Plasma Infusions in Immunologic Deficiency States: Metabolic and Therapeutic Studies

By E. Richard Stiehm, J.-P. Vaerman and H. Hugh Fudenberg

Current therapy for agammaglobulinemia consists of periodic intramuscular injection of commercial \( \gamma \)-globulin (Cohn fraction II), a preparation containing \( \gamma G \)-globulin alone. Agammaglobulinemic patients, deficient in all 3 immune globulins, as well as patients with isolated deficiencies of \( \gamma M \) or \( \gamma A \)-globulin (dysgammaglobulinemia, ataxia telangiectasia, the Aldrich syndrome) might be expected to benefit maximally by replacement therapy with a preparation containing the 3 immune globulins.

The functional diversity of the immune globulins provides theoretical support for this concept. Whereas the \( \gamma G \)-globulins account for most antibacterial, antiviral and antitoxic antibodies, other antibodies, such as natural isoagglutinins and typhoid O agglutinins, are mainly \( \gamma M \)-globulins, and still others, such as reagins, are primarily \( \gamma A \)-globulins. Furthermore, antibodies with the same specificity but belonging to different classes of immune globulin may vary in their ability to hemolyze cells, fix complement, and inhibit antibody formation. Finally, the distribution of these proteins is known to vary. \( \gamma G \)-globulins are distributed equally between the circulation and the tissues, \( \gamma M \)-globulins are localized primarily in the intravascular compartment, and \( \gamma A \)-globulins seem to be associated chiefly with tissues and exocrine gland secretions. It seems likely, therefore, that each of the 3 immune globulin classes provides certain unique defense mechanisms.

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At present, plasma is the only readily available substance containing all 3 immune globulins. Since Cohn fraction II became available, however, plasma has not been widely used as a source of passive antibodies except in the treatment of burns. Although both plasma and Cohn fraction II result in a lower incidence of pseudomonas infections, plasma is equally or more effective in preventing sepsis. In 1965, Fulginiti and Sieber reported that blood from recently vaccinated donors had been used successfully in the treatment of vaccinia gangrenosa in a hypogammaglobulinemic child who had not responded to treatment with vaccinia immune globulin, thiosemicarbazone or amputation.

These observations led us to investigate the effectiveness of plasma infusion in increasing the serum immune globulin levels in patients with agammaglobulinemia. In addition, survival times and distribution of the immune globulins were determined in selected agammaglobulinemic patients, newborn infants requiring exchange transfusion, and control subjects. This report presents the data obtained from these investigations, as well as the results of prolonged therapeutic trials of plasma infusions in 2 patients with agammaglobulinemia and 2 children with Aldrich's syndrome.

Materials and Methods

Subjects

The experimental group consisted of 8 hospitalized patients with immunologic deficiency diseases, all of whom had been treated with commercial y-globulin for periods ranging from 6 months to 11 years. 9 newborn infants who required exchange transfusions because of hyperbilirubinemia, and 6 adult control subjects without immunologic deficiency. The latter group included 2 lactating women who had undergone tubal ligation postpartum and were not breast feeding their infants.

Experimental Procedure

Two types of studies were performed: (1) The serum levels and biologic half-life of each of the serum immune globulins were determined by immunologic methods after infusion of plasma (agammaglobulinemic patients) or exchange transfusion (newborn infants). (2) In the 6 subjects without immunologic deficiency and 5 of the agammaglobulinemic patients, the half-life of either y_2-globulin or y_4-globulin was measured after injection of the isolated, purified proteins labeled with I131. The radioisotope studies included measurement of the immune globulin partition between the extravascular and intravascular compartments in some instances. In selected subjects, attempts were made to demonstrate injected y_4-globulin in saliva and breast milk.

Clinical Evaluation

The therapeutic effects were evaluated in all patients receiving plasma infusions. As a therapeutic trial, 2 agammaglobulinemic patients received plasma infusions (5 to 10 ml./Kg.) every 6 to 8 weeks for up to 6 months instead of monthly intramuscular injections of Cohn fraction II. In addition, 2 children,19 1 and 3 years old, with the Aldrich syndrome were also treated by plasma infusion (15 ml./Kg.) every 6 to 8 weeks for 17 and 23 months, respectively, preceded by injection of small amounts of y_2-globulin (0.1 mI/Kg.) to minimize the risk of serum hepatitis.

Immunologic Studies

Transfusion Procedures. To decrease the possibility of hypervolemia, plasmapheresis was
performed before plasma infusions. A disposable double unit plasmapheresis pack* was used. Blood was withdrawn into one unit of the pack. The unit was removed and centrifuged at 4,000 r.p.m. for 10 minutes to separate the plasma and red cells; during this interval the patient received saline solution infused through a sidearm of the plasmapheresis tubing. After centrifugation, the supernatant plasma was removed, and the autologous red cells were reinfused through the plasmapheresis tubing; to increase the rate of infusion a pressure cuff was placed around the unit. On occasion, a second unit of blood was withdrawn, and the procedure was repeated.

Immediately after plasmapheresis, fresh or fresh-frozen plasma, brought to 37 C. by means of a warming coil, was infused at a rate of 10 ml./min. The amount administered ranged from 3.3 to 15 ml./Kg. (200 to 750 ml.). In all cases the plasma was cross-matched with the recipient’s red cells by saline and antiglobulin methods. Plasma of compatible Gm (genetic y-globulin) type21 was usually given to avoid the possibility of plasma transfusion reactions.22,23 Because of the low levels of autologous y-globulin in the serum of agammaglobulinemic patients, Gm genotype was inferred from those obtained by typing family members.

For exchange transfusions, fresh whole blood with low isoagglutinin titer obtained from normal type O, Rh-negative adult subjects was administered through a catheter in an umbilical vein. Several of the infants required two or more transfusions.

