The Natural History of Factor VIII:C Inhibitors in Patients With Hemophilia A: 
A National Cooperative Study. II. Observations on the Initial Development of 
Factor VIII:C Inhibitors

By Campbell W. McMillan, Sandor S. Shapiro, Deborah Whitehurst, Leon W. Hoyer, A. Vijaya Rao, Jack Lazerson, 
and the Hemophilia Study Group

During a 4-year multicenter cooperative study of acquired factor VIII inhibitors in persons with hemophilia A, new 
inhibitors were detected in 31 of 1,306 patients who entered the study without an inhibitor or the history of an 
inhibitor. The incidence of new inhibitors was eight per 1,000 patient-years of observation. The factor VIII:C level 
before inhibitor development was ≤0.03 U/mL in 29 individuals and 0.06 U/mL and 0.07 U/mL in the remaining two. 
Factor VIII:Ag levels were measured in 27 individuals and were <0.03 U/mL in 23 and 0.05 to 0.11 U/mL in 
the remaining four. Maximum inhibitor levels ranged from 1.0 to 9,044 Bethesda U/mL. In seven patients under the age of 
20, relatively weak inhibitors (none higher than 4.3 Bethesda U/mL) were detected on only a single occasion 
despite continued factor VIII challenge. In the other 24 patients with inhibitors detected on multiple occasions, 
50% had appeared by age 20 and 71% by age 30. Seventeen of the 31 inhibitors, including 12 of 15 with maximum 
values >10 Bethesda U/mL, developed within 75 exposure days to factor VIII.

© 1988 by Grune & Stratton, Inc.

AMONG THE MOST SERIOUS problems in the treatment 
of patients with hemophilia A is the development 
of inhibitors (antibodies) against factor VIII:C. Gill has 
reported the characteristics of 216 patients with an inhibitor or 
the history of an inhibitor among 1,522 individuals with 
hemophilia who were enrolled in a cooperative study of factor 
VIIIIC inhibitors in patients with hemophilia A that was 
sponsored by the National Heart, Lung, and Blood Institute 
and conducted by 13 centers from June 30, 1975 to October 
31, 1979. In addition to these patients, inhibitors developed 
in 31 of the 1,306 individuals with hemophilia who entered 
the study free of this complication. This report describes 
epidemiological, clinical, and laboratory characteristics of 
these 31 patients. The data reported here are the first to be 
collected prospectively on a group of inhibitor patients.

MATERIALS

Patient population. Details of the study methodology and the 
patient population have been described previously. In addition to 
the entry and follow-up forms, a separate form was designed for 
reporting newly developed inhibitors, with particular reference to 
events possibly relevant to inhibitor occurrence. Reports were sent to 
the reference laboratory and the statistical center, and a plasma 
sample was forwarded to the reference laboratory for confirmation 
of the inhibitor.

Analysis of new inhibitors. A detailed profile was prepared by 
the statistical center on each patient developing a new inhibitor in 
the course of the study; those subjects with inhibitor activities below 
0.3 Bethesda U/mL were excluded as previously described. In addition, a questionnaire was sent to each center reporting a patient 
with a new inhibitor to obtain detailed information about factor VIII 
exposure days (the number of days a given patient was exposed to 
any source or amount of factor VIII) preceding inhibitor development 
as well as the in vivo response to factor VIII infusion, if 
available. The statistical center analyzed selected parameters of the 
subjects with new inhibitors and compared their characteristics with 
those of noninhibitor patients. The incidence of new inhibitors was 
calculated by using the life table and survival functions computer 
program (PIL) in the BMDP Biomedical Computer Programs, 
P-Series, 1979. For some analyses, "usual" rather than entry factor 
VIIIIC levels were used. The usual level took into account all basal 
factor VIII:C measurements on enrolled patients that were 
employed by participating centers and provided a better separation of 
the patient groups with ≤0.03 and >0.03 U/mL factor VIII:C. This 
approach was specifically relevant to those patients whose reported 
basal factor VIII:C ranged from <0.01 to 0.03 U/mL. We attribute 
these fluctuations to within-patient variation at the interface of 
severe and moderate factor VIII:C deficiency because assays of 
factor VIII:C should accurately separate activities in this range. 
Patients with only a single entry factor VIII:C measurement were 
excluded from these analyses.

