Studies on the Survival of Incompatible Cells in Patients with Hypogammaglobulinemia

By Hugh Chaplin, Jr.

Patients with hypogammaglobulinemia are being recognized with increasing frequency as physicians become aware of the typical clinical syndrome they present and as confirmatory laboratory tests become more widely accessible. In an early review of the subject, Janeway and his co-workers pointed out the uniform absence of naturally occurring blood group isoagglutinins in the pediatric patients who constituted the principal reservoir of clinical material up to that time. In a more recent review, Young noted that "because of the absence of isohemagglutinins, all (of these patients) are presumably 'universal recipients.'"

The present report describes the in vivo survival of incompatible red cells in four adult patients diagnosed as having "agammaglobulinemia" on the basis of paper electrophoresis. All four patients exhibited an absence of isohemagglutinins on routine laboratory examination.

Materials and Methods

Patients. The four patients were studied during their hospitalization at the Barnes Hospital, St. Louis, Missouri.

Tests for Anti-A and Anti-B Isohemagglutinins

(a) Routine procedure. The routine test for isohemagglutinins as performed by the blood bank at Barnes Hospital employs the addition of one volume of the patient's serum to one volume of a 2% suspension of pooled fresh A or B cells in saline. The serum and cells are mixed, centrifuged immediately and examined macroscopically and microscopically for agglutination.

(b) More sensitive procedure. Two volumes of the patient's serum were added to one volume of a 1% suspension of fresh A or B cells in saline. The serum and cells were mixed and allowed to stand at room temperature (22-25°C.) for one hour. The mixtures were then centrifuged at 1000 R.P.M. for two minutes, the cells gently resuspended, and the contents of the tube examined macroscopically and microscopically for agglutination.

Tests for Isohemolysins. To one volume of the patient's serum was added one volume of fresh group 0 serum known not to contain isohemolysin activity, plus one volume of a 1% saline suspension of fresh A or B cells. After incubation at 37°C. for one hour, followed by gentle resuspension of the cells, the mixture was centrifuged at 1000 R.P.M. for two minutes and the supernatant fluid was examined grossly for hemolysis.

In Vivo Red Cell Survival Studies

(a) Chromium method. The method of Ebaugh and his associates was employed. The red cells from 10 ml. of ABO incompatible blood, freshly drawn into ACD preservative...
solution, were mixed with 75 μc. of Cr as sodium chromate. After one hour's incubation at room temperature, the red cells were washed two times in three volumes of cold saline, resuspended to 10 ml. volume, and injected immediately.

For the special study of the survival of a large volume of incompatible blood (case 3), a 5 ml. aliquot of washed tagged cells was well mixed with 450 ml. of whole ACD blood from the same donor immediately prior to its administration. The total amount of radioactivity in the transfused blood was determined from counts per ml. of an aliquot of the mixture, multiplied by the volume transfused (based on careful weighing of the blood container before and after the transfusion, corrected by 1.000 to allow for the higher specific gravity of the whole blood).

(b) Ashby method. The patient (case 3) was group O, M-positive. The donor's cells were group B NN. Inagglutinable counts were performed by Dacie and Mollison's modification of the Ashby method, employing a potent anti-M powdered globulin (Lederle) which yielded a "blank" count of <3000 cells per cu.mm. The red cell count of the transfused blood was determined by counting over 4000 cells in a 1/200 dilution of the blood in saline containing 2% of donor plasma. The total number of donor cells transfused was determined by multiplying the red cell count by the volume transfused (see a. above).

The inagglutinable count (cells/cu.mm.) "expected" if there was 100% survival of the transfused cells was determined by dividing the value for the total donor cells transfused by the value for total blood volume.

Localization of sites of red cell destruction. Employing a directional scintillation counter, counts were recorded over the hepatic and splenic areas at repeated intervals, with the patient supine on a hard table and with the counter directed vertically at a standard height over areas carefully mapped at the beginning of each study.