Serum samples were taken 30 minutes, 4, 8 and 24 hours after the plasma infusion or exchange transfusion and once daily thereafter for 3 weeks (adult patients) or until the time of discharge (infants) for immune globulin determinations. Similar determinations were performed on saliva samples obtained from one agammaglobulinemic patient (M. C.) before and at 12-hour intervals after plasma infusion and concentrated 20-fold by lyophilization.

**Immunologic Determinations**

Immune globulin levels were measured quantitatively by the radial diffusion technic of Mancini and associates.24 with specific antisera to yG', yM', or yA'-globulin incorporated into agar plates as described in detail elsewhere.3 Purified immune globulins25 quantitated by Kjeldahl nitrogen analysis were used as standards. In our laboratory this method has a precision of 3 per cent when samples are tested in duplicate on the same plate or 10 per cent when duplicate samples are tested on different plates. In adult subjects the normal values by this method, in mg./100 ml., are 1158 ± 305 for yG', 99 ± 27 for yM', and 200 ± 61 for yA'-globulin.3

**Radioisotope Studies**

**Preparation of 111-In-Labeled Immune Globulins.** yG'-globulin was isolated from whole serum by diethylaminoethyl (DEAE)-chromatography26 with 0.01 M phosphate buffer, pH 8.0. The first peak through the column was pooled, pervaporated to a 1 per cent solution and dialyzed overnight in the cold before being labeled. 75 yA'-globulin was isolated from normal serum by the zinc sulfate technic of Vaerman and co-workers25 and from breast milk by fractionation with 18 per cent disodium sulfate and Sephadex C-200 gel filtration. The purity of the preparations was verified by immunoelectrophoretic analysis by the method of Scheidegger,27 using multivalent and monovalent antisera.

In initial studies the purified preparations were labeled by an iodine monochloride technic.28 which has an efficiency of 30 to 50 per cent. In subsequent experiments labeling was done by a chloramine-T method.29 which has an efficiency of 50 to 70 per cent with a ratio of 1 mole of I₂/mole of protein. Immediately after labeling, human serum albumin was added to the preparations to prevent possible damage to the immune globulins by self-irradiation. The preparations were dialyzed for 24 hours against multiple changes of saline

solution and sterilized by passage through a bacterial filter; aliquots of each preparation were counted in a well-type scintillation counter containing a thallium-activated sodium iodide crystal. All preparations were kept in the cold during the 48-hour interval between isolation and administration of the protein.

**Administration of Labeled Proteins and Collection of Samples.** The subjects were given Lugol’s solution before and during the entire study period to prevent thyroidal uptake of the administered $^{131}$I. Approximately 2.5 ml. of the iodinated preparation, containing 1 to 2 mg. of labeled protein, was injected intravenously from a disposable syringe. The exact amount of radioactive solution administered was determined by weighing the syringe before and after the injection.

Serum samples were taken at 5, 10 and 20 minutes after the injection for zero time calculations, at 4, 8 and 24 hours, and daily thereafter for 3 weeks. In 7 cases, 24-hour urine and stool specimens were collected for radioactivity measurements. Breast milk was obtained from the 2 lactating women twice daily. Saliva samples (after stimulation with lemon) were obtained at 12-hour intervals; they were collected in a Colby cup placed over Stensen’s duct to avoid contamination by mucus or food particles.

Aliquots, 1 to 2 ml. of all samples (serum, urine, homogenized stool, breast milk and saliva) and 25-μl aliquots of the $^{131}$I-labeled $\gamma_G$ and $\gamma_A$-preparations were counted in an automatic well-type scintillation counter. All counting was done at the end of the 3-week study period to eliminate the need to correct for isotope decay. Samples of breast milk and salivary secretion were also counted after being dialyzed against tap water for 24 hours to remove radioactivity not due to protein.

**Analysis of Data**

The data were plotted on semilogarithmic paper against time. Zero time values were (a) serum immune globulin levels at 30 minutes after plasma infusion, or (b) extrapolated values estimated from the radioactivity levels at 5, 10 and 20 minutes after injection of the $^{131}$I-labeled preparations. The values at any subsequent time were expressed as percentage of the zero time value. Since the values usually declined in a straight line after the initial equilibration period, the half-life ($T_{1/2}$) of the immune globulins could be estimated by graphic means. The disappearance curve of $^{131}$I-labeled $\gamma_G$-globulin was biphasic; the straight line portion of the curve, when extrapolated back through zero time, permitted calculation of the percentage of the protein that was intravascular. Accurate extrapolation of intravascular $\gamma_G$-globulin was not feasible because of the rapid disappearance of the labeled protein from the serum. If it is assumed, however, that an equilibrium exists between serum and tissue immune globulin levels, a daily plot of total body radioactivity, calculated by subtraction of cumulative radioactivity excreted in the urine and stool from the administered dose, should parallel the serum radioactivity curve. The intravascular distribution of $\gamma_A$-globulin was calculated by dividing the total plasma radioactivity (plasma concentration × plasma volume) by the total body radioactivity calculated as above.

**RESULTS**

The serum concentrations and immunologic survival times of the immune globulins after plasma infusion in the agammaglobulinemic patients are summarized in Table 1. Figure 1 shows the correlation between the postinfusion increase in serum concentrations and the amount of each immune globulin administered. Estimates based on the data in Figure 1 indicate that an infusion of 10 ml. of plasma$^*$/Kg. in an agammaglobulinemic patient results in an increase of 130, 20 and 30 mg./100 ml. in the serum $\gamma_G$, $\gamma_M$, and $\gamma_A$-globulin levels, respectively.

