Patients with hemophilia A without human immunodeficiency virus type 1 (HIV-1) infection have lower CD4+ counts and CD4+/CD8+ ratios than controls. This is usually interpreted as a therapy-induced immunodeficiency. Our data re-examine the effect of therapy on peripheral blood mononuclear cell immunophenotypic subpopulations in all congenital clotting disorders. Since late 1985 we have prospectively observed HIV-1 uninfected persons with all types and severity of disorder. Controls were household members without clotting disorders or HIV-1 infection. Analyses of immunophenotype and treatment included a longitudinal random effects model. Compared with controls, age-adjusted CD4+ counts were significantly lower in treated patients (P < .0001) and in patients with all types of clotting disorders who were seidem or never treated (P = .0005). Significantly lower values among both treated and untreated clotting disorder subjects (P < .05) were likewise found for total lymphocytes, several other T-cell subsets, and the CD4+/CD8+ ratio. For most indexes, including the CD4+ count and CD4+/CD8+ ratio, the type of clotting deficiency was not a significant variable. Comparing persons who had no or minimal therapy with those having the most showed increases in CD8+ (P = .0017) and CD20+CD21- counts (P = .0255), and a lower CD20+CD21+/CD20+ ratio (P = .0106) in the latter. Controls and persons with clotting disorders differ in CD4+ count. Among those with clotting factor disorders, there is no difference attributable to type of clotting disorder or factor therapy. Large amounts of treatment increased CD8+ and CD20+CD21- counts, but were not associated with a change in CD4+ count.

AQUIRED immunodeficiency syndrome (AIDS) was first reported in persons with hemophilia A in 1982, prompting immunologic studies of this group. These observations showed that patients, particularly those treated with factor VIII concentrate, had a lower number and/or percentage of CD4+ lymphocytes, an increased number and/or percentage of CD8+ cells, and a decreased CD4+/CD8+ ratio. The possibility of an infectious agent contaminating American-manufactured concentrate was considered, particularly in view of the use of plasma from paid plasmapheresis donors for source plasma, but an adverse effect of the heavy exposure of hemophiliacs to allotypically heterologous proteins was believed to be the more likely explanation. Contributing to the latter impression was the fact that similar changes were observed by investigators in Glasgow, Scotland, and Australia, where nationally produced factor VIII concentrates were derived from voluntary donor populations free of clinically diagnosed AIDS at that time.

The introduction of a test for antibody to human immunodeficiency virus type 1 (anti–HIV-1) demonstrated that severe immunologic changes in asymptomatic hemophiliacs could be largely attributed to HIV-1 infection, including those who exclusively received national products in Scotland and Australia. After it became possible to know which hemophiliacs had HIV-1 infection, there were still reports that uninfected persons had differences in some immunophenotypic subsets compared with controls as well as abnormalities in a number of functional assays applied in vitro to T- and B-cell populations. Ludlum et al found that CD4+ counts and CD4+/CD8+ ratios were low in 15 patients 1 year before their infection with HIV-1, and both indexes were also low in those receiving factor VIII and factor IX concentrates who remained uninfected. The Scottish investigators also stressed a relationship between the extent of lymphocyte changes and the amount of concentrate administered. Another group of investigators has suggested that changes in HIV-1–uninfected hemophiliacs require a number of years to develop. All of these observations have contributed to the present opinion that allotypically heterologous proteins result in lower CD4+ counts.

In the present analyses the Transfusion Safety Study has examined the effect of clotting factor treatment on 25 immunophenotypic indexes of peripheral blood mononuclear cells (PBMC) in an anti–HIV-1–negative population with all forms of congenital clotting disorders. Not only have we considered type, amount, and duration of factor therapy, but also included subjects who had never been treated or not treated since 1979, when the hemophilia population became at risk for HIV-1 infection. As controls, we tested members of households of clotting disorder subjects.

