Some Immunohematologic Results of Large Transfusions of Group O Blood in Recipients of Other Blood Groups

A Study of Battle Casualties in Korea


Because group O red cells contain no A or B antigens they may be transfused into anyone without precipitating a reaction in the ABO blood group system (excepting, of course, the very rare persons with anti-O or anti-H). Although the group O cells are innocuous the use of so-called universal donor blood in patients of groups A, B, or AB involves an incompatibility "on the minor side," since the plasma of the donor contains antibodies against the red cells of the recipient. Occasionally a dangerous universal donor is encountered whose plasma contains antibodies of a nature and of such high titer that transfusion into A or AB patients may cause a severe hemolytic reaction. With low titer group O blood, it is possible that the plasma of the recipient dilutes and neutralizes the foreign antibodies and prevents hemolysis.

Most of the knowledge of universal donor transfusions is based upon experience involving 1 or 2 pints of blood. What occurs when larger quantities of blood are used? If, for example, 20 pints of O blood were given to a subject of group A, B, or AB, would the accumulation of isoantibodies finally become pathogenic and destroy the recipient's native red cells? Would the patient's blood become temporarily altered to group O? If it were, would the transfusion of blood of the patient's hereditary group produce an incompatible reaction? An opportunity was recently afforded to study the effects of such transfusions in Korea. Only group O Rh-positive blood was shipped to the combat zone in Korea and this blood was given without preliminary cross matching to all casualties irrespective of their blood group. Enormous transfusions were sometimes used. In severely wounded men 10 or 20 or even 30 pints of blood might be given within a few hours. All of the blood transfused had been previously screened for the presence of high titer isoagglutinins to identify the dangerous universal donors. For this purpose, the screen appears to have been adequate. Thus, in the year 1952 over sixty thousand transfusions were given in Korea, and during this period only four patients were admitted to the Renal Insufficiency Center with a history of post-transfusion hemoglobinuria. Each of the four had been given blood that was procured locally in Korea.
IMMUNOHEMATOLOGIC RESULTS OF GROUP O BLOOD TRANSFUSIONS

The present study was undertaken to learn if less severe reactions occur on the basis of incompatibility on the minor side, and to learn if such reactions contribute anything to the development of acute renal failure in the severely wounded.

MATERIALS AND METHODS

1. General Conditions

The study was carried out in the laboratory of the Surgical Research Team of the U. S. Army in Korea during the winter of 1952-1953. The laboratory was attached to the 46th Army Surgical Hospital. The patients were young soldiers who were received by ambulance or helicopter usually within one to three hours after they had been wounded. Transfusions of whole blood or plasma substitutes had often been begun at aid stations before the patients reached the hospital. Transfusions were continued as needed throughout the period of resuscitation and surgery. In some patients as much as 37 pints of blood were used within a period of twelve hours. As much as 20 pints have been given within one hour. The blood shipped to Korea was collected in the United States or from United States troops in Japan. The blood was eight to ten days old when it was received at the hospital. Most of it was used before it was fifteen days old. It was discarded if it had not been used when it was twenty-one days old.

2. High Titer Screening

All of the blood was group O, Rh positive and was used without cross matching, irrespective of the blood group of the recipient. Each bottle of blood had been tested for high titer isoagglutinins active against group A and B red cells. The serum was diluted 1:200 (Tokyo) or 1:256 (California). Equal volumes of a 2 per cent suspension of red cells and the diluted serum were mixed, and readings were made after incubating 10 minutes at room temperature. In California the test was read on a tile; in Tokyo it was read in test tubes. Where agglutination occurred the blood was called high titer and was intended to be given to group O recipients. Where there was no agglutination the blood was considered to be low titer and could be given to anybody. In California 45 per cent of the O blood was high titer, but only 15 per cent of that flown to Japan was high titer. In Tokyo 35 per cent of the blood collected was high titer.