$^*$Ten ml. of normal plasma contain about 100 mg. of $\gamma_G$, 7.5 mg. of $\gamma_M$, and 15 mg. of $\gamma_A$-globulin.
Table 1.—Serum Concentrations and Half-Lives ($T_{1/2}$) of Immune Globulins after Plasma Infusion in Patients with Immunologic Deficiency Diseases

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr.) and Sex</th>
<th>Previous γ-Globulin Therapy*</th>
<th>Days Since Last Injection (ml.)</th>
<th>Amount Removed (ml./Kg.)</th>
<th>Plasma</th>
<th>Serum Level (mg./100 ml.)</th>
<th>Return to Pre-Infusion Level (days)</th>
<th>$T_{1/2}$ (days)</th>
<th>Serum Level (mg./100 ml.)</th>
<th>Return to Pre-Infusion Level (days)</th>
<th>$T_{1/2}$ (days)</th>
<th>Serum Level (mg./100 ml.)</th>
<th>Return to Pre-Infusion Level (days)</th>
<th>$T_{1/2}$ (days)</th>
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<tbody>
<tr>
<td>J. J.</td>
<td>14 M</td>
<td></td>
<td>11</td>
<td>2</td>
<td>0 12.5</td>
<td>(B) 59 - -</td>
<td>(B) 3 - -</td>
<td>(B) 3 - -</td>
<td>(B) 3 - -</td>
<td>(B) 3 - -</td>
<td>(B) 3 - -</td>
<td>(B) 3 - -</td>
<td>(B) 3 - -</td>
<td>(B) 3 - -</td>
</tr>
<tr>
<td>D. T.</td>
<td>37 M</td>
<td></td>
<td>10</td>
<td>12</td>
<td>40 8.7</td>
<td>(B) 246 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
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<tr>
<td>H. S.</td>
<td>41 M</td>
<td></td>
<td>4</td>
<td>4</td>
<td>20 6.5</td>
<td>(B) 60 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
<td>(B) 0 - -</td>
</tr>
<tr>
<td>A. S.</td>
<td>40 M</td>
<td></td>
<td>2</td>
<td>3</td>
<td>20 8.0</td>
<td>(B) 178 - -</td>
<td>(B) 8 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
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<tr>
<td>R. M.</td>
<td>53 M</td>
<td></td>
<td>6/12</td>
<td>18</td>
<td>20 10.7</td>
<td>(B) 16 - -</td>
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<td>(B) 4 - -</td>
<td>(B) 4 - -</td>
<td>(B) 4 - -</td>
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<td>(B) 4 - -</td>
<td>(B) 4 - -</td>
<td>(B) 4 - -</td>
</tr>
<tr>
<td>M. C.</td>
<td>38 F</td>
<td></td>
<td>1</td>
<td>30</td>
<td>10 12.1</td>
<td>(B) 95 - -</td>
<td>(B) 0 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
<td>(B) 5 - -</td>
</tr>
</tbody>
</table>

*Previous regimen.

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### Acquired Agammaglobulinemia and Thymoma

<table>
<thead>
<tr>
<th></th>
<th>D. J.</th>
<th>F</th>
<th></th>
<th></th>
<th>(B) 134</th>
<th>—</th>
<th>—</th>
<th>(B) 3</th>
<th>—</th>
<th>—</th>
<th>(B) 5</th>
<th>—</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>5/12</td>
<td>14</td>
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<td>8.3</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>9/12</td>
<td>30</td>
<td>30</td>
<td>2</td>
<td>8.0</td>
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<td></td>
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<tr>
<td></td>
<td>(A) 266</td>
<td>—</td>
<td>39</td>
<td>30</td>
<td>(A) 13</td>
<td>28</td>
<td>10</td>
<td>(A) 35</td>
<td>26</td>
<td>6.0</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>(B) 89</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>(B) 3</td>
<td>—</td>
<td>—</td>
<td>(B) 5</td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(A) 148</td>
<td>22</td>
<td>28</td>
<td>(A) 12</td>
<td>30</td>
<td>11</td>
<td>(A) 31</td>
<td>30</td>
<td>5.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dysgammaglobulinemia Type I

|    | R. G. | 1 1/2 | 6/12 | 14 | 6 | 0 | 15.0 | (B) 124 | — | — | (B) 127 | — | — | (B) 3 | — | — | (A) 187 | 11 | 23 | (A) 106 | — | — | (A) 20 | 23 | 6.0 |       |   |
|----|-------|-------|------|----|---|---|------|----------|---|---|-------|---|---|------|---|---|------|---|---|------|---|---|------|---|---|
|    |       |       | 6/12 | 14 | 6 | 0 | 15.0 |       |   |   |       |   |   |       |   |   |       |   |   |       |   |   |       |   |   |       |   |   |
|    |       |       |       |   |   |   |   | (B) 105 | — | — | (B) 31 | — | — | (B) 3 | — | — | (A) 202 | 27 | 32 | (A) 121 | 28 | 9.6 | (A) 29 | 30 | 5.9 |       |   |

*Commercial Cohn fraction II; protein concentration, 16 per cent.
†(B) indicates before infusion; (A) indicates immediately after infusion.
††Excludes R. G.
The immune globulin levels remained elevated for varying periods after plasma infusion. The duration of the increase in \( \gamma_0 \)-globulin was especially variable, ranging from 11 to 60 days; however, in some patients the pre-infusion \( \gamma_0 \)-globulin concentration had been increased above true endogenous base-line levels as a result of previous \( \gamma \)-globulin therapy. The average time taken to return to preinfusion levels was 27, 28 and 30 days for \( \gamma_0 \), \( \gamma_M \) and \( \gamma_A \)-globulins, respectively.