Factor VIII antigen (factor VIII:Ag) was measured on frozen 
plasma samples that had been obtained at entry, before inhibitor 
appearance. The technique used has been described previously, 
except that the standard curve was constructed by diluting the 
normal plasma with hemophilic plasma devoid of factor VIII:Ag 
cross-reacting material instead of with buffer.

RESULTS

Characteristics of the new inhibitors. New inhibitors 
appeared in 31 of 1,306 patients entering the study without 
an inhibitor. The incidence of new inhibitors was 8 per 1,000 
patient-years of observation. By using life table analysis, the 
probability of inhibitor development was .0088 per year and 
was linearly related to the length of observation (Fig 1).

Inhibitors were detected in 11 patients in the absence of 
concomitant bleeding; in the remaining 20 patients the sites 
and severity of hemorrhage were highly variable. There was 
no evidence that bleeding episodes, largely consisting of 
hemarthroses and extraarticular soft tissue hemorrhages, 
became more frequent or more severe after inhibitor development 
or were any different from those in patients with 
comparable levels of factor VIII:C but without inhibitors.
**DEVELOPMENT OF FACTOR VIII:C INHIBITORS**

![Fig 1. Probability of development of a factor VIII inhibitor. Data based on 1,306 noninhibitor patients entered in the study.](image)

As shown in Table 1, the factor VIII:C level before inhibitor development was <0.01 U/mL in 21 patients and ≤0.03 U/mL in 29 of the 31 patients. Two subjects with clinically mild hemophilia and factor VIII:C levels of 0.06 and 0.07 U/mL developed potent inhibitors with maximum levels of 83 and 18 Bethesda U/mL. For the entire study population, the incidence of new inhibitors in the 919 noninhibitor patients whose usual factor VIII:C was ≤0.03 U/mL was 3.2%, whereas the incidence in the 236 noninhibitor patients whose usual factor VIII:C was >0.03 U/mL was 0.85% \( (P < .05) \). There was no relationship between the preinhibitor factor VIII:C level and the height of the inhibitor response.

Factor VIII:Ag levels were measured in 27 preinhibitor plasmas (Table 1). The remaining four samples were either lost or used inadvertently for other studies. In general, there was good agreement between biologic and immunologic measurement of factor VIII. In three patients (A-19, B-2, B-6) the factor VIII:Ag level was disproportionately higher than the factor VIII:C level, whereas in one (A-14) the factor VIII:Ag level was substantially lower than the factor VIII:C level. These patients had no other distinguishing characteristics, but the antibodies arising in all four individuals were among the ten that disappeared during the course of the study (see the following paragraphs).

As shown in Table 1, the 31 subjects with new inhibitors could be divided into two categories. In 24 subjects (category A) inhibitor activity was repeatedly documented after its initial detection. The highest inhibitor titers measured in these patients varied from 1.3 to 9,440 Bethesda U/mL. In seven subjects (category B) inhibitor activity was documented only once, in connection with a routine 6-month follow-up visit, and was subsequently undetectable despite repeated treatment with factor VIII. These findings were

