotties from 35% to 11%, in Goldens from 15% to 6%, and in Schnauzers from 25% to 18%. The prevalence in the other commonly affected breeds is essentially unchanged. This probably reflects a combination of insufficient numbers tested to implement planned matings for control of the gene and/or the need to increase breeder and veterinary awareness and acceptance of the importance of VWD.

The accuracy of the testing program in detecting the VWD genotype has been evaluated by retrospective analysis of the results to date for all 3 mating types (normal x normal, normal x carrier, carrier x carrier). The rate of misclassification of genetic status by this test is only 2-3%, which means that in 97% or more

cases, the test is a reliable predictor for genotype. Cumulative data from these studies are currently being entered into a newly developed computer program to facilitate subsequent analyses.

Management and Treatment

General Considerations

Patients with bleeding disorder,3 cannot be properly treated without an appropriate physiologic and physical environment for hemostasis, tissue repair and prevention of recurrence. An extremely important aspect of medical management is avoiding use of drugs known to interfere with hemostasis [eg, aspirin, phenylbutazone, phenothiazine tranquilizers, estrogens, plasma expanders (Dextran, HES), nitrofurans, sulfonamides, anti-inflammatory drugs, penicillins, local anesthetics]. These are contraindicated for patients with moderate or severe hemostatic defects, since they impair platelet function and further compromise the stability of the hemostatic plug.

Any live-virus vaccine or viral infection can impair platelet and/or endothelial cell production and turnover. The effect occurs during the viremic phase after vaccination or exposure (usually at 5-10 days) and results in relative thrombocytopenia or endothelial injury, which may prolong bleeding time and predispose the animal to hemorrhagic problems. Platelet reductions of 100,000/ul can occur. During this period, animals with hemostatic defects are at risk and should be evaluated carefully for signs of bleeding. Elective surgical procedures, such as ear cropping, ovariohysterectomy, castration and dental surgery, should be performed within 48 hours after vaccination or should be postponed for 10-14 days. In most cases, animals admitted for elective surgery are vaccinated immediately or within 24 hours of surgery, which accounts for the relatively few vaccine related bleeding problems.

As mentioned earlier, hypothyroidism produces a bleeding tendency and exacerbates the clinical expression of concomitant VWD. Thus, asymptomatic heterozygotes for VWD can exhibit a bleeding tendency if they also become hypothyroid. This is a common situation in the Doberman Pinscher; many of these dogs have very low levels of T4 and/or T3 with abnormal TSH response tests, yet show none of the typical overt signs of thyroid disease. Hypothyroid animals with concomitant VWD usually show slightly to moderately reduced platelet counts (70,000-150,000/ul) and very long cuticle bleeding times, in addition to their low VWF activity.

Recent clinical experience with Dobermans admitted for bleeding episodes, such as nosebleeds or severe hematuria, has shown that thyroid supplementation alone reduces and then controls the bleeding within 24-48 hours. This finding supports our unpublished experimental studies that showed that when treated with T4 7 Dobermans with VWD and mild hypothyroidism had a 2 or 3 fold increase in their baseline levels of VWF activities within 24 hours. This peaked at 3 days and was sustained for another 3-4 days. The standard therapeutic dosage, based on body weight as recommended by the manufacturer, should be used and the animal should have a pretreatment serum specimen collected for resting T, and T, determinations. Follow-up of Dobermans treated with thyroid medication to control bleeding has shown that most were severely hypothyroid and the remainder were mildly abnormal or borderline normal. Therefore, our recommendation for all Dobermans with serious bleeding is to collect a serum specimen for thyroid and VWD measurements and then treat with thyroid replacement hormones pending results of blood tests.

Specific Therapy

Typical Treatment. Microcrystalfine collagen (Avitene: Alcon), a topical hemostat, is superior hemostatically to pressure alone and/or oxidized cellulose cloth (Oxycel: Parke-Davis) or thrombin-soaked gelatin sponge (Gelfoam: Upjohn). Thrombin itself also has been used as a topical agent to control bleeding.

Blood or Blood-Component Replacement. Details for the type and volume of blood or blood products recommended to treat moderate or severe bleeding disorders are discussed elsewhere. 1.16 The preferred anticoagulants for collection of whole blood for transfusion are acid-citrate-dextrose or citrate-

phosphatedextrose. Use of heparin is not recommended because it activates platelets, causing them to clump. Blood plasma products used to control and treat bleeding should be as fresh as possible or fresh-frozen, because coagulation factors and platelets are labile. As mentioned above, animals with bleeding disorders are likely to require repeated transfusions during their lifetimes and thus are at risk for transfusion incompatibihties. Use of um-natched whole blood, therefore, is contraindicated except in life-threatening emergencies. Appropriate therapy involves IV infusion of fresh universal donor or crossmatched blood at 3-5 mMb of body weight. The treatment of choice for VWD, when RBC are not required, is canine plasma factor VIII concentrates (cryoprecipitates), but these are not conunercially nor readily available for animals. An alternative is to give fresh-frozen, homologous plasma at 3-5 ml/lb of body weight once or twice daily.