Plasma hemoglobin was measured by the modified benzidine method described by Crosby.

Paper electrophoresis was performed as described by Jim.

Plasma volume was determined in the fasting subject using Evans Blue dye.

Total blood volume was determined from the plasma volume, employing the hematocrit, corrected for "plasma trapping" and for the body venous hematocrit ratio.

RESULTS

Pertinent clinical and laboratory data from the four patients are summarized in table 1. At the time the red cell survival studies were performed, a low total globulin was found in all the patients, and no gamma globulin was demonstrable in their sera by paper electrophoresis. Routine tests for anti-A and anti-B isoagglutinins were negative. Hepatomegaly was present in two cases, and splenomegaly in three, with a previous history of splenomegaly in the fourth. It is noteworthy that all the patients were males, over the age of forty years at the time of the investigation. Low total globulin concentrations were known to have been present for at least five years in two of the patients.

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<td>58</td>
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HUGH CHAPLIN, JR.

... attempting to evaluate the duration of the deficiency of gamma globulin by the history of recurrent infections, it was found that one patient (case 3) gave a life-long history of chronic upper respiratory illness culminating in pansinusitis, bronchiectasis, and diminished pulmonary reserve; 2 patients (case 1 and case 2) had the onset of repeated infections 15 and 2 years previously; and one patient gave no history of susceptibility to infections. One patient had chronic lymphocytic leukemia (case 2); the other three patients had a variety of abnormal findings of obscure etiology.

**Isoantibody studies.** Table 2 indicates the isoagglutinin results for the four patients in the present study, by both the conventional and the more sensitive methods of testing. Negative results were obtained in all by the conventional test, whereas three patients showed clearly demonstrable weak isoagglutinins by the more sensitive methods. Isohemolysins were not demonstrable in any of the patients.

**Intravenous injections of small volumes of tagged incompatible red cells.** ABO-incompatible Cr$^{51}$-tagged red cells from 10 ml. of donor blood were injected intravenously over a 3 to 4 minute interval. No immediate or subsequent signs of untoward reaction were observed in any of the patients. Three distinct patterns of in vivo survival of the incompatible cells were observed during the first hour after transfusion (fig. 1). No destruction of incompatible cells was observed in the patient (case 1) in whom no isoantibody had been demonstrable, even by the more sensitive tests. Rapid destruction of over 90 per cent of the incompatible cells within the first 45 minutes was observed in two of the three patients in whom a weak isoantibody was demonstrable by sensitive testing. The third patient with a demonstrable weak isoantibody showed an intermediate pattern; namely, destruction of approximately 25 per cent of the incompatible cells during the first hour.

The contrast between the three patterns is more clearly seen in figure 2 which illustrates the removal of incompatible cells during the 28 hours following transfusion. It is apparent that in two patients rapid disappearance was observed, the curves apparently representing simple exponential functions with half times of approximately 5 and 10 minutes, respectively. In the third patient with weak isoantibodies the disappearance of incompatible cells appears to follow a double exponential with 25 per cent of the cells being removed at a rate having a $T^{1/2}$ of 2 hours, and the remaining cells being removed at a rate having a $T^{1/2}$ of 10 hours. In the patient in whom no isoantibody was demonstrable, the disappearance of the incompatible cells followed.

<table>
<thead>
<tr>
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<th>Isoagglutinins</th>
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<td></td>
<td></td>
<td>Routine Test</td>
<td>Sensitive Test</td>
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<tr>
<td></td>
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<td>1 vol. ser. + 1 vol. 2% cells Centrif. Immed.</td>
<td>2 vol. ser. + 1 vol. 1% cells Incub. 60 mins. Centrif.</td>
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<tr>
<td>1</td>
<td>O</td>
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<td>3</td>
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<td>2+</td>
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<td>4</td>
<td>A</td>
<td>neg.</td>
<td>1+</td>
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Case 1
Weak Antib. ABSENT

