HEMOLYTIC REACTIONS PRODUCED IN DOGS BY TRANSFUSION OF INCOMPATIBLE DOG BLOOD AND PLASMA

I. SEROLOGIC AND HEMATOLOGIC ASPECTS

By LAWRENCE E. YOUNG, M.D., DONALD M. ERVIN, M.D., AND CHARLES L. YUILE, M.D.

HEMOLYTIC transfusion reactions occur more frequently than is generally appreciated and their incidence can be expected to increase for some time as the distribution of blood is facilitated. Many are doubtless overlooked because the outward manifestations may not be particularly striking, especially in anesthetized patients and in certain recipients transfused with plasma or with blood from universal donors. Despite the increasing importance of such reactions, their pathologic physiology remains poorly understood and cannot be adequately explored in human subjects. Consideration of these facts stimulated the authors to make observations on planned hemolytic reactions in dogs with the hope that the results might find general application in the field of immuno-hematology, and that they might throw light on the behavior of the kidney when subjected to certain types of insult.

The purpose of this paper is to describe preliminary serologic and hematologic observations on reactions produced in dogs by transfusion of incompatible whole blood and plasma. Typical experiments are cited to illustrate the usefulness of iso-immune systems in the dog in making quantitative studies of hemolytic phenomena. Alterations in renal physiology observed during these experiments are described in an accompanying report.¹

HISTORICAL

Individual Differences among Bloods of Mammals other than Dogs

In 1900 Ehrlich and Morgenroth² found that when one goat was injected with the blood of another goat, immune isolysins developed, and by using such iso-immune serum a number of varieties of goat blood could be differentiated. Since that time other investigators have employed similar methods in demonstrating individual differences in the blood of other mammals.³ Ottenberg and Thalhimer⁴ demonstrated immune iso-antibodies in the serum of repeatedly transfused cats and these authors described the course of events during hemolytic reactions following injections of incompatible whole cat blood. Their findings included hemoglobinemia, hemoglobinuria, oliguria, glycosuria, hemoglobin casts in the urine, jaundice, erythrophagocytosis and leukocytosis.

Individual Differences among Dog Bloods

In 1910 von Dungern and Hirschfeld⁵ used iso-immune sera to distinguish two agglutinogens and four groups among dog bloods, but their observations and the few described by other investigators since 1910 have by no means completely clarified the pattern of individual differences in this species.

From the Departments of Medicine and Pathology, The University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

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Ottenberg, Kaliski and Friedman demonstrated what appeared to be naturally occurring iso-hemagglutinins and hemolysins in dogs. The reactions described were for the most part weak and variable, but it is nevertheless significant that potent iso-hemolysins developed after repeated transfusions of agglutinable cells, and not after transfusions of non-agglutinable cells. Dogs whose serum appeared to contain naturally occurring iso-antibodies were transfused with apparently incompatible whole blood by use of the direct "artery to vein" technic. Hemolytic reactions were observed after repeated transfusions, but in only one instance did such a reaction occur after the first transfusion. The recipient in this case had previously been used as a donor and it is possible that this dog was immunized by cells which entered its circulation to some extent while the artery to vein anastomosis was intact. The sequelae of incompatible transfusions in dogs were similar to those observed by Ottenberg and Thalhim in cats. A finding of considerable interest was the appearance of many nucleated and polychromatophilic red blood cells, which in one case persisted in the recipient's circulation for five weeks. This change was attributed to the toxic effect of incompatible blood on the bone marrow.

Melnick, Burack and Cowgill and Melnick and Cowgill found iso-hemagglutinins and hemolysins in the serum of dogs after repeated injections of erythrocytes during the course of plasmapheresis experiments. The immune iso-antibodies reacted with red cells from about 50 per cent of the dogs available to these observers and the reactions did not appear to be related to sex or breed. In their experience the development of incompatibility was one-sided in that dogs designated by them as type "a" were capable of producing antibodies against cells from dogs of type "B", while "B" dogs did not produce antibodies when transfused with "a" cells. Salivation, vomiting, labored respirations, incontinence of urine and feces, prolonged clotting time and hemoglobinuria were observed in immunized "a" dogs during hemolytic reactions to the transfusion of "B" cells.

