"A"-Antigen Variation in Pigeon Erythrocytes

II. Selection against the "A"-Inagglutinable Cells in Circulating Blood

By J. C. Hierholzer, S. L. Scheinberg and P. A. Hansen

The irradiation experiments described in the previous report showed an effect of x-irradiation on the "A"-inagglutinable cell frequency of pigeons and also brought to light three findings suggestive of in vivo selection against the "A"-inagglutinable red blood cells: (1) A dose of 360 r of x-rays usually resulted in an increase in the "A"-inagglutinable cell frequency, whereas a dose of 900 r or greater resulted in a decrease. (2) Several birds did not respond with an increase in the inagglutinable cell frequency at 2 and 4 months following irradiation with 360 r. (3) Three of these "non-responders" were given an additional 360 r which resulted in further decrease in the inagglutinable cell frequency; 8 months later their frequencies rose until they approached the preirradiation levels. It was postulated that all of these negative responses to irradiation were the result of selection against the inagglutinable cells.

The terms "negative selection" and "selection against" are used here to indicate a process of reduced survival for a class of cells. Some of the "A"-inagglutinable cells are believed to be more defective than the "A"-agglutinable cells. The additional abnormalities in the inagglutinable cells would lead to reduced survival of such cells in the blood under the same conditions in which the "A"-agglutinable cells would have a normal cell survival. One of the ways in which negative selection might be demonstrated is by a reduction in red cell lifespan. Differential lifetimes of two cell types have been observed among cells with high or low glucose-6-phosphate dehydrogenase concentrations. In the present study a comparison of the lifespan of the "A"-inagglutinable red cells with that of the total red cell population was carried out in adult pigeons.

Methods

Blood Infusion and Erythrocyte Lifespan Determination. For red cell infusion experi-
ments blood was drawn from the alar (wing) vein into Alsever's anticoagulant solution and labeled with Cr\(^{51}\). The labeled cells were washed, adjusted to a 1:2 dilution in merthiolated saline, assayed for radioactivity, and checked microscopically for damaged cells. The procedures for Cr\(^{51}\) tagging and for radioactive counting were described in the previous report.\(^1\)

A known volume of labeled cells, usually 15 ml. of a 1:2 suspension, was infused into the alar vein with a disposable blood transfusion system. The circulating blood was sampled 40-50 minutes after infusion to determine the total blood volume by the dilution of the labeled cells. The blood was subsequently sampled every 2 to 4 days until radioactivity was no longer detectable. Each sample was compared to the initial specific activity to obtain the per cent of count remaining at that time. The red cell lifespan was thereby determined by the daily loss of Cr\(^{51}\)-labeled cells from the circulating blood. Both the 50 per cent and 5 per cent survival times are tabulated for comparison of the life spans.

**Determination of the Inagglutinable Cell Frequency.** The inagglutinable cell frequency was determined by an isotope dilution procedure described in the previous report.\(^4\)

**Experimental Procedures and Results**

The in vivo survival of the inagglutinable cells was measured by comparing the inagglutinable cell frequency (ICF) of the infused labeled blood with the ICF made prior to infusion. The lifespan of the inagglutinable cells was then determined by the change in ICF of the labeled cells, whereas the lifespan of the total cell population was followed by the loss of specific activity of the circulating blood. The ICF would remain constant if the lifespans of the two cell populations were equal because both types of cell would be removed at the same rate. Any significant difference in ICF between preinfusion and postinfusion determinations must, therefore, indicate different lifespans of the two cell types. A reduced lifespan would be regarded as a consequence of selection against the inagglutinable cells.

A preliminary experiment involving three steps was conducted as follows:

1. The base level or preinfusion ICF was determined in the usual manner.
2. A week later, 10 ml. of blood were drawn, and the red cells were labeled, diluted, and slowly infused into the alar vein.
3. At 7 days postinfusion the bird was bled for an ICF determination on the already-labeled cells.

