Editorial

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New Red Blood Cell Antigens in Dogs and Cats—A Welcome Discovery

Dr Karl Landsteiner published, in 1901, his findings that serum from normal humans could agglutinate the red cells of another person, and he recognized that this phenomenon had an immunological basis. He initially identified only 3 blood group antigens, which he termed A, B, and C.[1] Serum from group C subjects clumped the cells of those from groups A and B. The following year, 2 of Landsteiner's students, von Decastello and Sturli, confirmed his findings and also identified subjects with no agglutinins in their serum but whose red blood cells (RBC) were agglutinated by serum from subjects with all of the 3 previously discovered blood groups. Thus, group AB was discovered. The importance of Landsteiner's work was not recognized immediately, and blood grouping (typing) did not become a universal part of medical practice until the 1920s. In 1937, at a meeting of the Congress of the International Society of Blood Transfusion, the current ABO terminology was adopted.

A quarter of a century passed before other blood group systems were recognized. In 1939, Philip Levine, another of Landsteiner's pupils, published a case history of post-transfusion hemolysis in a woman with blood group O who received blood from her husband, who had the same O blood group. Incubation of the woman's serum with 80 other ABO compatible samples resulted in agglutination. This was the first report of Rhesus (Rh) antibodies, and the discovery of the Rh system.

For decades, these were the only known blood groups, and all transfusion reactions were erroneously thought to be because of antibodies against the antigens within these groups. But, as transfusions and pretransfusion compatibility testing became more widespread, more in vivo and in vitro reactions were investigated, resulting in the descriptions of several new RBC antigens and blood group systems. Now, at least 29 blood group systems have been recognized in humans.[2]

Interestingly, the discovery of the ABO blood group system stimulated the search for blood group systems in veterinary medicine. Canine blood groups were first recognized in 1910 by Von Dungern and Hirszfeld (as cited by Swisher and Young[3]), who defined 4 blood groups based on immune isoagglutinins. Swisher, Young, and coworkers further defined canine blood groups in the 1950s, describing blood group antigens A, B, C, D, E, F, and G. International workshops met in 1972 and 1974 to standardize canine blood groups as defined by isoimmune sera, and to standardize canine blood group system nomenclature. The second workshop adopted the designation dog erythrocyte antigen (DEA) followed by the number 1 onward for a locus, followed by a period (.) followed by another number for each allele recognized at the locus.[4] The nomenclature currently used in the United States is the DEA system, which includes DEA 1.1, DEA 1.2, DEA 3, DEA 4, DEA 5, and DEA 7. Other blood-group systems, such as DEA 6 and DEA 8, have been described but now remain uncharacterized because of a lack of typing sera.

Isoagglutinins were first noted in cats in 1915, but cat RBC antigens, designated O and EF, were not described until 1950. These antigens were again described in 1962 and given the designation A and B. Auer and Bell[5] provided further characterization of the blood groups in 1980 with the designation of the AB system with types A, B, and AB, which remains today. They were also the first to describe transfusion reactions resulting from naturally occurring isoantibodies in blood-type incompatible cats.

The above history serves to remind us that blood-group systems have been described in man and animals for over a century, and, yet, the process of discovery and description is by no means finished. The field of veterinary transfusion medicine finds itself in a particularly interesting situation, not unlike what occurred decades ago in the field of human transfusion medicine. Transfusions and pretransfusion testing in animals, especially in dogs and cats, are occurring with increasing frequency, providing the opportunity to observe and record potential problems or reactions. We now have the choice to either ignore in vitro or in vivo reactions in "type matched" animals, restricting them to our current knowledge of RBC antigens, or to recognize our limitations in this area and look beyond to the probability of more blood groups and new antigens yet to be identified.

Two studies addressing new RBC antigens in the dog and cat appear in the current issue of this journal. In the study of dogs (page 281), a DEA 1.1 positive Dalmatian was initially transfused with crossmatch compatible DEA 1.1 positive blood over a 3-day period. No adverse reactions were observed; however, a subsequent crossmatch 40 days after the initial transfusion revealed incompatible major crossmatches with 55 non-Dalmatian dogs. Crossmatches with 21 unrelated Dalmatians were also incompatible, but 4 unrelated Dalmatians were compatible. The alloantibody present was not against any blood type currently characterized in the dog, and the newly recognized blood type was given the name of *Dal*. The dog was later successfully transfused with blood from one of the *Dal* negative, crossmatch-compatible donors.