3. Hematologic Methods

The technical work of the present study was performed by one of us (WHC). Red cell counts were done by the method of Dacie in which 20 cu. mm. of whole blood were diluted in 5 ml. of normal saline (1:250). The same 5 ml. and 20 cu. mm. pipets were used for every determination. After thorough mixing the cells were counted in a standard hemacytometer. Differential agglutination (the Ashby technique) in A, B, and AB recipients was carried out by pipeting 0.3 ml. of the 1:250 red cell suspension into a small test tube that contained an estimated 5 mg. of dried anti-A or anti-B typing serum (Michael Reese). This caused agglutination of the patient's native red cells but did not agglutinate the transfused group O cells. After 30 minutes the tube was centrifuged at 400 rpm for 1 minute and the unagglutinated red cells were resuspended and counted in a hemacytometer. Baseline inagglutinable counts were not always obtained because transfusion was often begun before arrival of the patient at the hospital. When baselines were done, the count varied between 7000 and 15,000 per cu. mm. In making the total red cell counts and Ashby counts at least 1500 cells were counted; where the two values were almost equal, at least 3000 cells were counted. The Ashby counts were of value to establish the ratio of donor (group O) red cells to native (A, B, or AB) red cells after transfusion. Serial Ashby counts revealed alterations of the ratio. An increase in the proportion of agglutinable native red cells suggested a loss of transfused cells. An increase of inagglutinable group O red cells suggested a loss of native cells.
normal conditions transfused cells are replaced by newly generated native cells at the rate of 0.85 per cent per day. Reticulocyte counts were done by the method of Brecher using new methylene blue; normal counts were 0.4 to 1.0 per cent of total red cells. Plasma hemoglobin was performed by a method described elsewhere, modified by using benzidine rather than benzidine dihydrochloride as the indicator. This was in an aqueous solution rather than alcoholic, and the values obtained are probably about 30 per cent low. The normal plasma hemoglobin was less than 5 mg per 100 ml.

4. Immunologic Methods

The tests for antibodies were performed on serum or lightly heparinized plasma. There was no difference in results when serum and plasma were obtained and tested simultaneously. The blood was placed in a tube and allowed to clot or sediment at 37°C for 2 hours. There was no evidence of hemolysis in vitro in these tubes. The plasma was centrifuged and a quantitative test for plasma hemoglobin was done. In testing for agglutinins the serum or plasma was doubly diluted with saline and an equal volume of a 2 per cent suspension of red cells was added. When two or more types of red cells were used the suspensions were matched to assure the same concentration of cells. A1 cells were always obtained from the same source; no study was made with A2 red cells; B cells were obtained from two sources; O cells were obtained from numerous sources including stored blood. The serum-cell suspensions were refrigerated for 2 hours at 3 to 5°C. The tubes were then centrifuged at 400 rpm for 1 minute, returned to the ice bath for 5 minutes after which they were shaken and read. Agglutination was rated from trace to 4 plus. A trace was the least agglutination that could be detected grossly when compared with an unagglutinated control. At 4 plus all cells were clumped in one or two large masses. After refrigeration the tubes were placed in warm water for 20 minutes and the process of centrifugation and reading was repeated. At 37°C the first tube was examined for evidence of hemolysis. There was none but the addition of the small amount of typing serum that contained isohemolysin would cause the cells to lyse indicating adequate complement activity. Agglutination of group O cells was interpreted to be due to nonspecific cold agglutinins. Agglutination of A and B cells was compared with that of O cells. If it was no greater, it was called nonspecific. Where anti-A or anti-B titer exceeded the nonspecific agglutination it was regarded as due to a specific isoagglutinin. The titer was taken as the difference between the specific and the nonspecific agglutination. The blood of patients whose plasma contains isoagglutinins was matched against fifteen to twenty bloods each of groups A1 and O to confirm the specificity of the agglutinin against A. The direct Coombs test was performed according to the directions of Dacie, using an anti-human-globulin rabbit serum prepared at the Immunology Division, Army Medical Service Graduate School.