Holman, Mahoney and Whipple and Wright described similar reactions as complications of plasmapheresis, and Wright found antibodies in the sera of 3 recipient dogs which reacted with cells of 7 members of a group of 11 donor dogs. Hahn and Bale also encountered hemolytic reactions while measuring circulating red cell mass in dogs by transfusion of cells tagged with radioactive iron. They found, moreover, that all of the new isotopic cells, if incompatible, usually disappeared from the circulation of the recipient dog within ten minutes after transfusion. Miller, Robscheit-Robbins and Whipple observed hemolysis of recipient dogs' cells following transfusions of plasma from a dog that might have been immunized by previous injections of dog blood.

Methods

Dog iso-antibodies were titrated by mixing equal volumes (usually 0.1 ml.) of serial two-fold dilutions of serum with 5 per cent suspensions of dog cells in fresh, unheated autologous serum. Immune serum was inactivated by heating at 56 C. for thirty minutes and was routinely diluted with saline, since it was found that titers against cells suspended in unheated serum were invariably the same, regardless of whether the antiserum was diluted with saline or with normal dog serum. Titers were maximal when fresh normal dog serum was used either as a suspension medium for the cells or as a diluent for the antiserum, and were not further enhanced by employing normal serum both as a medium for suspending cells and as a diluent for the antiserum.

After standing fifteen minutes at room temperatures of 2.3-2.7 C. the tubes were centrifuged at 1000 RPM for one minute. The cells were then gently but thoroughly resuspended and examined over a well illuminated concave mirror. Titrations were expressed in terms of the final dilution of antiserum to agglutinate dog erythrocytes. Agglutinated cells were rapidly hemolyzed in tubes containing high concentrations of antibody and complement but in the last tubes of any given series the agglutinated cells seldom hemolyzed appreciably during the fifteen minute period. Nonspecific hemolysis was minimized by carrying out the titrations at room temperature rather than at 37 C. and by centrifuging the tubes after allowing them to stand for a relatively short period (fifteen minutes).

* The ability of certain dog antisera to agglutinate dog erythrocytes is enhanced by the presence of a heat-labile component of normal dog serum, as described in a separate report. This phenomenon has thus far been observed only in sera having so-called "anti-Do" or "canine anti-A" specificity.

† Only "Do" or "canine A" antibodies have thus far been found to act as hemolysins in the presence of complement. Other dog isoantibodies that have been encountered do not hemolyze cells specifically and do not fix complement.
Complement was measured by mixing serial two-fold dilutions of fresh dog serum in volumes of 0.3 ml. with 0.1 ml. volumes of sensitized sheep cells prepared by Wadsworth's method. The tubes were placed in a water bath maintained at 37 C., shaken at five minutes and examined for hemolysis at fifteen minutes. The 50 per cent end-point was then computed by the method of Heden which takes into account the degrees of hemolysis in the last four tubes showing reaction.

All transfused blood was drawn from normal donor dogs within one hour prior to the beginning of transfusion and was injected into one of the jugular veins of the unanesthetized recipient dogs at rates of 3 to 7 ml. per minute. A saturated solution of sodium citrate (1.0 ml. per 100 ml. of blood) was used as an anticoagulant in all but two transfusions, and in these two instances heparin was employed. Samples of blood from recipient dogs were drawn from the jugular veins with great care to minimize artificial hemolysis. It was found advantageous to coat the inner surfaces of syringes and needles with silicone in order to prevent coagulation during the withdrawal and delivery of large samples into multiple containers.

The concentration of hemoglobin in plasma was measured by the pyridine hemochromogen method of Flink and Watson, and bilirubin was quantitated by Ducci and Watson's modification of the method of Malloy and Evelyn. Osmotic fragility of erythrocytes, coagulation time of whole blood and prothrombin concentration were determined by procedures described elsewhere. Platelets were enumerated according to Wintrobe's description of the Rees-Ecker technic. Differential agglutination of dog erythrocytes (Ashby technic) was carried out by the method of Young, Platzer and Rafferty.