The results are given in Table 1. Of the three birds tested, two showed significant decreases in ICF by 7 days, and the third, which was not successfully tested at 7 days, showed a significant decrease when tested at 18 days postinfusion. The maximum lifespan of the total red cell population was normal in the three cases.

These limited results suggested that the method employed was suitable for testing the selection hypothesis. For this purpose 11 birds were chosen whose response to irradiation was known from previous experiments (Table 2).\(^1\) These birds were divided into two groups: those which had failed to respond to 360 r—i.e., showed no significant increase in the ICF at 2 or 4 months postirradiation—and those which had shown an increase in ICF after irradiation. It was expected that the inagglutinable cells of the “low-response” group would have a shorter lifespan than the total cell population, as reflected by a decrease in the ICF of the labeled cells. A shorter lifespan would indicate negative selection of the inagglutinable cells. The birds of the “high-response”
Table 1.—Preliminary Selection Experiments: ICF Determinations on Infused Blood

<table>
<thead>
<tr>
<th>Bird (*)</th>
<th>Age (yrs.)</th>
<th>Base Level (preinfusion ICF)</th>
<th>7-day Postinfusion ICF</th>
<th>Factor Change in ICF</th>
<th>Cell Life-span 50% removal (days)</th>
<th>50% removal (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3297</td>
<td>2.08</td>
<td>$7.52 \times 10^4$</td>
<td>$1.41 \times 10^4$</td>
<td>$-5.32$</td>
<td>14</td>
<td>34</td>
</tr>
<tr>
<td>P183</td>
<td>0.42</td>
<td>$9.04 \times 10^4$</td>
<td>$1 \times 10^4$</td>
<td>$-2.45$</td>
<td>(not completed)</td>
<td>(18 days)</td>
</tr>
<tr>
<td>P195</td>
<td>0.34</td>
<td>$3.93 \times 10^4$</td>
<td>$7.29 \times 10^4$</td>
<td>$-5.39$</td>
<td>14</td>
<td>29</td>
</tr>
</tbody>
</table>

* All three birds were White Carneau females, with an “A” agglutinogen titer of 256-512.

Group were not expected to demonstrate a decrease in the inagglutinable cell frequency during the period of test. In addition to providing information on the question of selection it was hoped that the results would help to explain the variability observed in previous irradiation experiments.

Both groups received the following treatment:

1. The birds were given 360 r to increase the number of inagglutinable cells, thereby raising the sensitivity of the method. Likewise, birds of a 512 titer were chosen because a change in the ICF would be detected more readily in such birds than in birds with low titers.

2. At 30 days postirradiation, which allowed for a substantial turnover of red cells, the birds were bled for the preinfusion ICF determination.

3. Five days later they were bled heavily to obtain a large volume of cells for labeling and infusion.

4. At 8 days postinfusion a sample of blood was drawn from each bird, and the ICF was determined on the labeled cells. Half of the birds had sufficient radioactivity left at 24 days postinfusion for a third ICF determination.

To detect effects of the experimental treatment, two birds were used whose red cells were not agglutinable by the standard titration method. (These birds did, however, give a score of 60 per cent on the mixed agglutination test, * indicating that antigenic sites were present on a large number of cells but were not detectable by the less sensitive standard titration method.) The procedure for these birds was the same as for the test subjects except that irradiation was omitted.

Controls of a different type also were used, in that each bird served as his own control. First, the number of inagglutinable cells was compared to the total cell number to obtain the ICF for each blood sample. Second, the ICF's of the preinfusion and postinfusion samples were compared to each other to obtain the factor change within each bird. These constituted the internal controls of the method.