Saliva was tested for the presence of A or B substance as follows: The saliva in a test tube was placed in boiling water for 20 minutes. It was then centrifuged and the clear supernatant material was diluted with saline 1:4 and 1:8. Higher dilutions were sometimes made. One-tenth ml. of this material was added to 0.1 ml. of anti-A or anti-B typing serum and allowed to stand at room temperature for 30 minutes. Then 0.1 ml. of a 2 per cent suspension of A or B red cells was added. After 30 minutes the tubes were centrifuged and examined for agglutination. A control tube contained no saliva and another control contained saliva of a known secretor. In the first control there was 4 plus agglutination and the same was found in the unknown when they were nonsecretors. In the case of secretors there was no agglutination, the testing serum having been neutralized by the blood group substance in the saliva. One or 2 plus agglutination was not common and a patient with such saliva was classified as a weak secretor. The concentration of A and B substance in plasma or serum was tested in the same manner. The typing serum used for these tests was obtained from the Michael Reese Research Foundation. Diluted with saline the typing serum produced a trace of agglutination at 1:100. The titer was not remarkably affected by cold. The serum contained isohemolysin as well as isoagglutinin.
IMMUNOHEMATOLOGIC RESULTS OF GROUP O BLOOD TRANSFUSIONS

TABLE 1.—FOREIGN ISOAGGLUTININS AFTER TRANSFUSIONS OF LOW TITER UNIVERSAL DONOR BLOOD

<table>
<thead>
<tr>
<th>Patient</th>
<th>ABO group</th>
<th>Secretor</th>
<th>Volume of transfusion (pints)</th>
<th>Isoagglutinin titer (5 C.)</th>
<th>Disappearance time of isoagglutinins from recipient’s blood</th>
<th>Direct Coombs test</th>
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<tr>
<td>A</td>
<td>A</td>
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<td>9</td>
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</tr>
<tr>
<td>B</td>
<td>A</td>
<td>No</td>
<td>20</td>
<td>1:64</td>
<td>10 days</td>
<td>Neg</td>
</tr>
<tr>
<td>C</td>
<td>A</td>
<td>No</td>
<td>9</td>
<td>0</td>
<td>—</td>
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</tr>
<tr>
<td>D</td>
<td>AB</td>
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<td>15</td>
<td>Anti-A 1:128</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>B yes</td>
<td></td>
<td>Anti-B 1:2</td>
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<tr>
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<td>A</td>
<td>No</td>
<td>8</td>
<td>0</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>B</td>
<td>?</td>
<td>37</td>
<td>1:8</td>
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<td>Neg</td>
</tr>
<tr>
<td>G</td>
<td>A</td>
<td>Weak</td>
<td>8</td>
<td>1:32</td>
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<td></td>
</tr>
<tr>
<td>H</td>
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<tr>
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<tr>
<td>M</td>
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<td>9</td>
<td>1:4</td>
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</tr>
<tr>
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<td>2</td>
<td>1:1</td>
<td>1 day</td>
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</tr>
<tr>
<td>O</td>
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<td>0</td>
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</tr>
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<td>P</td>
<td>A</td>
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<td>6</td>
<td>1:8</td>
<td>5 days</td>
<td></td>
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<td>6</td>
<td>0</td>
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<td>R</td>
<td>B</td>
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<td>0</td>
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<tr>
<td>U</td>
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<td>4</td>
<td>0</td>
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<td>3</td>
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<tr>
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<td>22</td>
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<td>?</td>
<td>22</td>
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<td>Died</td>
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<tr>
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<td>A</td>
<td>Yes</td>
<td>3</td>
<td>0</td>
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</table>

RESULTS

The plasma of twenty-five patients was examined for foreign antibodies immediately, and in most cases repeatedly, after receiving transfusions of group O blood. The results are shown in tables 1 and 2. In ten of these patients there were no demonstrable foreign isoagglutinins after receiving transfusions ranging in volume from 2 to 14 pints. In the rest of the patients foreign antibodies were found immediately after the transfusion. No follow-up was possible in three cases. In five cases (including case D's anti-B) the foreign antibodies were not present after one day. In five cases (including D's anti-A) the antibodies persisted for three days or longer.

The transfused agglutinins were more easily demonstrable in the cold. The agglutinations tended to fall apart as the red cell suspensions were warmed, although when the titer of cold agglutination was high some clumping of the cells persisted at 37 C. (table 3). Whole blood containing high titer of transfused agglutinins was incubated at 37 C. for 4 hours without hemolysis. Suspensions of test red cells in the serum of these patients incubated at 37 C. also gave no
evidence of hemolytic activity. Direct Coombs tests on such blood was negative, indicating an absence of incomplete antibodies on the remaining native red cells (table 1).