After initial equilibration the serum concentrations of the immune globulins declined in a linear fashion. Estimation of the survival half-life \( (T^{1/2}) \) by graphic means showed an average value of 32, 9.6 and 5.9 days for \( \gamma_0 \), \( \gamma_M \) and \( \gamma_A \)-globulins, respectively (Table 1). The results of a representative study are given in Figure 2. As shown, the disappearance rate of \( \gamma_M \) and \( \gamma_A \)-globulin decreased after 2 weeks, with curves approaching the base line asymptotically. In repeated studies on patients H. S. and D. J. (Table 1), the values for each immune globulin were in good agreement, except for a \( \gamma_0 \)-globulin \( T^{1/2} \) of 48 and 30 days in one case (H. S.). In 2 patients studied during episodes of infection (J. J., empyema, and R. G., pneumonia) the \( \gamma_0 \)-globulin survival times were shorter than the average value. In J. J. the \( \gamma_0 \)-globulin \( T^{1/2} \) was 24 days and the \( \gamma_M \) and \( \gamma_A \)-globulin half-lives were 10 and 6.5 days, respectively. In R. G., a patient with dysgammaglobulinemia type I (who has been described in detail elsewhere\textsuperscript{2}), the \( \gamma_0 \)-globulin half-life was 23 days (Fig. 3), whereas the \( \gamma_A \)-globulin \( T^{1/2} \) was 6 days; because of variations in the \( \gamma_A \)-globulin level, the \( T^{1/2} \) could not be determined.

The results of immunologic studies after exchange transfusion in the infants with hyperbilirubinemia are summarized in Table 2; a representative example is shown in Figure 4. Neonatal serum contains only trace quantities of \( \gamma_M \) and \( \gamma_A \)-globulins; however, after exchange transfusion the levels of all 3 im-
**PLASMA INFUSIONS IN IMMUNOLOGIC DEFICIENCY STATES**

**Immune Globulins**

<table>
<thead>
<tr>
<th>Serum Levels (mg/100ml)</th>
<th>Before Infusion</th>
<th>After Infusion</th>
<th>Half Life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XG</td>
<td>246</td>
<td>300</td>
<td>39</td>
</tr>
<tr>
<td>XM</td>
<td>0</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>SA</td>
<td>0</td>
<td>17</td>
<td>6</td>
</tr>
</tbody>
</table>

Fig. 2.—Results of immune globulin survival study in an agammaglobulinemic patient (D. T.) after plasmapheresis (1 unit) and infusion of 616 ml. of normal plasma (8.7 mg./Kg.). Initially, the serum immune globulin concentrations decreased rapidly; subsequently the rate of decrease declined.

Immune globulins approached the concentrations found in the sera of normal adult subjects. The average survival times of \(\gamma_m\) and \(\gamma_x\)-globulins were 7.4 and 4.3 days, respectively, compared with 9.6 and 5.9 days in the adult agammaglobulinemic patients. These values, however, are not strictly comparable since the post-transfusion levels of the \(\gamma_m\) and \(\gamma_x\)-globulins were much higher in the infants than in the adult patients. In 4 cases the \(\gamma_m\)-globulin levels 2 to 4 days after transfusion exceeded the immediate post-transfusion level (Fig. 5), making it impossible to calculate the \(\gamma_m\)-globulin half-life from the initial values; after this rise the levels declined with the characteristic half-life of \(\gamma_m\)-globulin. No correlation was found between the half-life of the immune globulins and the number of exchange transfusions or the birth weight or age of the infants.

In 5 agammaglobulinemic patients, studies with \(^{131}\text{I}\)-labeled \(\gamma_m\) and \(\gamma_x\)-globulins were performed on 6 occasions immediately after plasma infusion, allowing comparison of the survival times of the immune globulins as determined by radioisotopic and immunologic methods (Table 3). Two patients (M. C. and D. J.*) received injections of \(^{131}\text{I}\)-labeled \(\gamma_m\)-globulin from donor

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*Patient D. J. had a benign thymoma. External scanning over the thymic region after administration of \(^{131}\text{I}\)-labeled \(\gamma_m\)-globulin, however, showed no evidence of unusual catabolic activity.
Fig. 3.—Results of immune globulin survival study in a male infant (R. G.) with dysgammaglobulinemia (increased \( \gamma_M \)-globulin, marked deficiency in \( \gamma_G \) and \( \gamma_A \)-globulins) and pneumonia after infusion of 130 ml. of plasma (15 ml./Kg.).

plasma; the \( \gamma_0 \)-half-lives of 32 and 25 days were in good agreement with the respective immunologic values of 36 and 28 days, respectively. Patient D. J. also received an injection of \(^{131}\)I-labeled serum \( \gamma_A \)-globulin; the \( \gamma_A \) half-life was 2 days, compared with an immunologically determined half-life of 5 days. The rapid rate of disappearance of the labeled \( \gamma_A \)-globulin suggested denaturation either during the zinc-sulfate isolation or \(^{131}\)I-labeling procedures or during storage. Since the same method was used for labeling \( \gamma_0 \) and \( \gamma_A \)-globulins, denaturation of the \( \gamma_A \)-globulin probably occurred during the isolation procedure. Because \( \gamma_A \)-globulin of breast milk can be isolated without the use of zinc sulfate, labeled preparations of breast milk \( \gamma_A \)-globulin were used for radioisotopic studies in the remaining 3 patients. The \( \gamma_A \)-globulin half-lives of 4, 4 and 5 days, respectively, were comparable to the T\( \tau \) of 4.5, 6 and 6 days determined immunologically after plasma infusion.

In the 5 agammaglobulinemic patients, \( \gamma_0 \) and \( \gamma_A \)-globulin survival times were also determined by a plot of total daily body radioactivity. The results in all cases were in good agreement with plasma disappearance curves, indicating equilibrium of immune globulins between plasma and tissue.