Because platelets and coagulation factors have relatively short in *vivo* lives, control of bleeding episodes requires that the daily amount be divided and given as 2 regularly spaced transfusions . 2 This regimen also reduces the risk of circulatory overload. For elective or other surgery, clinically affected VWD patients should receive fresh, compatible whole blood, at 3-5 ml/lb, 2-4 hours beforehand. The ability of the transfused VWF to reduce the bleeding time lasts for up to 4 hours, whereas the other properties of the factor VIII complex remain active for 10-24 hours. For surgery on a VWD heterozygote with an unknown or no bleeding history, the cuticle bleeding time should be performed as a presurgical screen. If the time is within 5-6 minutes (normal), this does not preclude the existence of a mild underlying hemostatic defect but indicates that the surgeon probably will not encounter significant bleeding.

Factor VIll Complex

Factor VIll circulates in plasma as a complex of 2 proteins: the factor VIll-coagulant activity protein, which is severely deficient in hemophilia A and often is reduced in severe forms of VWD, and the VWF protein (also called after factor Vill-related protein), which has several important biologic properties that control bleeding and is deficient or abnormal in VWD but normal in hemophilia. Thus, one can readily distinguish between VWD and hemophilia even without a family history to establish the inheritance pattern, because animals with VWD have abnormal or low levels of VWF protein and hemophiliacs do not.

One of the properties of the VWF protein is its ability to cross-react in immunologic tests with antibodies formed against it in other species. This immunologic property of VWF protein is called factor VIII-related antigen (FVIIIR:Ag) and is measured routinely in plasma by the Laurell electroimmunoassay. Our screening program is based on this technique, using antibodies formed against VWF protein purified from normal canine plasma. (Such antibodies are not commercially available for animals, and cross-reactivity with readily available human antibodies varies among species, has less avidity, or is absent.)

The sensitivity, or lower limit of detection, of this technique is about 7%. Thus, levels of 7% of normal or less of this plasma protein are undetectable (zero) in the assay. However, by using a more sensitive research technique that detects as little as 0.1% of the antigen, dogs affected with VWD can be classified into 2 groups. Scottish Terriers and Chesapeake Bay Retrievers that are homozygous for the autosomal recessive form of VWD have no detectable antigen and are truly zero-level animals, whereas their heterozygous (carrier) parents and those with the other form of VWD (incompletely dominant expression) have reduced but measurable amounts of antigen.

To establish the normal range for canine FVIIIR:AG, we measured levels in plasma from over 125 healthy purebred dogs of breeds in which VWD has yet to be recognized.'," The antigen levels in these animals ranged from 60-172% of normal, with a mean value of 93 ± 33%."

Instructions for Preparation of Von Willebrand's Disease Samples*

Fill a blue-top Vacu-Tainer to capacity, mix well and centrifuge at 2500-3000 rpm for 15 minutes. Aspirate the supernatant plasma with a plastic pipette, siliconized pipette or a small plastic syringe, such as a tuberculin syringe. Place the plasma into a small plastic tube and freeze. Ship within 1-2 weeks after drawing.

All samples should be frozen initially and sent on cold pack to the laboratory. The sample may thaw in transit, but samples in shipment longer than 3 days may have slightly reduced values. Dry ice is not necessary, but samples should arrive in a cool condition. Shipping by regular mail is quite satisfactory if the above criteria are met (cool, in 3 days or less).

Test Restrictions for Genetic Screening of Healthy Dogs

Do not test unhealthy animals or animals receiving any type of medication for recent illness or vaccination within the previous 14 days. If the animal is being given long term medication or heartworm preventive, please indicate type and duration (eg, Caricide or thyroid medication). A fasting blood sample is not necessary.

Tests with borderline findings between "normal" and "suspect carriers" will be repeated. Therefore, in these cases, additional time will be required to repeat the test. Those with >60% FVIIIR:AG activity are normal, those with 40-60% are carriers, and those with less than 40% are considered FVIIIR:AG deficient.

* *These instructions are for specimens to be submitted to the Veterinary Reference Laboratory for analysis. Readers should consult with their local diagnostic laboratory for instructions if the Veterinary Reference Laboratory is not used.*

Summary
Von Willebrand's disease, the most common, mild, inherited bleeding disorder of animals, is an autosonial trait generally causing high morbidity and low mortality and affecting many breeds of dogs. Clinical signs include hematuria, epistaxis, gingival or genital mucosal bleeding, lameness, and prolonged bleeding from cut nails or wounds. Concurrent hypothyroidism exacerbates the disease. Affected dogs and carriers should not be bred or should be tested for von Wiflebrand's factor before breeding. Treatment involves IV infusion of fresh whole blood or plasma, at 3-5 ml/lb, with topical use of hemostatic compounds, and avoidance of drugs that interfere with hemostasis.