Reticulocytes were stained by mixing a small drop of oxalated blood on a glass cover slip with a large drop of 0.2 per cent suspension of brilliant cresyl blue in a 6 per cent solution of sodium chloride. The two drops were mixed for thirty seconds with a toothpick, after which time another cover slip was applied and smears were pulled, dried and counterstained with Wright's stain to make permanent preparations.

Blood used for enumeration of leukocytes, and for preparation of Wright's-stained smears on glass cover slips, was taken from a small incision in the marginal ear vein and was used without addition of anti-coagulant. Smears thus prepared were employed for differential leukocyte counts and were routinely examined for the presence or absence of spherocytosis and erythrophagocytosis. Both glass and plastic cover slips were used in making wet preparations of oxalated, defibrinated or heparinized venous blood to be examined for the presence or absence of spherocytosis, erythrophagocytosis and hemagglutination.

**Experimental Observations**

**Definition of Do-positive and Do-negative Dogs**

Our studies began with the demonstration of immune iso-hemagglutinins and hemolysins in the serum of a dog that had had a hemolytic reaction after a series of transfusions from several donors. Serum from this dog agglutinated and hemolyzed erythrocytes from about two-thirds of the dogs selected at random from the animal colony maintained by the University of Rochester School of Medicine and Dentistry.* Cells reacting with this serum, or subsequently with other dog sera having similar specificity, were tentatively labelled "Do-positive," while those that were neither agglutinated nor lysed were called "Do-negative."

Further serologic studies on more than 400 dogs indicate that, in addition to the Do factor, there are at least three other antigenic factors present in various combinations in dog erythrocytes. The antigenic structure of canine red cells has...
not yet been determined to our satisfaction but is now being explored more extensively and will be the subject of a later report. Our attention has until recently been devoted for the most part to the study of hemolytic transfusion reactions due to Do antibodies.

Iso-immunization of Dogs

The immunization programs in three typical experiments are illustrated in figure 1. The top graph shows that antibodies were first detected eleven days after a single large transfusion of Do-positive blood into a Do-negative dog that had not been previously transfused. Rapid disappearance of the donated cells at the time of antibody development was demonstrated with the Ashby technic by employing potent anti-Do serum. In the middle graph it can be seen that three small injections produced antibodies within eight days in a dog previously transfused with dog bloods of unknown type. The bottom graph shows that antibodies developed only after 10 injections over a period of thirty-five days in a relatively refractory dog that had not been previously transfused. Still more refractory dogs have recently been encountered. For example, one dog developed antibodies only after 17 injections had been given over a period of one hundred thirty days.

Characteristics of Dog Iso-antibodies

Do iso-antibodies have been found to fix complement both in vivo and in vitro and it has been repeatedly observed that in the presence of complement, aggluti-
nated Do-positive cells are subsequently hemolyzed in vitro at rates depending upon the amounts of antibody and complement present. The Do and Rh systems in the dog and human species respectively appear to have a number of features in common. An important difference, however, is that Do-antibodies hemolyze Do-positive cells relatively quickly in the presence of complement while Rh antibodies hemolyze Rh-positive human cells very slowly if at all. Under certain conditions Do-antibodies behave like incomplete Rh antibodies in that their attachment to erythrocytes can be demonstrated by developing tests employing anti-dog-serum rabbit serum and by the agglutination of sensitized cells when suspended in normal dog serum. Characteristics of dog iso-antibodies will be described in more detail in a separate report.\textsuperscript{13}

**Observations on Hemolytic Transfusion Reactions**

Serial observations have thus far been made during the course of twenty-three hemolytic reactions produced in 13 different recipient dogs by transfusion of incompatible whole dog blood or plasma. Prominent manifestations observed during the periods immediately following transfusion are recorded in Table 1 which, for purposes of the present discussion, requires no further comment.