In 2 of the 5 patients (Table 3), calculations based on cumulative radioac-
Table 2.—Half-Life (T½) of γM- and γA-Globulins after Exchange Transfusion in Newborn Infants

<table>
<thead>
<tr>
<th>Sex</th>
<th>Birth Weight (Gm.)</th>
<th>Number of Previous Transfusions</th>
<th>Age at Time of Last Transfusion (days)</th>
<th>T½ (Days)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>γM- Globulin</td>
</tr>
<tr>
<td>F</td>
<td>2400</td>
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<td>2</td>
<td>—</td>
</tr>
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<td>F</td>
<td>2480</td>
<td>2</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td>F</td>
<td>3860</td>
<td>0</td>
<td>3</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>3000</td>
<td>0</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Mean 7.4 4.3

Activity in urine and feces showed that 50 per cent of the labeled γM-globulin was intravascular. This value agreed (within 5 per cent) with values derived by extrapolation of the serum radioactivity curves. Similar calculations in the other 3 patients indicated that 25 per cent (mean value) of labeled γA-globulin was located in the intravascular compartment.

As a control 6 normal subjects were injected with the labeled γA-globulin preparations (Table 4). In studies on 4 subjects the T½ of γA-globulin isolated from serum was decreased (mean, 26 hours), again suggesting denaturation during the isolation procedure or storage. The T½ of γA-globulin isolated from breast milk determined in 2 subjects was 1½ and 5½ days. Calculations based on the cumulative radioactivity in urine and feces of the 2 subjects indicated that 15 and 20 per cent of the protein was located in the intravascular compartment.

In additional studies, attempts were made to demonstrate γA-globulin in saliva and breast milk. The γA-globulin content of saliva obtained from an agammaglobulinemic patient (M. C.) was determined immunologically before and after 3 plasma infusions. No postinfusion increase in salivary γA-globulin content above the base-line level (0.25 mg./100 ml.) could be demonstrated, although the serum γA-globulin level was increased from 5 to 50 mg./100 ml. After injection of I131-labeled serum γA-globulin, no labeled protein could be demonstrated in saliva from 2 of the normal subjects or in breast milk from the 2 lactating women. Dialyzable radioactivity appeared promptly in both saliva and breast milk, reaching a maximum in 48 hours. The total radioactivity at 48 hours exceeded that of an equal volume of simultaneously drawn serum, although the serum radioactivity was nondialyzable.
IMMUNE GLOBULINS

<table>
<thead>
<tr>
<th>Serum Levels (mg/100ml)</th>
<th>Half Life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Transfusion</td>
<td>After Transfusion</td>
</tr>
<tr>
<td>Y G</td>
<td>862</td>
</tr>
<tr>
<td>A M</td>
<td>7</td>
</tr>
<tr>
<td>A A</td>
<td>6</td>
</tr>
</tbody>
</table>

Exchange Transfusion

Fig. 4.—Results of immune globulin survival study in a newborn male infant weighing 2,370 Gm. after exchange transfusion with 500 ml. of whole blood from normal adult donor.

Clinical Evaluation

In the agammaglobulinemic patients infusion of plasma in average amounts (10 ml./Kg.) resulted in increases in the serum levels of all 3 immune globulins. The increase in the γ-globulin level at any given time was greater than that achieved by injection of 20 to 40 ml. of commercial Cohn fraction II (16 per cent solution). Objective clinical benefits of plasma infusion and γ-globulin injections were similar; no serious infections occurred in the patients treated with plasma infusions. One patient (D. T.) had chronic conjunctivitis, which was relieved by administration of Cohn fraction II but recurred periodically 3 or 4 weeks after each injection; after plasma infusion it recurred only after 6 weeks. Subjectively, the patients preferred plasma infusions because of the prolonged local discomfort resulting from intramuscular injection of large doses of commercial γ-globulin. The only side effect noted with plasma infusion was circumoral tingling, which disappeared immediately after the infusion.

The results of such therapy in the 2 children with Aldrich's syndrome were encouraging. Both children remained free of serious infection during the 17- and 23-month periods of treatment, although the younger infant had one epi-
IMMUNE GLOBULINS

<table>
<thead>
<tr>
<th>Serum Levels (mg/100 ml) Before Transfusion</th>
<th>After Transfusion</th>
<th>Half Life (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>695</td>
<td>652</td>
</tr>
<tr>
<td>RM</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>YA</td>
<td>0</td>
<td>53</td>
</tr>
</tbody>
</table>

Fig. 5.—Results of immune globulin survival study in a newborn infant weighing 2700 Gm. after a fourth exchange transfusion with 500 ml. of whole blood. The transient rise in γM-globulin levels in this and other transfused infants was an unexplained finding.

sode of gastrointestinal bleeding. The older child died suddenly at home with purulent meningitis 6 weeks after the last plasma infusion.