MATERIALS AND METHODS

The Transfusion Safety Study is a multicenter, cooperative investigation of factors that determine the occurrence or modify the expression of transfusion-transmitted infections. It also examines the immune consequences of blood components and plasma derivatives themselves. All patients and controls gave written consent for participation, including specific authorization for anti–HIV-1 testing.
Patients. Beginning in August 1983, study centers in New York, NY, Miami, FL, Detroit, MI, Seattle, WA, and San Francisco and Los Angeles, CA, tried to recruit all persons known by the participating hemophilia clinics to have any type of congenital clotting disorder, regardless of the need for therapy or regularity of clinic visits. If the patients could not be seen at one of the hemophilia centers, study nurse-epidemiologists obtained data and blood specimens at home or some other site convenient for the person. As controls, we solicited participation by spouses, parents, children, and any other persons without clotting disorders who were members of a household with one or more members with a congenital clotting disorder.

Among 1,230 persons with congenital clotting disorders observed on one or more occasions, 350 were males aged ≥5 years, who were anti–HIV-1 negative on entry, remained negative on all follow-up visits, and had one or more measurements of immunophenotypic subsets. Of the 350, there were 307 known from interview and/or records to have been treated with concentrates and/or components on one to multiple occasions from 1979 to the time of entry.

Control subjects were household members without any congenital clotting disorder. They were seen at the same intervals as the patients with clotting disorders, the same information was obtained, and the same laboratory tests were performed. For the present comparison we selected 164 males in the same age range as the patients with clotting disorders. Controls had a median age of 6 years older than patients (P < 0.01 by Wilcoxon rank sum test), but all values were age-adjusted in the analyses (see below).

Estimates of amount of factor therapy. To relate the type and amount of factor therapy to the pattern of lymphocytic immunophenotypes, we sought a complete history of clotting factor concentrates and blood components since January 1979. To the maximal practical extent, information from all sources was checked against blood bank and pharmacy records. For the preentry period, the study group summarized annual estimates as being the clotting factor units administered as factors VIII and/or factor IX concentrates, and/or calculated units of factor VIII activity from exposure through cryoprecipitate, fresh frozen plasma, and cellular components. The latter calculation was based on the usual content of factor VIII activity from the number of donors to whom there was exposure. The conversions were cryoprecipitate, 100 U per donation, fresh frozen plasma, 200 U, and platelets, 50 U.

Completeness of therapy records from 1979 to entry varied enormously because of differences in clinical records systems, the thoroughness with which individual patients kept treatment diaries, the proximity of the patient to the clinic for emergency situations, sources of supply other than the participating clinic, and re-location to the center from one in another city between 1979 and entry. Because the exact amount of factor therapy was not known for all patients, we gave detailed attention to documenting the dosage at the two extremes of therapy because some patients in the group who were classified as having intermediate amounts of therapy (221 subjects) could only be ranked approximately.

Patients initially classified as untreated from 1979 to entry and those classified as minimally treated from 1979 through 1987 had special reviews of clinic records, including other hospitals and clinics in the geographic areas covered by the six clinical centers. Among the 350 patients, we identified 43 who remained completely untreated from 1979 through approximately 2 years (4 visits) after entry. Twenty-eight of these patients stated they had never been treated; 13 had treatment on one to a few occasions before 1979.

To obtain larger groups at these extremes for statistical comparisons, the untreated category was supplemented by 36 patients who had received no more than 5,000 U in any calendar year, and were statistically similar to the untreated by exact testing. Their cumulative individual totals ranged up to 5,760 U.

This group of 79 persons with no or minimal therapy was compared with 53 patients who required the largest amount. Data concerning type and amount of treatment for the heavily treated subjects were sparse for 1979 and 1980, and the characterization of those receiving the largest amount was based on information beginning in 1981. They received treatment in every year from 1981 to entry; they had therapy during each of the four 6-month intervals after entry; and they received ≥25,000 U in at least two calendar intervals. Their individual cumulative totals ranged from 100,000 to greater than 2,000,000 U in the same interval. For patients classified as receiving the largest amount, the year-by-year consistency of the amount received was used as evidence supporting this classification.