When patients of blood groups A and AB were transfused with moderate or large amounts of group O blood there was evidence of selective destruction of the patients' red cells (table 2). In ten of fourteen cases on whom serial Ashby counts were performed, the proportion of donor cells increased for several days after the transfusion. Not all of these patients are shown in table 2; data on the others have been published in another report. Ebert and Emerson reported the same phenomenon in several casualties of World War II who received large transfusions. Selective hemolysis of native red cells occurred in patients whose sera contained transfused isoagglutinins (B, D in table 2) and also in those without foreign antibodies demonstrable in vitro (A, L, X). This manifested itself by an alteration of proportions of native and donor red cells. After the transfusion was concluded the proportion of donor cells continued to increase while the native cells decreased. In two of these patients (D, L) the prolonged slight elevation of the plasma hemoglobin gave evidence of low grade intravascular hemolysis. The destruction of the native red cells was not accompanied by a clinical reaction as has been described with transfusion of blood from dangerous universal donors. The patients gave no outward sign of hemolytic disease.

Red cell destruction due to other mechanisms was also taking place. During the twenty-four hours after transfusion of stored blood there was a modest loss of nonviable donor red cells that was often masked by the loss of recipient red cells (table 2). In uremia associated with acute post-traumatic renal insufficiency hemolysis was often exceptionally rapid, affecting donor and recipient cells alike (case X table 2). In the severely wounded there was evidence of hemolytic disease that destroyed donor and recipient red cells indiscriminately (B, D table 2). This occurred in the early days of convalescence. The patients were usually evacuated from the surgical hospital within a week or two. Five of the patients whom we studied in Korea were transferred to Walter Reed Army Hospital where the Ashby counts were continued. It was found that the blood given at the time of wounding and initial resuscitation ultimately survived normally for one hundred to one hundred and twenty days, excepting in one man who was group A, Rh negative. In him the group O, Rh-positive cells survived eighty days. This is only a moderate reduction of survival time, although it is definitely abnormal. The patient did not have any evidence demonstrable in vitro of antibodies against Rh or other blood groups. This patient later developed hepatitis. A survey is under way to determine among the wounded the rate of sensitization against Rh and other blood group antigens as a result of transfusion with universal donor blood given without typing for Rh and other blood group antigens.

Massive transfusion and selective elimination of recipient red cells produced a replacement of red cells in two patients that approximated 100 per cent (B, L). In the Ashby preparations the agglutinated cells were so few in number and the agglutinations were so small that it was possible actually to count the agglutinated red cells. They comprised less than 1 per cent of the total. When re-
### Table 2—Response to Large Transfusions of Group O Blood

<table>
<thead>
<tr>
<th>Patient</th>
<th>ABO blood group</th>
<th>Date</th>
<th>Cumulative total blood received (pints)</th>
<th>RBC (10^12)</th>
<th>Proportion of donor RBC (%)</th>
<th>Plasma hemoglobin (mg/100 ml)</th>
<th>Foreign isoagglutination (5°C)</th>
<th>Reticulocytes (%)</th>
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<td>A</td>
<td>A</td>
<td>14 Nov</td>
<td>9</td>
<td>6.66</td>
<td>4.27</td>
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<td>62</td>
<td>4.8</td>
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<tr>
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ticulocyte strain was added to the Ashby suspension and the cells were then examined under high magnification it was seen that practically all of the agglutinated red cells were reticulocytes. None of the unagglutinated cells contained reticulum. The reticulocyte count became elevated in patients who developed anemia during convalescence (table 2).

In three patients the secretor phenomenon was variable. When such a patient's saliva was tested just after resuscitation it did not completely inactivate the testing antiserum, although it did reduce the titer of the serum. When another specimen of the patient's saliva was tested several days later the amount of A substance had apparently increased (table 4). This sort of patient was referred to as a "weak secretor." Where transfused isoantibodies persisted more than a day the patient was found to be a nonsecretor or weak secretor of the blood group substance in question (table 1). Patient D, of group AB, was a secretor of B substance and a nonsecretor of A. He quickly eliminated anti-B agglutinins, but anti-A persisted in his plasma for nine days.