---

**Table 1. Selected Characteristics of the 31 New Inhibitor Patients**

<table>
<thead>
<tr>
<th>Patient No.*</th>
<th>Entry Factor VIII (U/mL)</th>
<th>Clinical Severity</th>
<th>Age at Time of Inhibitor Development (Nearest Year)</th>
<th>Maximum Inhibitor Activity Detected (Bethesda U/mL)</th>
<th>Exposure to Factor VIII Before Inhibitor Development (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-1</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>52</td>
<td>1.3</td>
<td>237</td>
</tr>
<tr>
<td>A-2</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>20</td>
<td>1.5</td>
<td>183</td>
</tr>
<tr>
<td>A-3</td>
<td>0.02</td>
<td>Severe</td>
<td>38</td>
<td>1.5</td>
<td>185</td>
</tr>
<tr>
<td>A-4</td>
<td>0.02</td>
<td>Moderate</td>
<td>3</td>
<td>1.5</td>
<td>8</td>
</tr>
<tr>
<td>A-5</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>42</td>
<td>1.8</td>
<td>159</td>
</tr>
<tr>
<td>A-6</td>
<td>0.02</td>
<td>Moderate</td>
<td>17</td>
<td>2.9</td>
<td>31</td>
</tr>
<tr>
<td>A-7</td>
<td>&lt;0.01</td>
<td>Mild</td>
<td>16</td>
<td>4.0</td>
<td>130</td>
</tr>
<tr>
<td>A-8</td>
<td>0.02</td>
<td>Moderate</td>
<td>4</td>
<td>4.3</td>
<td>18</td>
</tr>
<tr>
<td>A-9</td>
<td>0.01</td>
<td>Severe</td>
<td>3</td>
<td>6.2</td>
<td>44</td>
</tr>
<tr>
<td>A-10</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>22</td>
<td>13</td>
<td>250</td>
</tr>
<tr>
<td>A-11</td>
<td>0.01</td>
<td>Severe</td>
<td>54</td>
<td>14</td>
<td>130</td>
</tr>
<tr>
<td>A-12</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>4</td>
<td>14</td>
<td>48</td>
</tr>
<tr>
<td>A-13</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>3</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>A-14</td>
<td>0.07</td>
<td>Mild</td>
<td>24</td>
<td>18</td>
<td>75</td>
</tr>
<tr>
<td>A-15</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>26</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>A-16</td>
<td>&lt;0.01</td>
<td>Mild</td>
<td>5</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>A-17</td>
<td>&lt;0.01</td>
<td>Moderate</td>
<td>8</td>
<td>54</td>
<td>48</td>
</tr>
<tr>
<td>A-18</td>
<td>0.03</td>
<td>Moderate</td>
<td>48</td>
<td>64</td>
<td>173</td>
</tr>
<tr>
<td>A-19</td>
<td>0.06</td>
<td>Mild</td>
<td>28</td>
<td>83</td>
<td>32</td>
</tr>
<tr>
<td>A-20</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>4</td>
<td>95</td>
<td>8</td>
</tr>
<tr>
<td>A-21</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>62</td>
<td>324</td>
<td>28</td>
</tr>
<tr>
<td>A-22</td>
<td>&lt;0.01</td>
<td>Moderate</td>
<td>27</td>
<td>525</td>
<td>27</td>
</tr>
<tr>
<td>A-23</td>
<td>0.01</td>
<td>Moderate</td>
<td>10</td>
<td>820</td>
<td>28</td>
</tr>
<tr>
<td>A-24</td>
<td>&lt;0.01</td>
<td>Severe</td>
<td>52</td>
<td>9,044</td>
<td>42</td>
</tr>
</tbody>
</table>

B-1          | <0.01                    | Severe            | 12                                                | 1.0                                               | 232                                                  |
B-2          | <0.01                    | Severe            | 6                                                 | 1.2                                               | 133                                                  |
B-3          | <0.01                    | Moderate          | 2                                                 | 1.6                                               | 45                                                   |
B-4          | <0.01                    | Severe            | 8                                                 | 2.5                                               | 212                                                  |
B-5          | <0.01                    | Severe            | 13                                                | 4.0                                               | 250                                                  |
B-6          | <0.01                    | Severe            | 4                                                 | 4.0                                               | 102                                                  |
B-7          | <0.01                    | Severe            | 18                                                | 4.3                                               | 158                                                  |

*Category A, inhibitor detected on multiple occasions; category B, inhibitor detected only once.
confirmed by quantitative assays of factor VIII:C inhibitor activity on plasma samples forwarded to the reference laboratory. Maximum inhibitor levels in these patients were between 1.0 and 4.3 Bethesda U/mL. Inhibitors in category A developed by the age of 5 in seven patients, by the age of 20 in 12 patients, and by the age of 30 in 17 patients. The other seven inhibitors developed during the fourth, fifth, sixth and seventh decades. All seven transient inhibitors (category B) were detected before the age of 20. The incidence of new inhibitors was 5.6% (9/160) for noninhibitor patients less than 5 years of age at entry into the study and 1.9% (22/1,146) for those older than 5 years at entry (P < .01). Corresponding incidence figures for persistent inhibitors only (category A) were 4.4% and 1.5% (P < .01).

Inhibitors arose after eight to 250 cumulative days of exposure to factor VIII (Fig 2 and Table 1). Such exposure occurred over a time span of 1 to 60 years among these patients. Twelve of 15 inhibitors with maximum titers >10 Bethesda U/mL developed within 75 exposure-days to factor VIII. The development of lower titer inhibitors did not correlate with the number of exposure days, and the amount or source of factor VIII given during the year before appearance of these inhibitors was not different from the amount given to patients who developed more potent inhibitors. Although several high-titer inhibitor patients were not rechallenged with factor VIII after inhibitor appearance, all the low-titer patients were rechallenged at least once (often multiple times) after inhibitor detection. In the absence of factor VIII stimulation, five patients showed an exponential fall of inhibitor levels, with a mean half-time of 4.2 weeks.