* The mixed agglutination test is a test for low levels of agglutinogen. Pigeon cells are exposed to anti-A P. lunatus lectin, washed, and incubated with human "A" red cells. The score is the percent of pigeon cells with 1-6 human cells attached.
Table 2.—Background Information on the Selection Experiment Subjects

| Bird | Previous Irradiation Experiments | Previous 360 r (months before present exp.) | Factor Changes, Postirradiation  
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 mo.</td>
</tr>
<tr>
<td>A. Low Response to Previous Irradiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89</td>
<td></td>
<td>19</td>
<td>-1.81</td>
</tr>
<tr>
<td>948</td>
<td></td>
<td>19</td>
<td>+1.34</td>
</tr>
<tr>
<td>3375</td>
<td></td>
<td>13</td>
<td>-1.03</td>
</tr>
<tr>
<td>4293</td>
<td></td>
<td>19</td>
<td>+1.11</td>
</tr>
<tr>
<td>2609</td>
<td></td>
<td>13</td>
<td>+1.29</td>
</tr>
<tr>
<td>3499</td>
<td></td>
<td>14</td>
<td>-1.11</td>
</tr>
<tr>
<td>3297</td>
<td></td>
<td>0</td>
<td>-5.32</td>
</tr>
<tr>
<td>B. High Response to Previous Irradiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1804</td>
<td></td>
<td>13</td>
<td>+9.24</td>
</tr>
<tr>
<td>3737</td>
<td></td>
<td>19</td>
<td>+2.82</td>
</tr>
<tr>
<td>3966</td>
<td></td>
<td>13</td>
<td>+3.32</td>
</tr>
<tr>
<td>B11954</td>
<td></td>
<td>13</td>
<td>+7.55</td>
</tr>
<tr>
<td>C. Controls</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>08951</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>P15</td>
<td></td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* White Carneau and White King pigeons with an "A"-agglutinin titer of 512 were used, with the exception of the two controls whose erythrocytes had a zero titer.
* (Table 1. This factor change was observed at 7 days on prelabeled blood. The bird had not been irradiated but was placed in the low-response group because of the substantial negative factor change.

The results are given in Table 3.* At 8 days postinfusion the change in ICF of the seven birds in the "low-response" group averaged -3.75 with a standard error of ±0.56. At 24 days postinfusion the average change in ICF for four of the birds was -8.19 ±3.97. In marked contrast, the 8-day average postinfusion change in ICF of the "high-response" group was +0.80 ±0.88. The controls were -1.11 and -1.01 at 8 days and -1.21 and -1.36 at 24 days; these changes are not significant because they are within the error of the isotope dilution technique.† Because the ICF of the control birds remained constant, it would

* Detailed data for the ICF curves are available in a supplement upon request.
† The normal variation in the ICF found when periodically testing the same, non-irradiated individuals is +0.09 ±0.26 (mean with standard error), with a maximum range of ±1.53.
Table 3.—Selection against "A"-Inagglutinable Erythrocytes in Vivo

<table>
<thead>
<tr>
<th>Bird *</th>
<th>Initial (Preinfusion) ICF</th>
<th>8-day postinfusion ICF †</th>
<th>Factor Change (8 days)</th>
<th>24-day postinfusion ICF</th>
<th>Factor Change (24 days)</th>
<th>Cell Lifespan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50% removal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95% removal</td>
</tr>
<tr>
<td>A. Low-Response Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>89</td>
<td>$8.14 \times 10^5$</td>
<td>$3.36 \times 10^4$</td>
<td>$-2.43$</td>
<td>$5.82 \times 10^4$</td>
<td>$-7.49$</td>
<td>17</td>
</tr>
<tr>
<td>948</td>
<td>$6.16 \times 10^5$</td>
<td>$1.12 \times 10^4$</td>
<td>$-5.48$</td>
<td>$5.62 \times 10^4$</td>
<td>$-19.63$</td>
<td>21</td>
</tr>
<tr>
<td>3375</td>
<td>$4.36 \times 10^4$</td>
<td>$1.69 \times 10^3$</td>
<td>$-2.58$</td>
<td>$8.00 \times 10^3$</td>
<td>$-2.73$</td>
<td>15</td>
</tr>
<tr>
<td>4293</td>
<td>$6.67 \times 10^4$</td>
<td>$1.18 \times 10^3$</td>
<td>$-5.67$</td>
<td>$1.69 \times 10^3$</td>
<td>$-2.93$</td>
<td>14</td>
</tr>
<tr>
<td>2609</td>
<td>$1.10 \times 10^3$</td>
<td>$2.32 \times 10^2$</td>
<td>$-4.76$</td>
<td>$5.62 \times 10^2$</td>
<td>$-3.64$</td>
<td>21</td>
</tr>
<tr>
<td>3499</td>
<td>$2.18 \times 10^3$</td>
<td>$7.51 \times 10^1$</td>
<td>$-2.91$</td>
<td>$8.00 \times 10^1$</td>
<td>$-2.73$</td>
<td>21</td>
</tr>
<tr>
<td>3297</td>
<td>$4.93 \times 10^3$</td>
<td>$2.02 \times 10^2$</td>
<td>$-2.44$</td>
<td>$1.69 \times 10^2$</td>
<td>$-2.93$</td>
<td>14</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17</td>
</tr>
</tbody>
</table>