Case 2
Weak Antib. PRESENT

Case 3
Weak Antib. PRESENT

Case 4
Weak Antib. PRESENT

Fig. 1.—Cr$^{51}$-tagged ABO-incompatible red cell survival patterns during the first hour following injection of approximately 4 ml. of incompatible cells in four hypogammaglobulinemic patients. The incompatibilities were as follows:

<table>
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<th>Donor</th>
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<tr>
<td>Case 1</td>
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<td>A</td>
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<td>Case 2</td>
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<td>Case 3</td>
<td>O</td>
<td>A</td>
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<tr>
<td>Case 4</td>
<td>A</td>
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a simple exponential with a T½ of 9 days. It was not possible to study the life span of this patient's own cells by autotransfusion. Thus it is not possible to state whether the somewhat shortened T½ of 9 days represents an independent autoimmune hemolytic anemia, or indicates the deleterious effects of minute amounts of isoantibody which were not demonstrable by the laboratory tests which were employed.
Isoantibody reactions in serum obtained from each patient 10 to 20 days after the transfusion were indistinguishable from those observed prior to the start of the study. Thus, there was no evidence of stimulation of isoantibody as a result of the transfusion of incompatible cells in any of the four patients.

Localization of Sites of Red Cell Destruction

Figure 3 summarizes the results of scintillation counting over the hepatic and splenic areas of each of the three patients in whom weak isoantibodies had been demonstrated. It is evident that approximately equal counting rates were obtained over the liver and spleen, with a slight preponderance of activity over the liver for both of the patients who showed rapid removal of over 90 per cent of the incompatible cells in less than one hour. Essentially no change in the surface counts was demonstrable over the ensuing 24 hours in either patient. An interesting result was obtained for the third patient, who demonstrated two apparently distinct rates of removal of incompatible red cells. Surface counting immediately after the destruction of 25 per cent of the incompatible cells revealed approximately equal counting rates over the liver and spleen, with a slight preponderance over the spleen. However, at the end of the second phase of cell removal, there was a striking accumulation of radioactivity over the splenic area, with a spleen/liver ratio of 7/1.

Comparison of In Vivo Red Cell Survival Under Conditions of Antibody Excess and Antibody Insufficiency

In the studies described above, relatively small volumes of incompatible red cells (equivalent to 1.3-1.5 Gm. of hemoglobin) were employed, and in
at least two of the patients (cases 2 and 3) who showed very rapid destruction of the donor cells, the proportion of antibody to incompatible cells was presumably one of antibody "excess." It was decided to compare the survival of incompatible cells in a single subject under conditions of antibody "excess" and of antibody "insufficiency."

The patient who had previously shown the most rapid destruction of the small volume of incompatible cells (case 3) was selected for the study. The patient's blood volume was measured and the washed Cr\textsuperscript{51}-tagged erythrocytes from 10 ml. of incompatible blood were injected intravenously. Less than 10 per cent of the incompatible cells were present in the recipient's circulation 10 minutes after the injection, and there was no appreciable radioactivity in the patient's plasma. The rapid disappearance of cells was accompanied by an accumulation of radioactivity over both the liver and spleen, of approximately equal intensity in both areas (diagram on left, fig. 4). Sixty minutes after the injection, less than 5 per cent of donor cells were circulating, and the spleen/liver radioactivity was unchanged. In order to minimize changes in the patient's ultimate total blood volume, a phlebotomy of 250 ml. was then performed (an additional 200 ml. of blood was removed in sampling during the succeeding 4 hours). Immediately following the phlebotomy, cautious transfusion of 450 ml. of Cr\textsuperscript{51}-tagged blood from the original incompatible donor was begun. The patient's vital signs and clinical condition were observed closely, and blood samples were drawn after 8, 16, 32, 64, 96 and 180
ml. of donor cells had been transfused. An aliquot of each sample was centrifuged immediately after the blood was drawn and the plasma examined grossly for evidence of hemoglobinemia. All plasma samples were of normal color, and subsequent measurement revealed that no sample contained more than 3 mg. of hemoglobin per 100 ml. of plasma. After 120 ml. of incompatible cells had been transfused (over a 2-hour period), the patient complained of feeling flushed and somewhat weak. The systolic and diastolic blood pressures fell from 106/70 to 78/50, accompanied by a fall in pulse rate from 76 to 58. The skin was somewhat cool and damp and many small urticarial spots were noted. The transfusion was slowed, and 50 mg. of benadryl was administered orally. Examination of the blood revealed that almost all of the incompatible

