CORRESPONDENCE

Pure Red Cell Aplasia as an Autoimmune Receptor Disease

To the Editor:

Suppression of the erythroblastic compartment in the bone marrow is the hallmark of pure red cell aplasia (PRCA). The demonstration of IgG inhibitors of erythropoiesis has given a clear indication of the autoimmune pathogenesis of the disease. Indeed, two types of PRCA have been distinguished recently, the first with autoantibodies directed against the erythroid marrow and the second, which is much rarer, against circulating erythropoietin.

A very valuable side effect of the autoimmune concept has been the successful treatment of PRCA of the first type with cytotoxic immunosuppressive agents and with antilymphocyte globulin (ALG).

The mechanism by which humoral antibodies mediate the suppression of erythropoiesis, however, is still subject to discussion. At least three hypotheses have been put forward. Damage of the erythroblastic nuclei has been postulated because of an indirect immunofluorescence reaction, closely resembling the speckled pattern. It is highly unlikely, however, that these antibodies, which are far from being constant, are truly pathogenic. Besides representing most probably an antinuclear immunity of the marker kind not being able to penetrate into living cells, antinuclear antibodies have failed to interfere with DNA synthesis even in cell-free systems.

A second suggestion has been put forward by Krantz and his group, who have demonstrated an IgG factor cytotoxic to erythroblasts in the presence of complement. However, a morphologic description of erythroblastic damage in affected bone marrows has been provided by electron microscopy in only one case. On the other hand, immunofluorescent investigations of fixed erythroblasts exposed to PRCA-active sera have been consistently negative, even when preremission serum has been reacted with autologous, postremission erythroblast-rich bone marrow. Perhaps such investigations should be carried out in the fresh state.

However, there is also evidence that the inhibitor acts on an early, unidentified erythroid precursor. It has been suggested that various diseases could be accounted for by pathogenic immune responses to cell-surface receptors, which, being accessible to circulating hormones or neurotransmitters, should also be accessible to antibody. The anterythroid antibody of PRCA can be absorbed by erythroblast-containing bone marrow, a typical procedure for demonstrating receptor-reacting factors. In analogy with the hypothesis put forward by Ortega et al. for congenital hypoplastic anaemia associated with a humoral inhibitor, I suggest that a blockade of the erythropoietin receptor sites of the erythropoietin-responsive cells by the antibody, besides explaining the negative immunofluorescent findings, may be a useful working hypothesis for the understanding of the pathogenesis of type-A adult PRCA.

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The report by Richman et al.1 of an increase in circulating granulocytic stem cells (CFU) in peripheral blood following chemotherapy has far-reaching implications. We are interested in the concept of harvesting circulating stem cells from the peripheral blood of patients recovering from chemotherapy as a means of improving the treatment for childhood cancer. Cure rates for many pediatric neoplasms have increased substantially with the introduction of intensive combination chemotherapy, but efforts in this direction are currently limited, primarily by the problems of profound myelosuppression. The ability to harvest significant quantities of stem cells easily, to store them in liquid nitrogen, and then to return them to the patient after ablative doses of chemotherapy might considerably increase the therapeutic ratio of a variety of treatment regimens and significantly increase the percentage of cures obtained.

During investigations into the optimal conditions for procuring circulating stem cells by continuous-flow centrifugation using the Aminco celltrifuge, we have varied such factors as the speed of centrifugation and the site of the collection port in relation to the buffy coat. Our preliminary results with 27 experiments on normal donors have shown an increase in the concentration of CFUs/ml with a range of from 7.5 to 6697, with a median of 534. A 3.5-hr leukapheresis procedure collecting 200 ml of cells could therefore yield $10^3$ CFUs. When the optimal conditions for collecting CFUs are established, it is likely that the range in normals will be of the order of $2-5 \times 10^5$ per collection. If we extrapolate from the findings


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