unequal intervals. Thus, to handle the situation of incomplete or "censored" follow-up, various statistical techniques are used, mainly life-table and product-limit (e.g., Kaplan–Meier[1]) methods. Both techniques are described in many textbooks.[2] A simple interpretation of our 4 per cent cumulative-risk estimate would be that for every 100 patients who survive six years after treatment with semustine, 4 would be expected to acquire leukemia or preleukemia.

The comments of Drs. Rosner and Grünwald underscore the importance of conducting epidemiologic studies of sufficient size and power to assess the possible hazards associated with the variety of anticancer drugs in use today. Studies with small populations or short follow-up may give misleading results and need to be interpreted with caution. Advances in chemotherapy have contributed to major increases in survival times for patients with various forms of cancer. However, as increasing numbers of patients with formerly fatal disease survive as a result of improved treatment, the possible long-term effects of drugs and other therapies will need to be carefully monitored and evaluated.

JOHN D. BOICE, JR., SC.D.
MARK H. GREENE, M.D.
JOHN Y. KILLEN, JR., M.D.
JOSEPH F. FRAUMENI, JR., M.D.
National Cancer Institute
Bethesda, MA 20205

1. Kaplan EL, Meier P. Nonparametric estimation from incomplete observances. J Am Stat Assoc 1958; 53:457-81.
2. Lee ET. Statistical methods for survival data analysis. Belmont, Calif.: Lifetime Learning Publications, 1980.

ABNORMAL T-LYMPHOCYTE SUBSETS IN HEMOPHILIA: RELATION TO HLA PROTEINS IN PLASMA PRODUCTS

To the Editor: It seems beyond doubt that infusions of blood products are mainly responsible for the T-lymphocyte abnormalities and immune deficiency reported in hemophiliacs.[1,2] We have found that abnormalities of T-cell–subset distribution, characterized by low helper-to-cytotoxic/suppressor T-lymphocyte ratios (T4/T8 ratios), are more common in hemophiliacs who have had a high exposure to factor VIII.[3] In contrast, patients who have been treated with large quantities of factor IX more commonly have normal ratios.[3-5]

Opelz et al. first showed that transfusion of leukocytes into renal-allograft recipients enhanced the acceptance rate,[6] and it has been suggested that this apparent immune suppression may result from immunization to HLA proteins on the membranes of transfused lymphoid cells.[7]

HLA-A, -B, and -C antigens contain β_2-microglobulin. Figure 1 shows the β_2-microglobulin content, expressed as nanograms per unit of factor VIII or IX, in 39 batches of clotting-factor concentrate, four single-donor units of cryoprecipitate, and two 30-donor pools of cryoprecipitate. The commercial factor VIII concentrates, brands A through G, were prepared from plasma collected in the United States. The National Health Service (NHS) concentrates were prepared from volunteer-donor plasma at the Blood Products Laboratory, Elstree, England. It was confirmed, through elution chromatography of factor VIII concentrate, that the β_2-microglobulin was present in association with proteins of a mass approximately that of HLA-A, -B, and -C proteins (55,000 daltons) rather than in free form (immunoassay kits kindly provided by Seward, Bedford, U.K.).

The large amounts of β_2-microglobulin found in factor VIII concentrates and the abnormal distributions of T-lymphocyte subsets that are commonly observed in intensively treated hemophiliacs may be causally related. The observation that patients treated with large quantities of factor IX concentrate more commonly have normal T-cell–subset distributions, and the finding of very low concentrations of β_2-microglobulin in factor IX concentrate, are in accord with this hypothesis. It is noteworthy that both factor IX concentrate and polyelectrolyte-fractionated factor VIII concentrate were prepared by ion-exchange chromatography and had a very low β_2-microglobulin content.

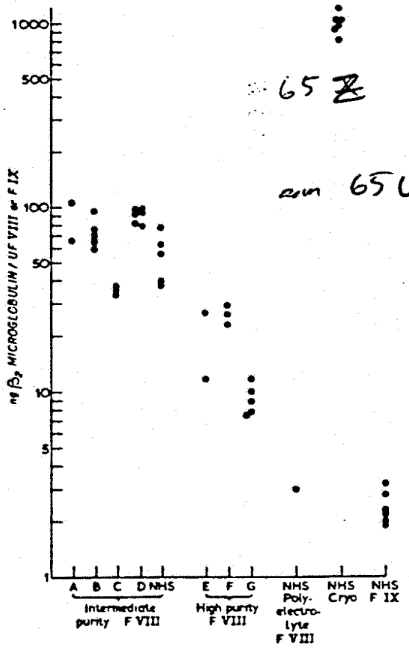

Figure 1. β_2-Microglobulin Content of Various Plasma Products.
For explanation, see text.

It is important to stress that although all patients with the acquired immunodeficiency syndrome have abnormal lymphocyte populations, very few hemophiliacs with abnormal lymphocyte populations have this disorder.[8] We do not postulate that long-term massive exposure to HLA antigens in clotting factor concentrates causes the syndrome, but that such exposure may contribute to increased risk.

CHRISTINE A. LEE, M.A., M.R.C.P., M.R.C.PATH.,
P. B. A. KERNOFF, M.D., M.R.C.P.,
PETER KARAYIANNIS, B.SC., PH.D., JENNY WATERS, B.SC.,
AND H. C. THOMAS, M.SC., PH.D., F.R.C.P.
Royal Free Hospital
London, NW3 2QG, England

1. Update on acquired immune deficiency syndrome (AIDS) among patients with hemophilia A. MMWR 1982; 31:644-6.
2. Menitove JE, Aster RH, Casper JT, et al. T-lymphocyte subpopulations in patients with classic hemophilia treated with cryoprecipitate and lyophilized concentrates. N Engl J Med 1983; 308:83-6.
3. Lee CA, Janossy G, Ashley J, Kernoff PBA. Plasma fractionation methods and T-cell subsets in haemophilia. Lancet 1983; 2:158-9.
4. Kessler CM, Schulof RS, Goldstein AL, et al. Abnormal T-lymphocyte subpopulations associated with transfusions of blood derived products. Lancet 1983; 1:991-2.
5. Saidi P, Kim HC, Raska K Jr. T-cell subsets in hemophilia. N Engl J Med 1983; 308:1291-2.
6. Opelz G, Terasaki PI. Post kidney-transplant survival in recipients with frozen-blood transfusions or no transfusions. Lancet 1974; 2:696-8.
7. van Rood JJ. Pretransplant blood transfusion: sure! but how and why? Transplant Proc 1983; 15:915-6.
8. White GC, Lesesne HR. Hemophilia, hepatitis and the acquired immunodeficiency syndrome. Ann Intern Med 1983; 98:403-4.

B_{12} DEFICIENCY IN α-THALASSEMIA

To the Editor: Green et al. noted that patients with α-thalassemia and pernicious anemia may present with mean corpuscular volumes as low as 97 fl.[1] Platt and Garvey expressed concern about the number of vitamin B_{12} estimations performed in patients with volumes below 100 fl.