| B. High-Response Group |                        |                         |                       |                        |                        |               |
| 1804   | $6.99 \times 10^4$       | $5.83 \times 10^3$      | $-1.20$               |                        |                        | 20            |
| 3737   | $1.42 \times 10^4$       | $1.03 \times 10^3$      | $-1.38$               |                        |                        | 13            |
| 2966   | $1.38 \times 10^4$       | $4.32 \times 10^2$      | $+3.14$               |                        |                        | 15            |
| B11954 | $7.87 \times 10^3$       | $2.09 \times 10^2$      | $+2.65$               |                        |                        | 16            |
| Average|                          |                         |                       |                        |                        | 16            |

| C. Controls |                        |                         |                       |                        |                        |               |
| 08951     | $6.46 \times 10^3$       | $5.82 \times 10^2$      | $-1.11$               | $5.35 \times 10^2$     | $-1.21$                | 16            |
| P15       | $6.55 \times 10^3$       | $6.48 \times 10^2$      | $-1.01$               | $4.83 \times 10^2$     | $-1.36$                | 15            |
| Average   |                          |                         |                       |                        |                        | 16            |

* All were 2.2 years old except B11954 (1.3 yrs).
† The total cell population at this time contained 80% of the labeled cells initially present.

not appear that the inagglutinable cells of the test subjects became agglutinable during the period of test and thereby contributed to the change in ICF.

The maximum cell lifespan of the total cell population of the test subjects averaged 40 days, compared to 41 days for the controls. The 50 per cent removal times were 17 and 16 days, respectively, and these values give a mean red cell life span of 34 and 32 days.† These results indicate that cell damage caused by handling was not significant. No differences in lifespan of the total red cell population were observed between males and females or between the low- and high-response groups. In addition, the overall averages of 40 days for the maximum cell lifetime and 34 days for the mean cell lifetime compare well with Rodnan's findings of 40 and 35 days, respectively.3

The lack of change in ICF of the "high-response" group indicates that the lifespan of the inagglutinable cells of this group was within the normal range of 30-40 days. But the decrease in ICF of the "low-response" group shows that the lifespan of the inagglutinable cells of this group was considerably reduced from the lifespan of the total cell population. In the "low-response" group of birds, the inagglutinable cell lifetime is calculated to be only 9-10 days. This reduced lifetime is evidence for in vivo selection against the inagglutinable red cells.

* The use of "maximum" and "mean" cell lifespans is in accordance with Rodnan et al.*
Retest of the High-Response Group

Results from Table 1 provided evidence for selection against the inagglutinable cells in unirradiated birds. It was of interest to determine whether the apparent absence of selection against the inagglutinable cells in the "high-response" group (Table 3) would persist. The desire to retest this group was also prompted by the observation that in this "high-response" group two of the birds showed increases in the ICF when retested at 8 days postinfusion.

The lifetimes of the inagglutinable cells were obtained on the "high-response" group a year after the first test. The birds were not irradiated and the experiment was conducted in a slightly different manner from the first infusion run. A large volume of blood was drawn; the red cells were labeled with Cr\textsuperscript{51}, washed, and diluted twofold in merthiolated saline. A sample of this suspension was kept for the initial ICF determination and the remainder was immediately infused into the donor bird. Thirteen days later a sample was drawn and another determination of the inagglutinable cell frequency was made of the already-labeled blood. The results of these determinations are summarized in Table 4.