**Table 1: Prominent Manifestations Observed during the Course of Twenty-three Hemolytic Transfusion Reactions Produced in 13 Different Recipient Dogs**

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Restlessness</td>
<td>Nearly 100%</td>
</tr>
<tr>
<td>Salivation</td>
<td></td>
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<tr>
<td>Vomiting</td>
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<tr>
<td>Incontinence</td>
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<tr>
<td>Fever</td>
<td>Variable</td>
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<tr>
<td>Shock</td>
<td></td>
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<tr>
<td>Hives</td>
<td>3 dogs</td>
</tr>
<tr>
<td>Immediate death</td>
<td>1 dog</td>
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**Transfusion of Incompatible Whole Blood**

Figure 2 illustrates the manner in which the concentrations of hemoglobin and bilirubin rose and fell in the plasma of a Do-negative recipient after typical transfusions of Do-positive whole blood. When the recipient's anti-Do titer was 1:256 the peak of hemoglobinemia was nearly twice as high after a transfusion of only 100 ml. of Do-positive blood as it was after a transfusion of 200 ml. from the same donor into the same 15 kilogram recipient at an earlier date when the anti-Do titer was only 1:2. The hemoglobinemia curve was flatter when the recipient's titer was low and the volume of transfused blood was large. The less rapid destruction of donated cells in vivo under these circumstances was in keeping with the results of in vitro experiments. The concentration of hemoglobin in the plasma was nevertheless maximal within 10 minutes after this transfusion was completed, and it was maximal, or nearly so, at 5 to 10 minutes in most of the other experiments. Bilirubinemia, on the other hand, was maximal at 3 to 6 hours after each
transfusion of incompatible whole blood and in nearly every instance the concentration of bilirubin in the plasma had returned to the normal range within 24 hours.

Observations made before and after another typical transfusion of incompatible whole blood are recorded in figure 3. In this experiment, the donated corpuscles were tagged with radioactive iron* and it was possible to show that these cells completely disappeared from the recipient's circulation within the first hour after the transfusion was completed. In fact, 84 per cent of the donated erythrocytes disappeared within 10 minutes after completion of the transfusion, or within 30 minutes after its start. In four other experiments employing tagged cells, nearly all of the donated erythrocytes disappeared within 30 to 90 minutes after com-

* Drs. James A. Bush, John W. Hayden and Henry Tesluk assisted with the measurements of radioactivity, which were made by a modification of the donor cell dilution method of determining red cell volume.25
by using the Ashby technic after this transfusion and in six other similar experiments. In no case could agglutinable Do-positive cells be demonstrated after transfusion by mixing potent anti-Do serum with samples of recipient's blood. When the Ashby method was applied to the Do-anti-Do system after transfusion of compatible cells, on the other hand, donated Do-negative corpuscles were shown to survive for at least three months in the circulation of a Do-positive dog. This observation on the life span of canine erythrocytes is in accord with estimates made by other methods.

The amount of complement present in the circulation of the recipient dog declined abruptly during this transfusion of incompatible whole blood. In each of 10

![Graph](image-url)

**Fig. 3.—Sequelae of Typical Transfusion of Do-positive Whole Blood into Immunized Do-negative Recipient (Weight 15 Kg.).**

other similar experiments the decline was equally precipitous and after large transfusions, complement was barely detectable for about five hours. Post-transfusion specimens of serum were not anticomplementary, despite their high content of free oxyhemoglobin. At twenty-four hours and for several days thereafter, the titer of complement was frequently higher than before transfusion. The fall and subsequent rise in antibody titer noted after this transfusion were observed in some of the other experiments but with much less regularity than the changes in concentration of complement.

Fluctuations in total and differential nucleated cell counts after the typical transfusion just referred to are recorded in figure 4. The transient leukopenia, followed by leukocytosis, shift to the left and a shower of nucleated red cells, was observed after nearly all injections of incompatible whole blood. Erythrophago-
FIG. 4.—Fluctuations in Total and Differential Counts of Nucleated Cells in Circulation of Immunized Do-negative Recipient after Same Transfusion Plotted in Fig. 3.