No relationship was found between inhibitor development and a number of other variables examined. These included illnesses occurring or drugs used within the preceding year, the changes in a number of clinical laboratory test results including blood counts and levels of liver enzymes and serum immunoglobulins. Regarding drugs, 17 patients received antibiotics (including seven who received penicillin) during the year preceding inhibitor development; the remaining 14 patients were not treated with antibiotics. Although a substantial number of patients in the study had HLA typing performed, only three of 31 new inhibitor patients were typed.

Four major patterns appeared among the newly detected inhibitors. The first group consisted of the seven patients with lower-titer inhibitors (maximum titer, ≤4.3 Bethesda U/mL) that were detectable on only a single occasion despite continued exposure to factor VIII (Table 1, category B). The second group consisted of five patients whose inhibitors persisted for varying periods of time and then disappeared. The low-titer inhibitor (maximum, 1.5 Bethesda U/mL) in patient A-4, a 3-year-old child, disappeared within 18 months of discovery despite continued treatment with factor VIII concentrates, and his clinical disease, which had become severe after inhibitor development, reverted to moderate severity. In patient A-7 the inhibitor disappeared within 6 months, but his treatment was changed entirely to prothrombin complex concentrates (PCC) after inhibitor development. Similarly, the inhibitor in patient A-12 disappeared within 13 months during treatment largely consisting of PCC. Patients A-14 and A-19, the only two with preinhibitor factor VIIIIC levels >0.03 U/mL, developed severe hemorrhagic signs and symptoms and factor VIIIIC levels <0.01 U/mL upon emergence of their inhibitors. Before this complication these two patients had infrequent bleeding problems and limited needs for factor VIII treatment (see Table 1), typical for mild hemophilia. In both patients the inhibitor gradually disappeared within 2 years despite continued therapy with factor VIII (A-14) or PCC (A-19). Concomitantly, there was a decrease in their bleeding problems and a return of their plasma factor VIIIIC to preinhibitor levels. The third group consisted of seven patients with persistent low-titer inhibitors that never exceeded 6.2 Bethesda U/mL despite exposure to factor VIII (A-1, A-2, A-3, A-5, A-6, A-8, and A-9), and in four of these patients inhibitor titers never exceeded 2 Bethesda U/mL. These seven patients continued to be treated effectively with factor VIII concentrates, although at somewhat higher doses than those used in uncomplicated hemophiliacs. The fourth group consisted of 12 patients who developed high-titer antibodies (maximum titers, ≤13 Bethesda U/mL) and were only treated with factor VIII when their titers fell; otherwise they were treated with PCC.

Response to factor VIII infusions. The response to infused factor VIII was studied in four patients in category A on a total of nine occasions and in a single occasion in one patient in category B. Because there was no protocol requirement for such studies, the data are somewhat fragmentary. In patients with low-titer inhibitors (1 to 6 Bethesda U/mL) there was no relationship between titer and in vivo yield. For example, patient A-9 was studied on six occasions; in vivo yields were 25% to 30% of expected values at inhibitor titers varying between 1.0 and 6.2 Bethesda U/mL. On the other hand, patient A-7 had an in vivo yield of 100% at an inhibitor titer of 4.0 Bethesda U/mL, whereas patient B-3 had a yield of only 10% when his inhibitor titer was 1.6 Bethesda U/mL. The half-life of factor VIII:C may have been more closely related to inhibitor titer than initial factor VIII:C yields. For example, patient A-9 had a factor VIII:C half-life of eight...
hours at an inhibitor titer of 1.0 Bethesda U/mL and only three hours when his inhibitor titer was 5.7 Bethesda U/mL. Substantially higher inhibitor titers were associated with unmeasurable factor VIII:C yields. For example, factor VIII infusion produced no measurable yields in patients A-23 and A-22 at inhibitor titers of 8.0 and 20 Bethesda U/mL, respectively.

**DISCUSSION**

Previous studies of factor VIII:C inhibitors in hemophilia A have relied largely on retrospective data. The prospective data reported here provide some new insights into inhibitor development and also allow an assessment of data collected retrospectively by ourselves and others.