None of the birds exhibited a significant change in their ICF during this 13-day period. The observed normal lifespan of the inagglutinable cells in all of these birds during the period of test indicates that negative selection is reduced or inoperative in this group. The persistent increase in the number of inagglutinable cells in bird \#1804 over the preirradiation frequency supports this conclusion. The observed increases in ICF during the previous 13-day test period in birds \#3966 and B11954 (Table 3) most likely represented responses to the irradiation given 30 days prior to that period. Finally, the results reported in Table 4 provide evidence against the concept that the inagglutinable cells can become agglutinable by contact with plasma of high-titered birds.

Discussion

The results of the experiments provide additional evidence that cell lifetimes of the inagglutinable cells of some of the irradiated birds are reduced over those of the agglutinable cells. In turn, these results indicate that selection against the inagglutinable cells takes place in vivo. It is clear that a substantial contribution to the individual response to irradiation is due to the differential action of selection in the irradiated birds.

The large difference observed between the "low-response" and "high-response" groups was due to intentional choice of the test animals on the basis of past irradiation results. In an unselected population of animals the results would not be so well distinguished but would exhibit all degrees of selection. Even within a single animal the result observed from irradiation would be the composite of opposite factors: somatic mutation which would tend to increase the number of inagglutinable cells, and negative selection which might remove these same cells from the circulation. Hence, the factor change in ICF depends upon which event occurs more rapidly and in greater degree as well as the time the blood sample is taken.

Selection provides a partial explanation for the variation observed in past...
irradiation experiments and for the lack of linearity in the x-ray dose-response curves.\textsuperscript{1} It is probable that negative selection occurs to some extent in all irradiated animals and perhaps even in normal subjects as a part of the body’s mechanism for maintaining a high level of function and homeostasis.

Little information is available on the interesting question of the origin of selection effects. Munkner\textsuperscript{4} has shown that the short lifespan of autochthonous red cells in many human hematologic disorders is due entirely to intracorpuscular defects. Such cells had the same short lifespan in heterologous subjects; conversely, heterologous cells had a normal survival period when transfused into the test patients. It would appear from the experiments presented in this paper also that selection arises from defects within the cell and not from extracorpuscular or environmental difficulties. This would follow if the inagglutinable cells arise from somatic mutations in the precursor stem cells as postulated. The mutational events which produce the inagglutinable cells might render the cell exceptional or abnormal in other respects also, as evidenced by the shorter lifespan of the inagglutinable cells in one group of birds tested. Hence, the negative selection encountered by the inagglutinable cells might be the result of intracorpuscular defects of sufficient magnitude to warrant the cells’ removal.

Atwood and Pepper\textsuperscript{5} reported that the frequency of inagglutinable cells did not show any marked correlation with the age of the human subjects tested. A correlation of this kind might be expected if somatic mutation were occurring continuously in bone marrow tissue during the lifetime of an individual. The results in the present paper require that selection be considered as one of the factors operating in vivo. Selection may tend to minimize the effects of somatic mutation by reducing the number of inagglutinable cells. The role of selection among individuals of different ages is a subject for future study. In the paper by Atwood and Pepper it was mentioned that the homozygotes possessed a higher frequency of inagglutinables than might be expected if single point mutations were responsible for the inagglutinable cells; the homozygotes presumably should give rise to a frequency of inagglutinable cells which would be the square of the heterozygote frequency or less. The basis for studying cell lifetime in the present series of studies was the belief that the inagglutinable cells as a class are heterogeneous. It was suspected that the “inagglutinable” cells of “A”-negative bloods would be found to have a normal lifespan, whereas some of the inagglutinable cells in high-titered, irradiated birds would have a shortened lifespan. The latter cells were expected to have cell defects in addition to the lack of “A”-antigen as a result of irradiation and would therefore suffer negative selection. The