During the period of observation, essentially all concentrates were of intermediate purity.

Clinical evaluation. Initially, a study nurse-epidemiologist obtained a medical history, and blood for serologic, hematologic, and immunologic laboratory measurements. Follow-up visits were scheduled at 6-month intervals, and included an interval medical history, factor treatment history and record review, and laboratory testing.

Virologic testing. For all clinical sites, HIV-1 negativity was established in the Coordinating Center Laboratory by enzyme-linked immunoassay (ELISA) for anti–HIV-1 in multiple specimens (Abbott Laboratories, North Chicago, IL). At least one serum from each patient consistently ELISA-negative for anti–HIV-1 was also tested by Western immunoblot assay.30 Selected anti–HIV-1-negative patients were evaluated by virus culture (University of California, Davis, CA) and/or polymerase chain reaction (PCR) assay (Pathology Institute, San Francisco, CA). The criteria for culture and/or PCR testing were ≥25,000 U of concentrate or cryoprecipitate from 1981 to entry, and one or more indeterminate bands on immunoblot assay.

Antibody to hepatitis B core antigen (anti-HBc) and hepatitis C virus (anti-HCV) were determined by ELISA (Ortho Diagnostics, Raritan, NJ). Positive results by the latter were evaluated by RIBA Second Generation Test (Chiron Corporation, Emeryville, CA).

PBMC immunophenotyping. Each clinical center performed complete blood counts, and analyzed the PBMC subsets using a whole blood staining technique and two-color flow cytometry ( Coulter EPICS-C, Hialeah, FL).21,22 All immunology laboratories used the same lots of MoAb (Coulter Diagnostics, Hialeah, FL) and used standardized protocols. CD2+ cells were measured in two different pairings (with anti-CD26 and anti-CD11b); CD4+ cells, in three pairings (with anti-CD8, anti-CD29, and anti-CD45RA); and CD8+ cells in three pairings (with anti-CD4, anti-HLA-DR, and anti-CD56). Algorithms for the best estimate of CD2+, CD4+, and CD8+ subpopulations were established and applied routinely.23 A quality control program monitored interlaboratory and intraaboratory comparability cross-sectionally and longitudinally.

Statistical analyses. To compensate for individual fluctuations and laboratory variations in immunophenotypic measurements, we used the first five observations or the number available during the first 2 years of follow-up to estimate a mean for each patient.

Inference about group differences among controls, untreated disorders, and factor-treated disorders was made using longitudinal random effects (LRE) regression analysis.7,24,25 This model estimated age-adjusted group effects. The LRE approach allowed use of data in which the number of measurements per person differed, and provided maximum likelihood estimates (MLEs) for means of the independent variables.

For Table 1, under the LRE regression model, a PBMC index for
subject $i$ ($i = 1, 2, \ldots, n$) at time $j$ ($j = 1, 2, \ldots, j_i$) among longitudinal observations ($Y$) is expressed by a linear combination of fixed regression coefficients ($\beta$) and a random effect ($\theta$), i.e.,

$$Y_i = \beta_0X_{i0} + \beta_1X_{i1} + \beta_2X_{i2} + \beta_3(x_i - 30) + \theta_i + e_i,$$

where $\beta_3$ is the fixed, age-adjusted (to age 30 years) mean of the controls, $X_{i0}$ is a dummy variable (0, 1) indicating the control subjects, $\beta_1$ is the fixed, age-adjusted mean of the factor-untreated patients, $X_{i1}$ is a dummy variable (0, 1) indicating the category of clotting disorder, $\beta_2$ is the fixed, age-adjusted mean of the factor-treated subjects, $X_{i2}$ is a dummy variable (0, 1) indicating the factor-treated disorder, $\beta_3$ is the regression coefficient for the fixed effect of age at entry, $\theta_i$ is the measure of the fixed effect of subject $i$, and $e_i$ is the usual normal error term with mean 0 and variance $\sigma^2$. The $\theta_i$ were assumed to come from a normal distribution with mean 0 and variance $\sigma^2$.