Perhaps the most interesting aspect of our data relates to the natural history of inhibitors after detection. Of the 31 new inhibitor patients, seven were detected on only a single occasion (category B). The phenomenon of the highly transient antibody to factor VIII:C has not been appreciated previously. All seven patients were under the age of 20 when the inhibitor was detected. In all cases, the inhibitor was easily measurable, and the results were corroborated by the reference laboratory. In six of the seven patients the inhibitor appeared after very prolonged exposure to factor VIII (102 to 250 exposure days). The significance of inhibitors measured on a single occasion is difficult to assess, and the reason these patients developed inhibitors but did not sustain their antibody response in the face of continued antigenic challenge is unknown. It will be of importance to follow these seven patients carefully to determine whether they will develop persistent inhibitors in the future.

Of the 24 patients whose inhibitors were demonstrable on multiple occasions (category A), inhibitors disappeared in three despite continued factor VIII therapy. Two of these (A-14, A-19) patients had mild hemophilia, and their inhibitors disappeared within 2 years. Inhibitors in such patients frequently disappear after cessation of factor VIII therapy and do not recur despite reexposure to factor VIII. The third inhibitor (A-4) appeared in a 3-year-old child with a factor VIII:C level of 0.02 U/mL and disappeared within 18 months. Inhibitors in two other patients (A-7, A-12) have disappeared, although these two patients had not been rechallenged with factor VIII. Thus, ten, and possibly 12, of the 31 new inhibitors detected during this study disappeared within 2 years. It is likely that category B inhibitors have been overlooked in all retrospective analyses including our own.

We were able to determine with some confidence the age of the patient at the onset of inhibitor development as well as the usual factor VIII:C level before inhibitor development. These variables are particularly difficult to assess retrospectively because in many cases inhibitor onset occurred years before the study began, at a time where inhibitor titers were not routinely measured and when factor VIII:C measurements were not as well standardized as they are today. In particular, retrospective data might be expected to indicate as the age of onset the time when an inhibitor became a clinically significant factor in replacement therapy. Low-titer inhibitors could possibly have been overlooked for several years. It is of some importance, therefore, that the data in this paper are very similar to our retrospective data and, with respect to age of onset, to the data published by Rizza and Matthews. Nearly two thirds of all inhibitors were detected by the age of 20, and 94% arose in patients whose usual factor VIII:C level was \( \leq 0.03 \) U/mL. On the basis of our prospective data, we calculate that the relative risk of inhibitor formation is about four times higher for patients under the age of 5 years than for older patients. Similarly, we find that the risk of inhibitor formation in patients with factor VIII:C levels \( \leq 0.03 \) U/mL is about four times higher than it is in the group of patients with factor VIII:C levels \( >0.03 \) U/mL.

The basis for factor VIII:C antibody production is unknown. Because factor VIII:C antibodies in patients with hemophilia occur only in response to infused factor VIII, the suggestion has been made that antibodies might only form in individuals lacking factor VIII:C. Data from this study demonstrate some difficulty in reproducibly measuring factor VIII:C levels \( <0.01 \) U/mL because even patients who had levels \( <0.01 \) U/mL on repeated testing had occasional levels reported as 0.01 or even 0.02 U/mL. Thus, we have considered all patients with factor VIII:C levels \( \leq 0.03 \) U/mL as a single group. Although 94% of inhibitors occurred in individuals with preinhibitor factor VIII:C levels \( \leq 0.03 \) U/mL, three of our patients had at least some immunoassayable factor VIII:Ag, which suggests that absence of factor VIII molecules is not a requirement for inhibitor development. In fact, the prevalence of factor VIII:Ag in these samples is not different from that in a large population of patients without inhibitors. Thus, it is possible that a specific abnormality in the immune surveillance system in some patients with hemophilia may be important in the elicitation of antibodies to factor VIII:C. Nevertheless, it is of great interest that in all three individuals with disproportionately more factor VIII:Ag than factor VIII:C the inhibitor was transient.

As previously suggested by Allain and Frommel, inhibitor patients seem to fall into two major groups with respect to their inhibitor titers. Thus, seven of our 19 patients with persistent antibodies seem to be low responders in that their inhibitor levels never exceeded 6.2 Bethesda U/mL despite repeated exposure to factor VIII. Four of the patients had maximum inhibitor levels \( \leq 2 \) Bethesda U/mL, a figure in good agreement with the corresponding prevalence (24.1%) in our retrospective data on 216 patients with inhibitors. Similarly, the prevalence of high responders, defined arbitrarily as patients with inhibitors persisting throughout the period of this study and maximum titers \( >10 \) Bethesda U/mL, is 63.2% (12/19) compared with 60.2% in the retrospective analysis. Although our overall data suggest that perhaps 20% of patients with persistent inhibitors will not develop maximum titers greater than 2 Bethesda U/mL, it is possible that some of these patients may later develop higher titers in response to further factor VIII treatment.