Fig. 4.—Survival of group B red cells in a group O hypogammaglobulinemic subject (case 3) under conditions of antibody “excess” (left) and antibody “insufficiency” (right). Note that time scale on left is minutes and on right is days. In the graph on the right, the body surface counts were performed, respectively, 30 minutes, 14 days and 28 days after completion of the 450 ml. transfusion.
cells were surviving in the patient's circulation. The urticaria increased to giant confluent wheals, widely distributed over the entire body surface. Itching was minimal, the blood pressure returned to normal within 20 minutes without vaso-pressor therapy, the temperature remained normal and the patient had no complaints. The transfusion was continued at a somewhat slower rate and completed uneventfully over the ensuing 75 minutes.

The fate of the transfused cells was determined by both the Cr\textsuperscript{51} and Ashby methods on each of the samples drawn during the administration of the blood (fig. 5). It is interesting that there was a steadily increasing discrepancy between the Cr\textsuperscript{51} and Ashby results, such that by the end of the transfusion, there was 86 per cent survival of the transfused cells by the Ashby method and "apparent" 120 per cent survival by the Cr\textsuperscript{51} method. This discrepancy was almost certainly the result of the return to the circulation of some of the Cr\textsuperscript{51}-tagged cells from the initial 10 ml. injection. Jandl\textsuperscript{19} has previously reported that a proportion of ABO incompatible cells may be sequestered in such "filter beds" as the recipient's liver and lung, with subsequent return to the circulation if there is an absence of incompatible isoantibody in the recipient's plasma. Twenty-four hours later, 90 per cent of the transfused cells were circulating, according to the Ashby method, and these cells disappeared gradually over the ensuing 55 days. A comparison of the survival (Cr\textsuperscript{51} method) of the incompatible cells under conditions of antibody "excess" and "insufficiency" is shown in figure 4. The half-survival times were 4 minutes and 17.5 days, respectively. The survival of the patient’s
cells in his own circulation was approximately normal (T½ 25.5 days) when measured as soon as all the incompatible cells had disappeared. The small rise in the spleen/liver radioactivity ratio during the month following transfusion (fig. 4) is not significantly outside our normal limits for a long-term study, and does not resemble the unusual splenic pattern observed in case 4 (fig. 3).

Figure 6 illustrates the results of antibody titrations during the course of the experiment. The sensitive test for isoagglutinin activity (see Methods) revealed the initial titer of anti-A to be 1/6 and of anti-B 1/2. The anti-B titer fell to zero after the initial injection of 4 ml. of washed incompatible cells and remained zero until all the incompatible cells had disappeared from the patient's circulation. Thereafter, anti-B activity reappeared but remained weak, showing no evidence of antibody stimulation in response to the incompatible transfusion. An unexpected finding was a clearly demonstrable droop in the anti-A titer from its initial value of 1/6 to 1/2 after the injection of 4 ml. of washed B cells. The subsequent rise in anti-A titer reflects the transfusion of anti-A antibody in the group B donor's plasma.