### Table 2.—Continued

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<th>Patient</th>
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<th>Cumulative total blood received (pints)</th>
<th>Total RBC (10⁹)</th>
<th>Inagglutinable RBC (10⁹)</th>
<th>Proportion of donor RBC (mg./100 ml)</th>
<th>Plasma hemoglobin (1 C.)</th>
<th>Foreign isoagglutinin (1 C.)</th>
<th>Reticulocytes (1 C.)</th>
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The transfused blood was cold. This may have something to do with the tendency of the titer of cold antibody to be low after surgery.

Non-specific cold agglutinins active against group O red cells were noted at one time or another in most patients. The titer often seemed to be reduced after resuscitation and recovered during the period of convalescence. In only two patients did the titer exceed 1:16, which is considered to be the upper limit of normal for non-specific cold agglutinins (table 5).

**DISCUSSION**

The transfusion of large quantities of low titer group O blood into patients of other groups did not produce an acute hemolytic reaction of the sort that has sometimes occurred with dangerous universal donors. However, it is clear from the evidence presented above that selective destruction of recipient red cells did occur, but the reaction was not abrupt or shocking. The selective destruction of recipient red cells was probably due to transfused isoantibodies.
In several patients it was possible to demonstrate transfused isoagglutinins during the time that hemolysis was taking place (table 2, patient D). In other patients there were no isoagglutinins in the plasma, yet hemolysis of the patients' red cells occurred for several days after transfusion had been given. Patient L is an example. Patient X showed a less obvious reaction. There was no alteration of the proportion of donor to recipient red cells for several days. Most of the red cells in his blood were donor cells; only 5 to 8 per cent were his own. His reticulocyte count was slightly elevated, but all of the reticulocytes were native red cells. On January 9 for example 2.5 per cent of the total red cells were reticulocytes and 5 per cent of the total were native red cells. Thus 50 per cent of the native red cells were reticulocytes. This suggested that the native red cells were being turned over at a very rapid rate, which implies selective destruction. In both L and X little or no isoantibody could be demonstrated against red cells of the patients' blood group, and the direct Coombs test was negative immediately after transfusion. This is reminiscent of hemolytic disease of the newborn when it occurs on the basis of an anti-A incompatibility. Transfused group A red cells are selectively eliminated from the infant's circulation, but the Coombs test is negative. Apparently there are antibodies which we are incapable of detecting except by their pathogenic activity in vivo.

Where isoagglutinins against the patient's red cells persisted in his plasma it was, of course, impossible to cross match the patient's blood with red cells of his own hereditary group. This has been a problem of some clinical importance in Korea. Patients who became anemic during the early days of their convalescence were often transfused with fresh blood obtained from troops in the vicinity. On several occasions the use of group-specific blood has been associated with disastrous transfusion reactions. It is suggested that the transfused isoantibodies persisting in the patient's plasma may react against the group-specific red cells when they are injected into the patient. Ervin and Young have encountered transfusion reactions in patients of group A2 who had been transfused, first with O blood and later with A1 blood. The reaction occurred because the patient had no A1 antigen to neutralize the A1 isoantibodies in the O blood. These antibodies, therefore, remained free and they reacted with the A1 red cells at the second transfusion. This may have been the cause of the reactions that have happened uncommonly in Korea. Or they may have been due to the persistence of A1 antibodies in A1 patients following a heavy dose of transfused isoantibodies. As noted below the persistence of A1 antibodies did occur in A1 patients. Whether or not this was pathogenic was not submitted to test by transfusing the patient with blood of his hereditary group. It was felt that regardless of the mechanism of the transfusion reaction the procedure was not justified: patients who had received large transfusions of group O blood should not receive blood of another group before sufficient time had elapsed to allow the foreign isoantibodies to disappear. It was recommended that if transfusions were needed meanwhile the use of group O blood should be continued.