\begin{table}
\centering
\begin{tabular}{cccc}
\hline
Bird & Age (yrs.) & Initial ICF (at infusion) & 13-day postinfusion ICF & Factor Change \\
\hline
1804 & 3.3 & $1.92 \times 10^{-8}$ & $1.72 \times 10^{-8}$ & $-1.12$ \\
3737 & 3.2 & $1.01 \times 10^{-6}$ & $9.63 \times 10^{-6}$ & $-1.05$ \\
3966 & 3.2 & $3.37 \times 10^{-6}$ & $4.05 \times 10^{-6}$ & $+1.20$ \\
B11954 & 2.3 & $3.93 \times 10^{-6}$ & $5.52 \times 10^{-6}$ & $+1.40$ \\
\hline
\end{tabular}
\caption{Retest of the High-Response Group}
\end{table}
“mutants of Drosophila” provide abundant evidence that most mutants have
defects in addition to the defect which categorized it as a mutant. In an
analogous fashion mutant cells would be more likely to have multiple defects,
particularly prior to selection.

The hemopoietic process producing the inagglutinables which are not se-
lected against (zero-titer bloods) may be different from that which is involved
in the production of the inagglutinables with a shorter lifespan (high-titer
bloods). The latter cells may represent spontaneous mutations, the former a
process which mimics the effect but is a regular process in cell development.

The homozygotes of Atwood and Pepper may therefore possess inagglutina-
able cells which are a mixture; some of these cells will be found to possess a
shorter lifespan and some will be normal in this respect.

SUMMARY

Experiments were carried out for testing selection effects against the “A”-
inagglutinable red cells. Three birds picked at random and not exposed to
x-irradiation showed decreases in the number of inagglutinable cells in a
Cr51-labeled cell population at 7 days. Two of these decreases were quite
large, being >5-fold, and the three averaged an ICF change of -3.57-fold. The
substantial reduction in survival of the “A”-inagglutinable cells was attested
by the lowered inagglutinable cell frequency at 7 days postinfusion.

Seven birds uniform in titer and in their negative response to previous
irradiation (360 r) averaged a 3.75-fold decrease in ICF at 8 days postinfusion.
Four birds of a similar group but which had been very responsive to previous
irradiation were treated in identical fashion. At 8 days postinfusion the average
change in ICF was +0.80. This change is not significant, being within the
experimental error of ±1.5-fold.

The marked difference in results between the “low-response” group (-3.75
±0.56) and the “high-response” group (+0.80 ±0.88) was interpreted to be
due to negative selection operating strongly in the former group.

SUMMARIO IN INTERLINGUA

Esseva effectuate experimentos pro testar effectos de selection contra le erythrocytos “A”-
inagglutinabile. Tres ayes, prendite aleatorimente e non exponite a radios X, manifestava
declinos in le numeros del inagglutinabile cellulas in un population de cellulas marcate con
Cr51 post un intervallo de 7 dies. In duo del tres casos, le declinos eseva notable. Le
factor medie del alteration in le frequentia de inagglutinabile cellulas eseva—3,57.

Septe ayes, uniforme in titro e in le responsa negative al previe irradiation (360 r),
manifestava un declino medie (8 dies post le infusion) per un factor de—3,75 in le
frequentia de inagglutinabile cellulas. Quatro ayes ab un simile gruppo sed le quales habeva
esite responsivissime al previe irradiation eseva tractate in le mesme maniera. In illos le
alteration medie in le frequentia de cellulas inagglutinabile eseva caracterisate per un
factor de +0,80. Iste alteration non es significative. Illo se trova intra le limites del error
experimental.

Le marcate differentia inter le gruppo a “basse responsa” (-3,75±0,56) e le gruppo a
“alte responsa” (+0,80±0,88) eseva interpretate como effecto de un selection negative
que ageva fortemente in favor del prime gruppo.

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"A"-ANTIGEN VARIATION IN PIGEON ERYTHROCYTES. II.

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REFERENCES


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