**DISCUSSION**

Early reports of the uniform absence of isohemagglutinins in patients with hypogammaglobulinemia concerned pediatric patients who presumably were examples of the "congenital" form of the disease. More recently, Good7 has reported weak isoagglutinins in 2 of 5 hypogammaglobulinemic pediatric patients (ages 15 and 20 months). In the increasingly frequent case reports of "acquired" hypogammaglobulinemia developing in adulthood15,17,21,23 isoagglutinins are stated to have been absent in approximately half of the patients and present in low titer in the remainder. Since there has been

**Fig. 6.**—Possible in vivo absorption of cross-reacting antibody following injection of 4 ml. of washed B cells (case 3). The rise in anti-A titer during subsequent transfusion of B blood represents passive transfer of anti-A isoagglutinin in the donor's plasma.
no uniformity in the methods of testing for isoagglutinins, it is difficult to assess the comparative incidence of demonstrable isoantibody activity in the congenital and acquired groups. All four of the patients in the present study were adults, over 40 years of age, who probably should be classified as examples of the “acquired” form of the disease. It is evident from the results of the present study (table 2) that increasing the sensitivity of the test will increase the reported incidence of demonstrable isoantibody in the adult group. It is not known whether the same will be true for the pediatric group. There will probably remain a small group of adult patients in whom no antibody will be detectable by even the most sensitive in vitro tests available.

The inability of patients with hypogammaglobulinemia to respond to stimulation by a provocative foreign antigen (e.g., typhoid and paratyphoid vaccines, pneumococcal polysaccharides) is well borne out by the failure of appropriate isoantibody response to incompatible transfusion in all four of the author’s cases. These results are consistent with previous reports of failure of isoantibody stimulation in such patients following parenteral administration of ABO-incompatible cells.

It has been pointed out that there are at least three components to the ABO-isoantibodies present in the sera from group O subjects: anti-A, anti-B, and a “cross reacting” antibody active against both A and B cells. Thus, in vitro, it can be shown that the absorption of a group O serum with, for example, B cells results in a measurable lowering of the anti-A titer of the serum, as well as markedly lowering the anti-B titer. It is possible that the fall in anti-A titer illustrated in figure 6 represents an in vivo example of the absorption of cross-reacting antibody. The experimental in vivo demonstration of this phenomenon would rarely be feasible except in patients with hypogammaglobulinemia, and an attempt should be made to confirm these observations in future studies.

It is impossible at this time to interpret the different patterns of red cell destruction illustrated in figure 3. The in vitro isoantibody studies in cases 2 and 3, who evidenced rapid red cell destruction with equivalent hepatic and splenic sequestration, were indistinguishable from those in case 4, who evidenced slower red cell destruction with striking splenic sequestration. The findings suggest that there are at least two distinct mechanisms for the extravascular destruction of ABO-incompatible cells. However, case 4 had received two blood transfusions eight years previously, and it is possible that sensitization to a blood group antigen outside the ABO system had occurred. A careful search employing saline, albumin, and antiglobulin technics was made for evidence of specific antibodies in this patient’s serum, but the only clearly demonstrable antibody was that weakly active against all group B cells. It is certainly possible, however, that the red cell destruction was related to “occult” incompatibility outside the ABO system and not demonstrable by available compatibility tests, as in the two cases reported by Jandl.

It should be emphasized that measurement of the in vivo survival of a small volume of isotope-tagged incompatible cells provides an extremely sen-
sitive index of the presence of minute quantities of circulating antibody. For example, destruction within 10 minutes of 90 per cent of 4 ml. of incompatible cells administered to case 3 (fig. 4) was conclusive evidence of the presence of antibody. When this same patient was given 180 ml. of incompatible cells, approximately 90 per cent of the cells survived in the patient’s circulation 24 hours after the transfusion. It appears that in this instance, 20 ml. of incompatible cells were required to exhaust (“saturate”) the total supply of anti-B antibody in the recipient’s circulation. The incompatible cells in excess of those needed to “saturate” the antibody survived more nearly normally, the somewhat shortened half-survival time probably reflecting the patient’s continued production of small amounts of anti-B antibody. It should be pointed out that as Cr51 of higher specific activity becomes available, it will be possible to test for minute amounts of antibody employing as little as 0.2 to 0.5 ml. of incompatible cells. It should be interesting to apply such sensitive in vivo tests to pediatric patients, to delineate more sharply whether fundamental differences exist between the congenital and acquired forms of hypogammaglobulinemia.