The reason for the persistence of isoagglutinins in some patients and not in others is not entirely clear. There are two sides to the matter: the dose of antibodies in the transfused plasma and the capacity of the recipient to remove or neutralize those antibodies. All of the plasma given to the patients in the present
study was of low titer, but the exact titer is not known. The expression low titer refers only to isoagglutinins active at room temperature. It does not refer to hemolytic or incomplete antibodies or to the sort that cause hemolysis in vivo without showing absorbed antibodies in vitro. The hemolysins and incomplete antibodies are of more pathogenic importance than the agglutinins. The agglutinin screen to identify high titer blood is effective because a high titer of pathogenic antibodies is usually associated with a high titer of isoagglutinins. However, this is not always the case. Group O blood may have a low titer of isoagglutinins and a high titer of isohemolysins or of incomplete antibodies or both. With the present screening procedures about 40 per cent of O blood is classified as high titer or potentially dangerous. It would be more economical if the proportion of high titer blood could be reduced. There exists a need for a general re-evaluation of the problem of the universal donor and an appraisal of the different types of isoantibodies in his serum. Such a survey is in progress. Meanwhile, we are unable to define the dose of antibodies given the battle casualties beyond saying that all of the blood was of low agglutinin titer. In several of the men the agglutinins persisted and were demonstrable in the plasma even though they represented an incompatibility, since not all of the native red cells had been eliminated. Other men who receive a transfusion of similar size quickly cleared the agglutinins from the circulating plasma (table 1). If we assume that comparable doses of agglutinin were given, it must follow that the patients differed from one another in their ability to dispose of the antibodies. The specific ability to neutralize isoantibodies resides in the blood group substances A and B. These substances are present on the red cells and in the circulating plasma. In some people they are also present in other tissues and body fluids. These people are called secretors because of the group substances found in their saliva, gastric juice, etc. One might suspect that the secretors, having A or B substance in more tissues than the nonsecretors, would be better able to neutralize transfused anti-A and anti-B. To some extent this appeared to be the case. The two patients who had a persistent high titer of foreign cold agglutinin were both nonsecretors (table 1). Persistence of the agglutinin was also found in three weak secretors, patients in whom the concentration of A substance in the saliva was found to be considerably reduced after transfusion (table 4). The persistence of anti-A agglutinin in an A subject was not an example of A1 agglutinins in an A2 subject. The native A cells in his blood formed hard agglutinations when suspended in his own cold serum. Furthermore, it was evident that the native red cells were selectively destroyed in vivo by the anti-A antibodies.

The failure of anti-B agglutinins to persist for long in any of the B or AB patients may have been fortuitous. There were few of them. B antibodies appear to be less troublesome than A. Perhaps they are more easily disposed of. The reactions that follow the transfusion of high titer anti-B plasma are less severe than those encountered with the same titer, or less, of anti-A. People appear to differ in their ability to cope with the transfused incompatible isoantibodies. Perhaps the blood of the “dangerous universal donors” is especially dangerous to those whose protective shield of soluble A substance is a weak one.

The nature of the transfused antibodies that persisted in the plasma of these patients was examined. No hemolysins were detected. This is not surprising
because, as Ervin, Christian, and Young have noted, the isohemolysin is the form of isoantibody most readily neutralized by the soluble blood group substances. Also, the direct Coombs test was negative in our patients. This is in agreement with the observations on hemolytic disease of the newborn when it is due to anti-A activity against the red cells of the infant; the Coombs test may be negative but group A red cells are rapidly destroyed in vivo. In the present series the isoagglutinins were the only form of foreign antibody that could be demonstrated in the plasma of the recipients. Anti-A and B agglutination is known to be more effective in the cold. The isoagglutinins of the ABO system exist as both warm and cold agglutinins. The isoantibodies transfused into these patients were of all varieties: warm and cold agglutinins, hemolysins, incomplete antibodies, and others that caused hemolysis in vivo but could not be demonstrated in vitro. This last type of antibody tended to persist and cause selective destruction of the native red cells. Incomplete antibodies and classical hemolysins disappeared quickly. Warm agglutinins were demonstrable in patients whose serum showed a high titer of foreign cold agglutinins (table 3). As the titer declined after the transfusion it was possible to demonstrate agglutination only in the cold.