We fitted additional regression model terms for age to eliminate any confounding of the estimates of $\beta_0$, $\beta_1$, and $\beta_2$ by that variable. For consistency, the results in Table 2 include adjustment for linear and quadratic terms in age.

Because the type of congenital clotting disorder differed so markedly between the factor-untreated and -treated patients (Table 3), we also adjusted in the statistical model for type of disorder by adding additional variables to represent each of the five categories in Table 3. Year-to-year laboratory variations in MLE means and their confidence limits during the period in which these observations were made were also examined; the trend of CD4+ values approached statistical significance in 1989 ($P = 0.0688$); accordingly, an additional variable was introduced in the LRE model for laboratory trend.

Only percent CD4+ values were normally distributed. A normal distribution was approximated by a logarithmic transformation of: percent CD4+; counts of CD4+, CD8+, CD8+DR+, CD8+CD56+, CD2+CD14+, and CD14+DR+. The statistical significance levels ($P$ values) given are two-sided.

RESULTS

PBMC indexes in controls and untreated and treated patients. Variations in the distribution of clotting disorders by amount of treatment (Table 3) showed no significant effect either by exact testing or by the coefficients in the longitudinal random effects model. We have therefore pooled the results for all clotting disorders.

Of the 43 subjects we classified as untreated, 28 stated that they recalled no therapy or transfusion for any reason, and 15 had received some therapy before 1979. The MLE of
Table 2. Group Comparisons of HIV-1-Infected Males With Untreated and Treated Congenital Clotting Disorders and Healthy Household Contacts

<table>
<thead>
<tr>
<th>Ratio of MLE of Group Means</th>
<th>A Untreated (n = 43)</th>
<th>B Treated (n = 307)</th>
<th>C Treated (n = 307)</th>
<th>P for Paired Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytes</td>
<td>Controls (n = 164)</td>
<td>Controls (n = 164)</td>
<td>Untreated (n = 43)</td>
<td></td>
</tr>
<tr>
<td>CD2+</td>
<td>0.85</td>
<td>0.87</td>
<td>1.02</td>
<td>0.0022</td>
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<tr>
<td>CD2+CD26*</td>
<td>0.76</td>
<td>0.72</td>
<td>0.93</td>
<td>0.0015</td>
</tr>
<tr>
<td>CD2+CD56+CD2+</td>
<td>0.91</td>
<td>0.92</td>
<td>0.90</td>
<td>0.0099</td>
</tr>
<tr>
<td>%CD4+</td>
<td>0.93</td>
<td>0.90</td>
<td>0.97</td>
<td>0.0005</td>
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<tr>
<td>CD4+</td>
<td>0.79</td>
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<td>0.98</td>
<td>0.0005</td>
</tr>
<tr>
<td>CD4+CD29+</td>
<td>0.81</td>
<td>0.85</td>
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</tr>
<tr>
<td>CD4+CD29*/CD4+*</td>
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<td>1.09</td>
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<td>0.2977</td>
</tr>
<tr>
<td>CD4+CD45RA*</td>
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<td>0.74</td>
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<tr>
<td>%CD8+</td>
<td>0.93</td>
<td>0.97</td>
<td>1.05</td>
<td>0.3067</td>
</tr>
<tr>
<td>CD8+</td>
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<td>1.03</td>
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<tr>
<td>CD8+CD5+</td>
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<td>0.97</td>
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<td>CD8+CD5+CD8+</td>
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<td>CD8+CD5+CD8+</td>
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<td>0.94</td>
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<td>0.96</td>
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<td>CD14+</td>
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<td>1.07</td>
<td>1.01</td>
<td>0.3617</td>
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<tr>
<td>CD14+CD11b*</td>
<td>1.01</td>
<td>1.02</td>
<td>1.02</td>
<td>0.9093</td>
</tr>
</tbody>
</table>

Untreated means no transfusion or factor treatment ever (n = 28) or on a few occasions before 1979 (n = 15). MLE is ratio for paired age-adjusted means.

the means and the 95% confidence intervals (95% CI) for the CD4+ count as cells per microliter were very similar: 745 (539, 1031) and 896 (592, 1355), respectively. The respective CD4+/CD8+ ratios were 1.54 (1.12, 2.13) and 1.54 (1.13, 2.32).