FIG. 5.—Erythrophagocytes in Wright’s Stained Smear of Venous Blood of Recipient Dog Five Minutes after Transfusion of Incompatible Whole Blood. 1000 X. Although two macrophages containing red cells are seen in this photomicrograph, it was necessary to search many fields before finding such cells.
cytosis (fig. 5) was observed to a slight extent in smears of venous blood prepared during the first few minutes after such transfusions, but it was always necessary to search many microscopic fields before finding macrophages containing red cells. Wet preparations proved to be less satisfactory than fixed smears for detection of erythrophagocytosis. In none of the wet preparations of venous blood from recipient dogs was hemagglutination (suggesting intravascular agglutination) observed. Platelets became slightly less numerous for a few hours after injections of whole blood, and transient increases in coagulation time and decreases in prothrombin concentration* were observed in some instances.

Electrophoretic studies* were carried out on samples of plasma taken before transfusion, and at 30 minutes, 4 hours and 23 hours after a transfusion of 60 ml. of incompatible whole blood. The only significant change in the patterns was the appearance at 30 minutes of a large peak with a mobility between that of fibrinogen and beta globulin. The area of the peak corresponded with the concentration of hemoglobin in the plasma as determined by the pyridine hemochromogen method. Light transmitted through the cell in the region of this peak showed the absorption bands characteristic of oxyhemoglobin. At 4 hours the height and area of the peak had slightly diminished and at 23 hours the peak had almost disappeared. It is worthy of note that at 30 minutes and at 4 hours the hemoglobin migrated with an abnormally low mobility, but at 23 hours the mobility of hemoglobin had returned to normal.

Nearly all post-transfusion specimens of plasma were examined with a hand spectroscope in an effort to detect the presence of methemoglobin or methemalbumin. The absorption bands were invariably those of oxyhemoglobin; absorption in the red portion of the spectrum was not observed.

The concentrations of sodium and potassium in the serum were not significantly increased after transfusions of incompatible whole blood.* These negative findings are of interest in view of the relatively high content of sodium and low content of potassium in dog erythrocytes as compared with human red cells.25 Muirhead et al.,26 on the other hand, have reported high concentrations of potassium in the serum of human recipients following transfusions of incompatible human cells.

Transfusion of Incompatible Plasma

When Do-positive dogs were transfused with plasma from immunized Do-negative dogs the course of events was distinctly different from that seen after administration of incompatible whole blood. It is evident in figure 6 that after transfusion of 45 ml. of plasma with an anti-Do titer of 1:256, the concentration of hemoglobin in the plasma of the 16 kilogram Do-positive recipient did not reach its peak until the fifth hour. Hemoglobinemia persisted for more than 72 hours and hyperbilirubinemia for more than 24 hours. In order to sustain this dog's life it was necessary to give 260 ml. of compatible Do-negative whole blood 5 hours after injection of the incompatible plasma. Despite this large transfusion, the recipient dog's hematocrit gradually fell to 22 per cent on the ninth day, after which time

* Determinations of prothrombin concentration were made by Dr. Ralph F. Jacox, electrophoretic studies by Dr. Eric Alling and measurements of serum sodium and potassium by Dr. Jacob W. Holler.
the hematocrit began to rise due to the formation of new cells. The peak of the reticulocyte response was reached on the thirteenth post-transfusion day.

It is of interest that there was only a moderate decrease in the titer of complement.
during the first five hours after this transfusion of plasma and that at no time could the donated Do-antibodies be demonstrated in the recipient dog's serum. The osmotic fragility of the recipient dog's erythrocytes, as observed over a period of four weeks after transfusion of incompatible plasma, is plotted laterally in figure 7. Spherocytosis (fig. 8) and increased fragility were evident for twenty days, and the period of marked increase in fragility corresponded well with the nine day period of falling hematocrit shown in figure 6. These findings were similar to those reported by Banti,29 Dameshek and Schwartz30 and Tigertt and Duncan31 who injected dogs and guinea pigs with immune hetero-antibodies produced in other species.

FIG. 8.—SPHEROCYTES IN SMEAR OF VENOUS BLOOD OF DO-POSITIVE RECIPIENT SEVEN DAYS AFTER TRANSFUSION OF ANTI-DO PLASMA. 1500 X.