In the study of cats (page 287), crossmatch testing of plasma from a healthy type A domestic shorthair (DSH) blood donor cat named "Mike," who had not received a transfusion, revealed incompatibilities when combined with RBC from 55 type A cats, 3 type B cats, and 2 type AB cats. Subsequent testing of other blood-donor cats identified 2 other type A donor cats who also showed incompatibilities when their plasma was combined with RBC from several type A cats. It was determined that these donor cats had an antibody against an antigen that they lacked; this antigen was given the designation "*Mik*" antigen. The relevance of this naturally occurring

anti-*Mik* alloantibody was clear when a renal transplant recipient cat suffered a hemolytic reaction after transfusion. The cat was subsequently shown to be *Mik* negative and had received blood from *Mik* positive donors. The study documented the first description of a blood group and corresponding clinically relevant, naturally occurring alloantibody distinct from the AB blood-group system in cats.

The numbers of donors used in these cases to find a compatible crossmatch, and, thus, compatible donors would far exceed the numbers used in most veterinary practices, but such numbers were necessary to show that compatible potential donors existed. The take-home message should not be that every practice needs numerous blood donors but rather that both typing and crossmatching should be routinely performed in dogs and cats who require blood products and that incompatible crossmatches should not be ignored, despite the availability of type-matched blood. Should incompatibilities be identified, appropriate steps can then be taken through veterinary commercial or university blood banks to identify an appropriate donor. Sera containing unidentified alloantibodies could also be saved for future testing or research. More antigens and corresponding alloantibodies are likely to be discovered, but only if clinicians and blood bankers recognize their potential existence and actively look for them.

Both of the studies in this issue underscore the need for accurate crossmatching before transfusion of blood to dogs and cats.[6,7] Crossmatching misidentification of compatible donors occurred in one of these studies,[7] with consequences to the cat. So, how is the average veterinarian to proceed? The standard tube crossmatching technique can be time consuming and difficult to perform for the clinician or the technician not well versed in crossmatching procedures. Comparison studies examining crossmatching methods, including incubation times and temperatures and the ideal ratio of antigen (RBC) to antibody (plasma or serum) are lacking in the veterinary literature. The current studies proposed the use of gel testing as a possible way to better standardize crossmatching and ease its interpretation. Gel tests are a form of a column agglutination assay, where RBC agglutinates caused by antigen-antibody reactions become trapped and remain in the gel, while the free RBCs pass through and form a button at the bottom of the tube. The endpoint reactions are more stable and last longer than conventional tube or microtiter plate agglutination reactions. The gel tubes used in the studies were bound to small cards, requiring a specialized incubator and centrifuge for their physical accommodation. Gel-based testing for typing, crossmatching, and antiglobulin testing is common in human medicine. It is a promising technique that warrants further investigation in the veterinary field.

The studies also point out how nomenclature could become an issue as more alloantibodies and corresponding antigens are found. As an example, how does one fit the designation *Dal* into the current DEA system? An international workshop to standardize canine and feline blood-group system nomenclature should be considered, with stipulations made for the appropriate designation of newly found antigens.

The aim of transfusions is to improve the life of the animal, and knowledge of any potentially foreign antigens or antibodies that might be transfused can be vital to a successful outcome. The discovery and documentation of these new RBC antigens is thus an exciting and welcome addition to the current body of knowledge in veterinary transfusion medicine and will hopefully prompt further research in this area.

References

1. Giangrande PLF. The history of blood transfusion. Br J Haematol 2000;110:758–767.

2. Daniels GL, Cartron JP, Fletcher A, et al. International Society of Blood Transfusion Committee on terminology for red cell surface antigens: Vancouver report. Vox Sang 2003;84: 244–247.

3. Swisher SN, Young LE. The blood grouping systems of dogs. Physiol Rev 1961;41:495–520.

4. Vriesendorp HM, Albert E, Templeton JW, et al. A joint report of the second international workshop on canine immunogenetics. Transplant Proc 1976;VIII:289–314.

5. Auer L, Bell K. The AB blood group system of cats. Anim Blood Groups Biochem Genet 1981;12:287–297.

6. Blais M-C, Berman L, Oakley DA, Giger U. Canine Dal blood type: A red cell antigen lacking in some Dalmations. J Vet Intern Med 2007;21:281–286.

7. Weinstein NM, Blais M-C, Harris K, Oakley DA, Aronson LA, Giger U. A newly recognized blood group in domestic shorthair cats: The *Mik* red cell antigen. J Vet Intern Med 2007;21:287–292.

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