To assess the reliability of the transfusion histories of the factor-untreated patients, we examined their frequency of antibody to the two common transfusion-transmitted hepatitis viruses. Among the 28 who were never treated, 2 (7%) were anti-HBc positive and 1 (4%) was anti-HCV positive. For the 15 patients who stated they had received transfusions or treatment earlier, 5 (33%) and 6 (40%), respectively, were positive for these antibodies.

For an overall comparison of controls (n = 164), untreated patients (n = 43), and those with any treatment since 1979 (n = 307), Table 1 gives the MLE means (95% CI) for 25 lymphocyte indexes. Table 2 gives the ratios of the estimated means in paired comparisons to show the direction and magnitude of the difference and the statistical significance of the paired difference.

 Compared with the controls, we found statistically significant lower values for CD4+ counts in both the untreated (P = .0005) and the treated (P < .0001) subjects. There were no differences in CD8+ counts in the three comparisons, resulting in CD4+/CD8+ ratios that were lower in both untreated (P = .0185) and treated (P < .0001) patients.

Other indexes in which both the untreated and treated subjects had lower values (P < .05) than controls (comparisons A and B) were: absolute counts for lymphocytes, CD2+, CD2+CD26+, CD4+CD29+, CD4+CD45RA+, and CD2+CD11b+. The CD56+ and CD8+CD56+ counts were decreased to approximately the same extent in untreated as treated subjects (comparisons A and B), but only the latter were clearly significantly different from the controls.

Comparison of treated and untreated subjects (comparison C) did not show any differences that approached P < .05 except for a lower CD20+CD21+ count (P = .0541) and decreased CD20+CD21+CD20+ ratio (P = .0213).

Amount of factor administered in relation to lymphocyte indexes. Comparison of the subjects with no or minimal treatment (n = 79) and the largest amount of treatment (53) showed statistically similar CD4+ counts: 756 and 718 cells/μL, respectively. With large amounts of treatment, CD8+ counts were significantly higher with means of 470 and 587...
cells/μL, respectively. CD20⁺CD21⁻ counts were significantly lower among those with no or minimal treatment (117/μL) compared with the most heavily treated (145/μL) \( (P = .0255) \). The number of resting B cells (CD20⁺CD21⁺) was lower with large treatment amounts, but this difference was not significant. The CD20⁺CD21⁺/CD21⁻ ratio was significantly lower in those most heavily treated \( (P = .0106) \).

**DISCUSSION**

The Transfusion Safety Study protocols were designed to recruit persons exposed to various types, sources, and amounts of blood components and clotting factor concentrates, including those receiving no or minimal treatment. As a result, we recruited not only persons being regularly seen in hemophilia centers, but also those who seldom or rarely attended because they had very few clinical problems related to their disorder. Data on prevalence of anti-HBc and anti-HCV in the latter group supported the clinical history of no or minimal exposure to components and concentrates.

We found that T-cell abnormalities, including lower CD4⁺ percentages and counts, occur in untreated as well as factor-treated patients. The failure to recognize this fact previously seems attributable to the comparison of moderate and severe forms of hemophilia A with normal controls, but not with persons whose clotting disorders was untreated or minimally treated. Because lower values are now demonstrated for all types of clotting disorders in untreated as well as treated patients, the T-cell abnormalities can no longer be attributed to alloreactive stimulation by factor therapy.

The T-cell deviations we observed in both untreated and treated patients with congenital clotting disorders were in the CD4⁺ T-cell and CD56⁺ natural killer cell subsets. The absolute values were 20% to 25% below controls. At all three levels of therapy evaluated, the unprimed/suppressor-inducer subset (CD4⁺CD45RA⁺) and the primed/helper-inducer/memory subset (CD4⁺CD29⁺, CD2⁺CD26⁺) were decreased proportionately. Although decreased CD4⁺ counts of this magnitude do not seem to be clinically significant, they may contribute to the in vivo skin test anergy and decreased in vitro lymphocyte proliferation responses reported in HIV-I-negative hemophiliacs.

