Summary of Informal Discussion on Clinical Obstacles to the Control of Leukemia

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Host defenses are depressed markedly in patients with acute leukemia, both as a result of the disease process and as a result of anti-leukemic treatment. With improved anti-leukemic therapy, increased survival, and improving antibiotic treatment, the spectrum of infecting agents continues to shift in the direction of opportunistic, antibiotic resistance, microorganisms. Efforts to obtain more effective antibiotics are being pursued. In this session direct approaches to improving host defense against infection and perhaps against leukemic cells were presented.

Granulocytes from donors with chronic myelocytic leukemia will circulate in granulocytopenic recipients with acute leukemia. Such transfusions have proven effective in the treatment of Pseudomonas septicemia and other severe infections. Occasionally allogeneic grafts result which persist for up to 60 days. Although these studies demonstrate the feasibility of white cell transfusion, the transfusion of leukemic cells has limited long-term usefulness.

Dr. Djerassi presented data with respect to the important problem of whether the transfusion of normal homologous white cells would survive in recipients and cause infections. Fresh buffy coat from units of blood taken from 30–40 normal cross-matched donors were transfused on 2 separate occasions to a recipient with aplastic anemia and serious infection. The estimated number of white cells transfused was approximately 10^{11}. On both occasions a 1000–2000/cu mm increment of granulocytes in the blood of the recipient occurred, representing a recovery of 10–25%. Evidence for control of the infection and for the presence of transfused cells at sites of inflammation was presented.

Dr. Finch emphasized that it is the presence of granulocytes in the tissue at sites of inflammation rather than the number of circulating granulocytes which is crucial to the control of infections. A method was presented for the quantitative determination of the entry of granulocytes and mononuclear cells into sites of experimental inflammation. This, in essence, consisted of a fluid-filled chamber applied to a site of experimental inflammation on the skin. The rate of infiltration of leukocytes in normal controls was fairly reproducible. In the majority of patients with acute leukemia, there was a marked reduction in the number of granulocytes entering the chamber, and this did not correlate particularly well with the number of circulating granulocytes. Of additional interest was the preliminary observation that the patients with acute leukemia with quantitatively good entry of granulocytes into the chamber responded well to chemotherapy.

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Thus deficient granulocyte production is one of the major host-defense deficits in acute leukemia, and replacement treatment is feasible. The acquisition of large numbers of normal leukocytes is a current major obstacle. Biomedical and engineering scientists are collaborating in the development of a centrifuge designed to separate leukocytes and return red cells and plasma to the donor as a continuous process. In addition to acquiring large numbers of granulocytes, such an apparatus should permit the sampling in quantity of leukemic cells and other peripheral blood products essential to virologic, biochemical, immunologic, and other studies of leukemia.

Dr. Cohen demonstrated how pure preparations of leukocytes could be made by specific agglutination of erythrocytes with horseshoe crab serum. The specificity of certain leukoagglutinins in a panel of leukocyte preparations was demonstrated. Dr. Cohen has demonstrated that leukocytes stored in dimethylsulfoxide in the frozen state will remain viable, as evidenced by *in vitro* tests, for as long as 1 year.

A novel approach to leukocyte replacement has been cross-circulation between a patient with irreversible renal failure and normal blood leukocytes and a patient with markedly depressed numbers of circulating normal leukocytes and normal renal function (acute leukemia). Such cross-circulation is mutually beneficial and temporarily corrects both the granulocytopenia and uremia.

Another approach to the control of marrow failure has been allogeneic marrow transplantation. With appropriate doses of total body X-irradiation and bone marrow cells, permanent allogeneic grafts can be achieved in large animals (dogs) with some degree of reproducibility. Evidence was presented that such grafts in rodents not only may protect against lethal X-irradiation but may destroy (graft *versus* host tumor cells) persistent leukemic cells. The graft *versus* host reaction may be terminated with antimetabolites. The extension of these studies to patients with acute leukemia has been most interesting and has been attended with some success. The clinical nature and treatment of secondary disease have been clarified. In 1 patient a prolonged complete remission associated with a persistent allogeneic functioning marrow graft has occurred.

Other obstacles related to the above which deserve and are receiving major research emphasis include the tissue culture of bone marrow with the production of mature corpuscular elements, the quantitative *in vitro* assay of histocompatibility, the identification of effective agents for the treatment of fungal and Pseudomonas infections, and the development of effective reverse isolation procedures for patients at risk of infection.