The pathogenicity of isoagglutinin anti-A is open to question. Where reactions to the plasma of dangerous universal donors have occurred, it seemed that isohemolysins and incomplete antibodies were the important ones. Patient B (table 2) provides similar evidence. Almost 100 per cent of his red cells had been replaced by group O donor cells during his original transfusion. Because of anemia his bone marrow produced red cells at an increased rate and by November 20, 10 per cent of the total red cells were his own. In spite of anti-A agglutinins present at a titer of 1:16, these group A red cells were able to exist in his circulation. (In undiluted serum the agglutination of A cells, including the 10 per cent of the patient's own red cells, was 4 plus.) On that day, because of anemia, the patient was given 2 pints of fresh, group O blood locally procured. The 10 per cent of native group A red cells immediately disappeared from his blood stream. The titer of cold agglutinins increased by 2 tubes, but it is possible that other more destructive anti-A antibodies contributed to the loss of native A red cells.

A selective loss of the recipient red cells was not the only process of red cell destruction in these patients. Three other hemolytic mechanisms were identified. One was the loss of nonviable red cells present in the bank blood. A second was the hemolytic disease that appeared in patients who developed uremia on the basis of acute post traumatic renal insufficiency. Patient X developed clinical uremia rather late in the course of his convalescence. The fall in red cell count of 500,000 during a twenty-four hour period January 11 to 12 was probably related to uremia (table 2). A third hemolytic process was observed in the most severely wounded whose wounds involved damage or destruction of large masses of tissue. Patient B for example had a bilateral traumatic amputation of the thighs. He was given 20 pints of blood during resuscitation and surgery. He was not in shock. On the basis of computed loss and measured blood volume we were unable to account for 8 pints of blood immediately after the operation. Subsequently, he became progressively anemic although very little blood oozed...
from the stumps of his thighs. We believe that a hemolytic disease was present in such patients, but the mechanism is not known. Donor and recipient cells were lost indiscriminately.

The etiology of post-traumatic renal insufficiency is obscure. It has been suggested that hemoglobin liberated during the massive transfusions might play a role. It will be seen in table 3 that the amounts of plasma hemoglobin encountered during and after such transfusions are not great and certainly not of the order of magnitude (800 to 2000 mg. per 100 ml.) shown to be pathogenic in shocked dogs. We were unable to correlate hemoglobinemia with the appearance of acute renal insufficiency. It is true that the two are associated in severe hemolytic transfusion reaction. In Korea all patients who developed acute renal insufficiency were evacuated to the Renal Insufficiency Center at the 11th Evacuation Hospital. In 1952 only four patients out of seventy-four admitted to that Center had a history or evidence of post-transfusion hemoglobinuria. Each of the four had been given group specific blood that was locally procured. In two cases there had apparently been an error of blood grouping. The other two had been given large transfusions of group O blood and were then switched to group specific blood. So far as we know there have been no hemoglobinuric transfusion reactions due to transfusions of low titer group O blood into recipients of other groups. During the present work of the Surgical Research Team in Korea, the minor side incompatibility has not been shown to be harmful. Nor was there any statistical evidence of renal injury by group O blood among the casualties of the Italian campaign in World War II. The incidence of hemoglobinuric nephrosis was not higher in men of blood group A than it was in group O where the minor side incompatibility did not exist.

**SUMMARY**

1. Following large transfusions of low titer group O blood into patients of group A, B, and AB it was not possible to demonstrate foreign isoagglutinins or incomplete antibodies in the serum of recipients. Cold isoagglutinins were frequently demonstrated immediately after the transfusion, but they usually disappeared rapidly. In several patients the titer of foreign anti-A isoagglutinin was quite high and the antibody persisted in the circulation for several days. It was suggested that the persistence of these agglutinins may have been possible because there was a relatively small amount of A substance in the body of the recipient. Where the transfused isoagglutinins persisted the patients were found to be nonsecretors or weak secretors of A substance in the saliva.