In the light of the findings in this report, it is necessary to modify the concept of the hypogammaglobulinemic patient as a “universal recipient.” It may well be that as more sensitive tests are applied it will be possible to detect appropriate isoantibodies in all hypogammaglobulinemic subjects.

SUMMARY

1. Four adult patients are described whose sera showed a complete lack of gamma globulin by paper electrophoresis.
2. All four patients might have been considered “universal recipients” because of the absence of isohemagglutinins on routine laboratory tests.
3. Weak isohemagglutinins were detectable in the sera from three of the four subjects when the sensitivity of the in vitro test was increased.
4. Following intravenous administration of 4 ml. of ABO-incompatible cells, red cell survival was shortened in all of the patients, with a wide range of half-survival times from <10 minutes to as long as 9 days.
5. Although in vitro tests for antibody activity revealed no qualitative differences among the sera from the three patients with detectable isohemagglutinins, two different mechanisms of red cell removal were observed, one which entailed nearly equal activity by both liver and spleen, the other being primarily a function of the spleen.
6. The survival of incompatible cells under conditions of antibody “excess” and antibody “insufficiency” was compared in one of the patients. The findings emphasize the sensitivity of in vivo survival studies employing small volumes of incompatible cells to detect minute quantities of circulating antibody.
7. A fall in anti-A titer following the administration of group B cells to one hypogammaglobulinemic subject is interpreted as a possible in vivo example of the absorption of “cross-reacting” antibody in the ABO system.
8. In the light of the in vivo and in vitro findings, none of the 4 hypogamma-
globulinemic patients in the present series could be categorized as "universal recipients."

SUMMARY IN INTERLINGUA

1. Es describite quatro casos de patientes adulte in qui le sero se monstrava —in electrophorese a papiro—completemente disproviste de globulina gamma.

2. On haberea potite considerar omne le quatro como "recipientes universal," proque in omnes le routinari tests de laboratorio monstrava absentia de iso-hemagglutininhas.

3. In tres del quatro individuos, le presentia de debile iso-hemagglutininhas se manifestava quando le sensibilitate del test in vitro esseva augmentate.

4. Post le administration intravenose de 4 ml de cellulas ABO-incompatibile, le superviventia erythrocytic esseva reducite in omne le patientes, ben que le valores de medie-vita variava inter minus que 10 minutas e un maxim de 9 dies.

5. Ben que tests in vitro pro activitate anticorporee revelava nulle differen-
tiasi qualitative inter le seros obtenite ab le tres patientes in qui tracias de iso-
hemagglutininhas poteva esser detegite, duo differente mechanismos esseva
observate quanto al elimination del erythrocytos. Le prime comprendeva quasi
equal activitates per le hepate e per le splen, durante que le secunde esseva
primarimente un function del splen.

6. In un del patientes un comparation esseva effectuate inter le superviventia
de non-compatibile cellulas sub conditiones de "excesso" de anticorpore e
lor superviventia sub conditiones de "insufficientia" de anticorpore. Le consta-
stationes in iste experimento signala de novo le sensibilitate de studios de
superviventia in vitro quando micr volumines de non-compatibile cellulas es
usate pro deteger minuscule quantitates de anticorpore in le circulation.

7. In un del subjectos hypogammaglobulinemic le titro de anti-A descendeva
post le administration de cellulas de gruppo B. Isto esseva interpretate como
un exemplo possibile del absorption in vivo de anticorpore a "reaction cruciate"
in le systema ABO.

8. In le lumine del constatationes in vivo e in vitro in le presente casos,
nulle del quatro patientes hypogammaglobulinemic poteva esser classificate
como "recipiente universal."

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