**Discussion**

The prolonged destruction of recipient dogs' Do-positive cells after injection of incompatible plasma is in striking contrast to the very rapid elimination of donated Do-positive corpuscles after transfusion to immunized Do-negative recipients. In the human species, recipients' cells are likewise known to be destroyed over long periods of time after transfusions of incompatible plasma or of blood from dangerous universal donors,32–34 while incompatible donated cells often disappear with relative rapidity.35–36 In neither species, however, is it entirely clear how the various destructive mechanisms operate under these circumstances.
With the evidence at hand it seems likely that the very rapid elimination of donated Do-positive cells is due in large measure to intravascular hemolysis, both by the direct action of complement on sensitized cells and by the traumatic effect of circulation on injured and agglutinated cells. Intravascular erythrophagocytosis probably plays a very minor role.

The concentration of hemoglobin in recipient dogs' plasma is usually maximal, or nearly so, within five to ten minutes after incompatible cells are injected, but the peak may not be reached until three to five hours have elapsed. Review of the experiments thus far completed shows that the 'maximal plasma hemoglobin mass,' calculated on the basis of highest plasma hemoglobin concentration and estimated blood volume, is in each case equivalent to approximately 50 to 75 per cent of the hemoglobin contained in the transfused incompatible cells. In estimating the total amount of hemoglobin liberated intravascularly, however, one must also take into account (a) hemoglobin excreted in the urine or taken up by renal tubules or by other tissues prior to the moment at which maximal plasma hemoglobin concentration is reached, and (b) hemoglobin liberated intravascularly after the concentration in the plasma reaches its peak.

Data thus far obtained therefore indicate that well over 50 to 75 per cent of the cells that rapidly disappear from the recipient's circulation are destroyed intravascularly and that a relatively small proportion of the cells may be sequestered and destroyed extravascularly by the reticulo-endothelial system. This conjecture is based upon the assumption that hemoglobinemia is the result of intravascular hemolysis and that hemoglobin liberated from erythrocytes by reticulo-endothelial cells is converted to bilirubin before being released into the blood stream. In any event, when anti-Do plasma is transfused, the relative importance of the several destructive mechanisms may be quite different from that encountered after injection of incompatible cells.

Experiments in progress should demonstrate more precisely how dog erythrocytes are destroyed in vivo under a variety of conditions simulating those encountered clinically.

**Summary**

1. Dogs injected intravenously with dog erythrocytes containing one or more antigenic factors lacking in their own red cells developed iso-hemagglutinins and hemolysins exhibiting characteristics of immune antibodies.

2. Transfusions of incompatible whole dog blood and plasma were carried out under controlled conditions. Pretransfusion observations were made and followed by closely spaced post-transfusion measurements of serologic and hematologic alterations.

3. The rate of destruction of incompatible donated corpuscles was determined by tagging the cells with radioactive iron and also by employing the technique of differential agglutination of erythrocytes. It was thereby shown that all of the

* Because of technical difficulties encountered in measuring mechanical fragility of dog erythrocytes, this aspect of the problem will be dealt with in a separate communication.
incompatible donated cells disappeared from the recipient's circulation within the first thirty to ninety minutes following transfusion. The probable mechanisms and relative importance of intra- and extravascular destruction of erythrocytes are briefly discussed.

4. Destruction of recipient dogs' corpuscles by donated immune plasma was relatively slow, and spherocytosis and increased osmotic fragility of the recipients' cells were evident for periods as long as twenty days. These observations are compared with those made in human beings after transfusions of plasma and of blood from dangerous universal donors.

5. The titer of complement in the sera of recipient dogs was sharply reduced for at least five hours after all transfusions of incompatible whole blood, but iso-agglutinin titers were less regularly reduced after such transfusions.

6. Other notations of interest included estimates of the concentrations of serum bilirubin, sodium and potassium, determinations of clotting time, prothrombin concentration, and observations on red cell morphology, intravascular erythrophagocytosis, and shifts in distribution of leukocytes and in the electrophoretic patterns of plasma.

CONCLUSION

The transfusion experiments thus far completed with dog blood are considered only exploratory. They are sufficient nevertheless to justify the conclusion that the iso-immune systems in the dog may be used to advantage in quantitative studies on certain hemolytic phenomena that cannot be satisfactorily investigated in human beings.

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