It should be emphasized that this analysis of responder categories includes only those patients whose inhibitors, whether high or low, persisted throughout the study. We suggest that transient inhibitors should be excluded from
calculations of prevalence. Indeed, some patients with transient inhibitors like those in category B (Table 1) might well have had their inhibitors emerge and disappear between testing periods and therefore could have been missed completely. Nonetheless, we acknowledge that if transient inhibitors were not excluded from our calculations the prevalence of high-responder patients as defined earlier would be 48.4% (15/31) rather than 63.2% (12/19) and low-responder patients would thus predominate.

In any case, the distinction between the two responder categories is further underscored by the data on factor VIII exposure before inhibitor development. Twelve of 15 inhibitors whose maximum titer was >10 Bethesda U/mL were elicited after 75 or fewer exposure days to factor VIII. Low-titer inhibitors occurred over a very wide range of preceding exposure. Our data support those of Strauss who reported in 1969 that high-titer inhibitors generally developed after less than 90 exposure days to factor VIII.

All told, the following findings suggest a genetically determined component to the factor VIII:C antibody response in patients with hemophilia A: (a) a greatly increased risk of inhibitor formation under the age of 5; (b) the occurrence of most inhibitors before the age of 30; (c) the elicitation of most high-titer inhibitors after less than 75 exposure days to factor VIII; and (d) the apparent existence of low-responder and high-responder inhibitor categories, although it is possible that chronic factor VIII therapy may reduce significantly or even eliminate potent inhibitors as shown by Rizza and Matthews and Brackmann. Further data in support of a genetic role in the development of factor VIII inhibitors among patients with hemophilia A have been reported by Shapiro.

REFERENCES


ACKNOWLEDGMENT

The authors wish to thank Jeanne Romanic, Sandra McNamara, and Wanda Braxton for their expert secretarial assistance.

APPENDIX

Principal investigators of the Hemophilia Study Group: S.S. Shapiro, MD and J.E. Palascak, MD, Cardeza Foundation, Jefferson Medical College, Philadelphia (Reference Laboratory and Coordinating Center); F.M. Gill, MD, Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine; P.H. Levine, MD, Memorial Hospital, University of Massachusetts Medical School, Worcester; M.E. Eyster, MD, and J.O. Ballard, MD, The Milton Hershey Medical Center of the Pennsylvania State University, Hershey; L.M. Aledort, MD, and M. Diaz, MD, Mt Sinai School of Medicine, New York; M.W. Hilgartner, MD, New York Hospital-Cornell Medical Center; W.E. Hathaway, MD, and H.S. Hathaway, MD, University of Colorado Medical Center, Denver; J.R. Edson, MD, University of Minnesota Medical School, Minneapolis; C.W. McMillan, MD, P.M. Blatt, MD, H.R. Roberts, MD, and G.C. White II, MD, University of North Carolina School of Medicine, Chapel Hill; S.H. Goodnight, MD, University of Oregon Health Sciences Center, Portland; C.K. Kasper, Orthopaedic Hospital, University of Southern California, Los Angeles; J.M. Lusher, MD, and A.I. Warrier, MD, Children's Hospital of Michigan, Wayne State University School of Medicine, Detroit; J. Lazerson, MD, Medical College of Wisconsin and Milwaukee Children's Hospital, Milwaukee; W.K. Poole, PhD, and A.V. Rao, PhD, Research Triangle Institute, Research Triangle Park, NC (Statistical Methodology and Analysis Center); J.C. Fratantoni, MD, T. Edson, MD, and A.P. Ball, PhD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD (Project Officers).

The natural history of factor VIII:C inhibitors in patients with hemophilia A: a national cooperative study. II. Observations on the initial development of factor VIII:C inhibitors

CW McMillan, SS Shapiro, D Whitehurst, LW Hoyer, AV Rao and J Lazerson

Updated information and services can be found at: http://www.bloodjournal.org/content/71/2/344.full.html

Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at: http://www.bloodjournal.org/site/subscriptions/index.xhtml