DISCUSSION

Earlier metabolic studies of "gamma" globulin (and presumably antibody), performed without consideration of its structural heterogeneity and by various technics, gave widely varying results. In 1951, Wiener reported a γ-globulin half-life of 30 days in Rh-negative newborn infants as determined by serologic studies of the rate of disappearance of transplacental anti-Rh antibodies. This value was in good agreement with T1/2 values derived from serial immunochemical determinations after administration of γ-globulin to agammaglobulinemic patients. Other early studies based on the disappearance of trace-labeled γ-globulin reported a more rapid turnover in normal subjects and patients with myeloma, but the data are questionable because of insufficient criteria of purity and because of overiodination during labeling, degradation during isolation technics by alcohol fractionation, and other factors, such as reincorporation of C label. Recent studies of chromatographically isolated γM-globulin, pure by immunoelectrophoretic criteria and trace-labeled
Table 3.—Half-Life ($T_{1/2}$) of $\gamma_0$ and $\gamma_A$-Globulins as Determined by Radioisotopic and Immunologic Methods in Patients with Agammaglobulinemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr.) and Sex</th>
<th>Labeled Protein</th>
<th>Radioisotopic $T_{1/2}$ (days)</th>
<th>Immunologic $T_{1/2}$ (days)</th>
<th>Percentage in Intravascular Compartment†</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. C.</td>
<td>38 F</td>
<td>$\gamma_0$ Donor plasma</td>
<td>32</td>
<td>36.0</td>
<td>50</td>
</tr>
<tr>
<td>D. J.</td>
<td>54 F</td>
<td>$\gamma_0$ Donor plasma</td>
<td>23</td>
<td>28.0</td>
<td>50</td>
</tr>
<tr>
<td>A. S.</td>
<td>40 F</td>
<td>$\gamma_A$ Serum</td>
<td>2</td>
<td>5.0</td>
<td>—</td>
</tr>
<tr>
<td>R. M.</td>
<td>53 F</td>
<td>$\gamma_A$ Breast milk</td>
<td>4</td>
<td>6.0</td>
<td>20</td>
</tr>
<tr>
<td>D. F.</td>
<td>37 M</td>
<td>$\gamma_A$ Breast milk</td>
<td>5</td>
<td>6.0</td>
<td>35</td>
</tr>
</tbody>
</table>

*After injection of $^{131}$I-labeled protein.
†After infusion of plasma.
‡Calculated from data on cumulative radioactivity in urine and feces.

Table 4.—Half-Life ($T_{1/2}$) and Distribution of $^{131}$I-Labeled $\gamma_A$-Globulin in Normal Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr.) and Sex</th>
<th>Status</th>
<th>Source of Labeled Protein</th>
<th>$T_{1/2}$</th>
<th>Percentage in Intravascular Compartment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>P. S.</td>
<td>42 M</td>
<td>Normal</td>
<td>Donor serum</td>
<td>30 hr.</td>
<td>—</td>
</tr>
<tr>
<td>S. B.</td>
<td>53 M</td>
<td>Normal</td>
<td>Donor serum</td>
<td>24 hr.</td>
<td>—</td>
</tr>
<tr>
<td>M. D.</td>
<td>36 F</td>
<td>Lactating, postpartum</td>
<td>Donor serum</td>
<td>30 hr.</td>
<td>—</td>
</tr>
<tr>
<td>M.</td>
<td>34 F</td>
<td>Lactating, postpartum</td>
<td>Donor serum</td>
<td>20 hr.</td>
<td>—</td>
</tr>
<tr>
<td>H. M.</td>
<td>35 M</td>
<td>Normal</td>
<td>Breast milk</td>
<td>1 1/2 days</td>
<td>15</td>
</tr>
<tr>
<td>J. W.</td>
<td>52 M</td>
<td>Normal</td>
<td>Breast milk</td>
<td>5 1/2 days</td>
<td>20</td>
</tr>
</tbody>
</table>

*Calculated from data on cumulative radioactivity in urine and feces.

with $^{131}$I, have confirmed the 20 to 30 day half-life of $\gamma_0$-globulin in normal subjects.11-13

The shortened $\gamma_0$-globulin $T_{1/2}$ observed in 2 agammaglobulinemic patients (J. J. and R. G., Table 1) can be attributed to infection, which is known to increase $\gamma_0$-globulin catabolism even when hypergammaglobulinemia is not present.29 The increased catabolic rate and elevated serum levels of $\gamma_0$-globulin observed in human diseases associated with hypergammaglobulinemia11,12,40 and in experimentally induced hypergammaglobulinemia in animals41 empha-
size that the catabolic rate is influenced both by serum concentration and pool size. The importance of these factors is also evident from the prolonged γ₀ survival time in association with low serum γ₀-globulin levels found in the present and previous studies on agammaglobulinemic patients. Synthetic rate has only a secondary effect on γ₀-globulin catabolism, as indicated by the normal γ₀ half-lives in individuals with low synthetic rates, e.g., newborn infants whose serum γ₀-globulin levels have been raised by transplacental passage of the protein, and patients with agammaglobulinemia whose γ₀-globulin levels have been raised to normal by intensive therapy.

The γ₁-globulin half-lives derived by immunologic determinations in our agammaglobulinemic patients and newborn infants were considerably shorter than the γ₀-globulin half-lives. They were not, however, as short as the γ₃ half-lives reported in the isotopic studies of Cohen and Freeman and Barth et al. The latter investigators found a mean γ₃ half-life of 5.1 days in 7 normal subjects and of 4.2 days in 4 agammaglobulinemic patients, a predominantly intravascular localization (mean, 76 per cent) in both groups, and no evident relationship between catabolic rate and serum level. In the present study the rate of catabolism of γ₁-globulin was more rapid in the infants after exchange transfusion (mean T₁/₂, 7.4 days) than in the agammaglobulinemic patients after plasma infusion (mean T₁/₂, 9.6 days). This difference, however, may be related to the fact that the serum γ₃-globulin concentrations were higher in the infants after transfusion (mean, 70 mg./100 ml.) than in the agammaglobulinemic patients after plasma infusion (mean, 12 mg./100 ml.). Furthermore, the asymptotic nature of the survival curves (plotted semilogarithmically) as base-line values are approached indicated a diminished rate of catabolism at low serum concentrations. In one instance (J. J., Table 1) γ₃ survival was not influenced by infection which seemingly decreased γ₀ survival.

The transitory rise in γ₃-globulin concentrations after exchange transfusion in the neonates is unexplained. The infant is potentially capable of synthesizing more γ₃-globulin than γ₀- or γ₁-globulin. Therefore, this peak, in part, may represent γ₃-globulin synthesized by the fetus, although the subsequent decline does not support this hypothesis.