Our observation that CD4⁺ cells are low in untreated as well as treated clotting disorders does not necessarily conflict with the in vitro observation of Hay et al.\(^{22} \) that there is a functional suppression from factor exposure. They found that T-cell activation was decreased by factor VIII concentrates compared with normal controls. However, before making any inferences about the effect of therapy, untreated hemophiliacs must be included in the comparisons. Our observation that CD4⁺ cells are low in untreated as well as treated clotting disorder suggests that there is a report of abnormal monocyte phagocytic function following factor VIII concentrate administration.\(^{29} \)

Similar studies in HIV-I-uninfected, congenital clotting disorder patients have either been limited to hemophilia A or very few observations concerning other conditions reported.\(^{17} \) Our search for untreated or minimally treated subjects resulted in our having an HIV-I-uninfected group with a disproportionate number of subjects with clotting disorders other than hemophilia A (Table 3). This happened because of a lower risk associated with factor IX than factor VIII concentrates; less frequent need for therapy in some disorders; and, a clinical ability to manage a relatively larger percentage of disorders other than hemophilia A and B with small amounts of cryoprecipitate and fresh frozen plasma. We looked for and found the same immunophenotypic PBMC changes in CD4⁺ and CD56⁺ populations in all forms of clotting disorders.

Our thought when we first noticed immunophenotypic differences even in untreated clotting disorder subjects was that lower CD4⁺ counts would be caused by genetically determined factor(s) associated with hemophilia A, because it is the most frequent clotting disorder. We did not expect a comparable decrease in CD4⁺ counts to be seen in all congenital clotting disorders because of their diverse genetic features.
characteristics. One possible explanation we considered was that even a mild bleeding tendency could produce immunophenotypic changes from clinically inapparent hemorrhage; nonetheless, it seems likely that any such mechanism would cause more CD4+ depression in severe compared with mild bleeding disorders. Another possibility is that there is some modification in vascular endothelial-lymphocyte interaction that alters the trafficking patterns and/or distribution of specific cell populations between peripheral blood and tissues.12

An effect of amount of treatment on immunophenotypic counts was found among patients receiving the largest amounts of treatment compared with those receiving no or only minimal treatment. Persons receiving the largest amount had a mean CD8* (cytotoxic/suppressor) count increased by 25%, although neither the CD8*DR* (activated) nor CD8*CD56* (natural killer) subsets were disproportionately increased. The CD8* change has been reported previously17 and seems from our data probably attributable to amount of treatment. The CD20*CD21* (nonresting B cells) and the CD4*CD29*/CD4* (helper/inducer) ratios also increased with treatment amount, which are phenotypic findings consistent with activation following antigenic stimulation. Our immunophenotypically based observation of B-cell activation is consistent with the hypergammaglobulinemia seen in HIV-1-uninfected hemophilia, and with the in vitro finding that B cells are activated but unresponsive to further specific stimulation.29,30,33

We observed two apparently independent sets of immunophenotypic changes in subjects with congenital clotting disorders: decreases in the CD4+ T-cell and CD56+ natural killer cell subsets, which are present in all forms of clotting disorders and are not altered by type or amount of treatment, and increases in the CD8+ T-cell and activated (CD20*CD21*) B-cell subsets, which are treatment related. Therefore, we do not think any benefits ascribed to high-purity products for HIV-1–negative hemophiliacs should be based on improving CD4+ T-cell counts.

ACKNOWLEDGMENT


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Effect on lymphocyte subsets of clotting factor therapy in human immunodeficiency virus-1-negative congenital clotting disorders. The Transfusion Safety Study Group

J Hassett, GF Gjerset, JW Mosley, MA Fletcher, E Donegan, JW Parker, RB Counts, LM Aledort, H Lee and MC Pike