2. In most of these patients there was evidence of a selective destruction of recipient red cells after the transfusion of O blood. This was probably due to the activity of transfused isoantibodies in the plasma of the O blood. This hemolytic activity was observed where it was not possible to demonstrate the presence of foreign isoantibodies. It is suggested that there may exist forms of antibody that cannot be demonstrated by laboratory methods. These antibodies manifest themselves only by causing destruction of red cells in vivo.

3. Clinically the hemolytic disease on the basis of such transfused isoantibodies while causing destruction of native red cells did not threaten the lives or impede the recovery of these patients. No reactions were encountered and none were
heard of in Korea that might have been ascribed to a dangerous universal donor. The partition of group O blood into high titer and low titer on the basis of dilution of 1:200 to 1:256 has proved in practice to be safe.

4. The persistence of foreign antibodies after a large transfusion of group O blood may make it impossible to cross match the patient’s blood with blood of his hereditary group. Severe transfusion reactions have occurred when group specific blood has been given following large transfusions of group O blood. It has been recommended that after a large transfusion of group O blood has been given, group specific blood should not be used for at least two weeks.

**SUMMARIO IN INTERLINGUA**

1. Le cognoscentias previemente accumulate super transfusiones de sanguine ab donatores universal esseva bassate super experientias con parve quantitates de sanguine. Remaneva sin responsa objective le question de si o non le effectos observate esserea le mesme si in loco de un litro o minus de sanguine, quantitates de dece o mesmo dece-cinque litros esses transfundite. Le frequentemente enorme transfusiones administrate a vulneratos de guerra in Corea promitteva clarificar alicunes de ille questiones e forma le base del presente studio.

2. Post voluminose transfusiones de sanguine a titro basse del gruppo O a in patientes del gruppos A, B, e AB, il non esseva possibile demonstrar le presentia de extranee isohemolysinas o incomplete anticorpores in le sero del recipientes. Frigide isoagglutininas esseva frequentemente demonstrate immediatemente post le transfusion, sed in general illos dispareva rapidemente. In plure patientes le titro de extranee isoagglutininas anti-A esseva alte e le anticorpores persisteva in le circulation durante plure dies. Il pare plausibile supponer que le persistentia de iste agglutininas esseva rendite possibile per un relativamente basse contento de substantia A in le corpore del recipient. In le casos ubi le transfundite isoagglutininas persisteva, il esseva constatabile que le patientes esseva non-secretores o leve secretores de substantia A in lor saliva.

3. In le majoritate de iste patientes il se trovava indicationes de un selective destruction del erythrocytas del recipiente post le transfusion de sanguine O. Isto resultava probabilmente del activitat.de transfundite isoanticorpores in le plasma del sanguine O. Iste activit.ate hemolytic esseva observate etiam in casos ubi il non esseva possibile demonstrar le presentia de extranee isoeant. corpores, lo que suggere le supposition que typos de anticorpore existe que non pote esser constatatate per medio del methodos nunc disponibile. Iste anticorpores se manifesta solo per causar le destruction de erythrocytas.

4. Del puncto de vista clinic il es a remarcar que le hemolyse resultant.de tal transfundite isoanticorpores (ben que destruente erythrocytas autochthone) non menaciava le vita o impediva le restabilimento del patiente. Esseva ni observe ni reportate ulle reactiones que poterea haber essite ascribite a un periculoose donator universal. Le distinction de sanguines O a alte e basse titro secundo le dilution 1:200 usque 1:256 se ha provate practicamente utile e sin risco.

5. Le persistentia de extranee anticorpores post un major transfusion de sanguine O es forsan apte a render impossibile le combination del sanguine del paciente con sanguine de su grupo hereditari. Serie reactiones ha essite observate...
IMMUNOHEMATOLOGIC RESULTS OF GROUP O BLOOD TRANSFUSIONS

in casos ubi sanguine a typo specific esseva administrate post major transfusiones de sanguine O. On deberea recommendar que post un major transfusion de sanguine O, nulle sanguine a typo specific sia usate durante al minus duo septimanas.

REFERENCES

Some Immunohematologic Results of Large Transfusions of Group O Blood in Recipients of Other Blood Groups: A Study of Battle Casualties in Korea

WILLIAM H. CROSBY, LT.COL. and JOSEPH H. AKEROYD, LT.COL.

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