Our immunologic studies of γ₅-globulin seem to indicate a relationship between catabolic rate and serum levels similar to that found for γ₀-globulin. The γ₅-globulin T₁/₂ of 4.3 days in the transfused infants (mean serum level of 140 mg./100 ml. immediately after transfusion) differs significantly from the T₁/₂ of 5.9 days in the agammaglobulinemic patients (mean serum level of 29 mg./100 ml. immediately after infusion). Furthermore, semilogarithmic plots of the data again showed asymptotic survival curves. The short half-life of γ₅-globulin observed is in agreement with data obtained in studies on patients with γ₅ myeloma. Drivsholm using autologous protein, noted a mean half-life of 6.4 days in 3 patients with γ₅ myeloma. Tomasi et al. using homologous γ₅ myeloma protein in myeloma patients and 3 controls, noted a mean survival time of 5 days (and a 40 per cent intravascular distribution).

In 3 agammaglobulinemic subjects, simultaneous survival studies of γ₅-
globulin of breast milk and serum revealed slight differences ($T_1/2$ of 4.4 and 5.5 days, respectively). Recent evidence suggests that serum and breast milk $\gamma\lambda$-globulins are not identical.$^{14}$ Breast milk $\gamma\lambda$ may have an additional protein subunit attached to the serum $\gamma\lambda$ molecule, resulting in a sedimentation constant of 11S instead of 7S and possibly facilitating transfer from serum to the lumen of excretory glands.

We were unable to demonstrate transport of $\gamma\lambda$-globulin from serum to breast milk or saliva by either immunologic or radioisotopic technics. Tomasi et al.$^{14}$ also reported inability to demonstrate $I^{131}$-labeled $\gamma\lambda$-globulin in saliva. In contrast, South et al.$^{46}$ in immunologic studies on a patient with chronic sinopulmonary disease, found that plasma infusion resulted in a rise in salivary $\gamma\lambda$-globulin. If transport of $\gamma\lambda$-globulin does take place, it may occur only above a certain threshold serum level. In our immunologic study of saliva from patient M. C., the postinfusion serum $\gamma\lambda$-globulin level was only 50 mg./100 ml., which may be below the critical level.

The apparently contradictory data might reflect different etiologic mechanisms in the two types of disease or might be explained by synthesis of $\gamma\lambda$-globulin de novo in exocrine glands.$^{14}$ The latter explanation is favored by the data obtained in this study, by radioautographic demonstration of $\gamma\lambda$ synthesis in the cells of the breast and parotid glands,$^{14,47}$ by the histologic changes in breast tissue preceding lactation (influx of plasma cells and lymphocytes),$^{48}$ and by the nonidentity of antibody activity in serum, saliva and breast milk.$^{49}$ (Perhaps 7S $\gamma\lambda$-globulin is synthesized in the more usual sites of immune globulin synthesis, whereas the "polymer" (9S-17S) types of $\gamma\lambda^{25}$ are synthesized in exocrine glands and spill over into the serum.)

Calculation of precise rates of local $\gamma\lambda$-globulin synthesis is not feasible at present, but it appears that significant local synthesis does occur. The short half-life (mean, 6 days) and the extravascular localization (65 to 85 per cent) of serum $\gamma\lambda$-globulin demonstrated in our studies indicate that a synthetic rate of 25 mg./Kg./day is required to maintain an adult serum level of 200 mg./100 ml. This rate of synthesis is similar to that of $\gamma\omega$-globulin and far exceeds that of $\gamma\omega$-globulin.$^{10,11,13}$

**Plasma Therapy**

As shown in the present study, the chief advantage of plasma infusion is the ease of administering large amounts of $\gamma\omega$-globulin. An average infusion of plasma is followed immediately by increases in the serum $\gamma\omega$-globulin level 50 to 100 mg./100 ml. greater than those obtained with large intramuscular doses of Cohn fraction II. The increases in the $\gamma\omega$- and $\gamma\lambda$-globulin levels are less striking, because their concentrations in the infused normal plasma are only 10 to 20 per cent of the $\gamma\omega$-globulin concentration. Furthermore, although the short half-life of the immune globulins results in a rapid fall to near baseline levels, preinfusion levels are not reached for 3 to 4 weeks. Whether the slight increases in $\gamma\lambda$- and $\gamma\omega$-globulin are of therapeutic value is not known; however, the presence of $\gamma\lambda$-globulin in the tissues, possibly at
PLASMA INFUSIONS IN IMMUNOLOGIC DEFICIENCY STATES

the expense of serum γₐ-globulin, may provide protection to areas not reached by the circulatory system.

Other theoretical advantages are the increased biologic activity of the administered immune globulins, inasmuch as the denaturation (and probable diminution of antibody activity) associated with chemical fractionation is avoided. The intravenous route of administration also avoids the tissue pooling and local proteolysis, as well as the local discomfort, associated with intramuscular injections of commercial γ-globulin.

The main disadvantages of plasma therapy are the risks of serum hepatitis and transfusion reactions. Since agammaglobulinemic patients are unusually susceptible to hepatitis, precaution in the selection of plasma donors is indicated. We recommend plasma for the routine management of patients with agammaglobulinemia only when several volunteer donors, preferably family members, known to have no history of hepatitis are available for repeated donation of blood. As a further precaution the infusions may be preceded by injection of Cohn fraction II. Transfusion reactions apparently are not a major problem; they did not occur in any of our patients. Both plasma infusion and administration of γ-globulin can result in the formation of antibodies to genetic γ-globulin groups absent in the recipient. While this is a common occurrence in immunologically normal persons, it is most unlikely in patients with immunologic deficiencies.

In the Aldrich syndrome, the obscure nature of the immunologic deficit, the risk of hemorrhage following intramuscular injection of large doses of γ-globulin, and the favorable response of our 2 patients to 17- and 23-month therapeutic trials have led us to a cautious endorsement of plasma infusion, preceded by small injections of γ-globulin to minimize the risk of viral hepatitis, as the treatment of choice.

It is hoped that the ideal replacement therapy for patients with immunologic deficiency, a virus-free product rich in all 3 immune globulins for intravenous use, may soon become available. Studies of γₒ-globulin preparations for intravenous administration are in progress. Extension of these studies to encompass preparations containing γₐ- and γₐ₁-globulins as well are eagerly awaited.

SUMMARY

Serial immunologic measurements were used to study the metabolic behavior of the immune globulins (γₒ-, γₐ- and γₐ₁-globulins) in patients with agammaglobulinemia after plasmapheresis and plasma infusion and in newborn infants after exchange transfusion. These studies were supplemented by metabolic and distribution studies of ¹³¹-I-labeled γₐ-globulin (isolated from serum or breast milk) and ¹³¹-I-labeled γₒ-globulin in normal and agammaglobulinemic subjects. The therapeutic benefit of periodic plasma infusions in patients with agammaglobulinemia and the Aldrich syndrome was also assessed.

In the agammaglobulinemic patients, the mean half-lives of γₒ-, γₐ- and γₐ₁-globulin were 32, 9.6 and 5.9 days, respectively. In the transfused infants, the mean half-lives of γₐ- and γₐ₁-globulins were 7.4 and 4.3 days, respectively.
Agreement existed between simultaneously determined immunologic and radioactive survival times, except when $^{131}$I-labeled $\gamma_A$-globulin isolated from serum was used; this preparation had a shorter half-life than the $\gamma_A$-globulin of infused plasma, probably as a result of denaturation during the isolation procedure. Studies on 2 normal and 3 agammaglobulinemic subjects showed that 65 to 85 per cent of breast milk $^{131}$I-labeled $\gamma_A$-globulin was distributed within the tissues. $^{131}$I-labeled $\gamma_A$-globulin was not demonstrable in the breast milk of 2 lactating women or in the saliva of 2 normal subjects. No $\gamma_A$-globulin could be demonstrated in the saliva of an agammaglobulinemic patient after plasma infusion which raised the serum $\gamma_A$-globulin concentration to 50 mg./100 ml.

The use of plasma instead of commercial $\gamma$-globulin for the therapy of immunologic deficiency states has several advantages. Plasma contains all three immune globulins, provides greater quantities of $\gamma_0$-globulin than can be given by intramuscular injections, and is more acceptable to the patient. Because of the risk of serum hepatitis, this mode of therapy in the routine management of agammaglobulinemia is endorsed only if special precautions are taken. A therapeutic trial of plasma infusions in 2 patients with the Aldrich syndrome gave promising results.

**Summario in Interlingua**

Serial mesurationes immunologic esseva usate in studiar le comportamento metabolic del globulinas immun (globulinas $\gamma_0$, $\gamma_M$, e $\gamma_A$) in patientes con agammaglobulinemia post plasmapherese e infusion de plasma si ben como in neonatos post transfusiones de excambio. Iste studios esseva supplementate per studios metabolic e del distribution de globulina $\gamma_A$ marcate con $^{131}$I (isolate ab sero o ab lacte mammari) e de globulina $\gamma_0$ marcate con $^{131}$I in subjectos normal e agammaglobulinemic. Esseva etiam evalutate le beneficio therapeutic de periodic infusiones de plasma in patients con agammaglobulinemia e le syndrome de Aldrich.

In le patientes con agammaglobulinemia, le valor medie del periodo de medie valor de $\gamma_0$, $\gamma_M$, e $\gamma_A$ esseva 32, 9,8, e 5,9 dies, respectivemente. In infantes recipiente transfusiones, le valor medie del tempores de medie valor de globulina $\gamma_M$ e $\gamma_A$ esseva 7,4 e 4,3 dies respectivemente. Esseva constatate un accordo inter simultaneemente determinate tempores de superviventia immunologic e radioactive, excepte quando globulina $\gamma_A$ marcate con $^{131}$I isolate ab sero esseva usate. Iste preparato habeva un plus breve periodo de medie valor que le globulina $\gamma_A$ de plasma infusinate, probablemente como resultato del denaturation occurrente durante le effectuation del isolation. Studios in 2 subjectos normal e 3 subjectos agammaglobulinemic mostra que 65 a 85 pro cento del globulina $\gamma_A$ marcate con $^{131}$I del lacte mammari esseva distribuite intra le tissus. Globulina $\gamma_A$ marcate con $^{131}$I non esseva demonstrabile in le lacte mammari de 2 feminas o in le saliva de 2 subjectos normal. Nulle globulina $\gamma_1$, esseva demonstrabile in le saliva de un paciente con agamaglobulinemia post le infusion de plasma le qual augmentava le concentration de globulina $\gamma_1$ del sero a 50 mg per 100 ml.
Le uso de plasma in loco de commercial globulina γ por le therapia de statos de carentia immunologic ha plure avantages. Plasma contine omne le tres globulinas immun, illo provide plus grande quantitates de globulina γG que lo que pote esser administrate in injectiones intramuscular, e illo es plus acceptable ab le puncto de vista del paciente. A causa del risco de hepatitis seral, iste modo de therapia in le tractamento routinari de agammaglobulinemia es recommandate solo quando special mesuras de precaution es prendite. Un essayo therapeutic con infusiones de plasma in 2 patientes con le syndrome de Aldrich produceva resultatos promittente.

ACKNOWLEDGMENTS

We are indebted to Miss Katrina Hug and Miss Gloria Johnson for technical assistance and to Fenwal Laboratories for providing the plasmapheresis equipment used in these studies.

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Plasma Infusions in Immunologic Deficiency States: Metabolic and Therapeutic Studies

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