OPENING DISCUSSION – FREDERICK STOHLMAN, JR., M. D.

The data presented at this meeting seemed to be leading toward the inevitable conclusion that leukemia in man is associated with a reverse transcriptase which may represent the "foot prints" of an RNA tumor virus. From this it may be suggested that human leukemia is in fact of viral origin. The chemical and immunologic properties of transcriptase which have been described in acute myelocytic leukemia, chronic myelocytic leukemia, and the lymphocytic leukemias are similar. The end results, i. e., the leukemia, however differ substantially in their clinical manifestations. One might suggest therefore various subspecies of transcriptase or virus with similar general physical and biochemical properties but each with significant differences that permit the development of varying types of leukemia. Alternatively the determinant as to the type of leukemia may rest within the cell which the virus infects, or perhaps the site of infection within the pluripotent cell.

To date the studies on transcriptase have required fantastic amounts of tissues which have not permitted adequate controls from normal tissues or the sequential evaluation of the leukemia as the patient enters remission and relapse. Perhaps the best control is the phytohemagglutinin stimulated lymphocyte but even this has been criticized by some. Further, the relative insensitivity of the techniques currently available for evaluation of transcriptase have precluded detailed study of the cells in question. The purification of the enzyme promises that specific antibodies may be developed which can be applied with immunofluorescent techniques to evaluation of the single cell. This together with differential separation of bone marrow cells should permit the evaluation of the importance and distribution of transcriptase in stem cells. Development of such technology in my view is critical to gaining meaningful insight into the role of reverse transcriptase and viruses in human leukemia.

In reflecting on the role of reverse transcriptase there are several considerations which come to mind. Leukemia may be viewed as a disease in which there is abnormal information presented to the cell, presumably at the pluripotent stem cell level, which results in abnormal growth patterns. Although there are several different types of myeloid leukemia, e. g. acute myelocytic, progranulocytic, etc., the number is circumscribed. Does this reflect a high specificity of the viral effect at a few sites on the DNA molecule or does it reflect that most of the viral directed effects are lethal and hence a leukemic clone does not develop, there being a random chance that the transcriptase affects the human stem cell in such a way that leukemia eventuates.

I gather from the discussion at this meeting that it is yet to be established whether the viral information is passed vertically and awaits only derepression or whether a more complicated hypothesis must be invoked. It is clear, however, that whatever theories are advanced they must take into account the leukemogenic effects of irradiation, alkylating agents and other leukemogenic drugs such as chloramphenicol. In the case of irradiation there is a suggestion of a dose-effect relationship at high dose levels. Is this due to somatic mutation, derepression of an oncogene or a more complicated method of initiating viral infection?

Clearly information on reverse transcriptase in patients with acute myelocytic leukemia thought to be secondary to irradiation or alkylating agents is of importance. The lag phase between the primary insult and the development of clinical leukemia and the events which transpire at a molecular level need to be explored. Investigation of these relationships, however, is dependent on the development of microtechniques for the evaluation of reverse transcriptase and RNA tumor virus. Without it we are left with gross correlations.

The characteristic of the cell in myeloid leukemia should be considered. These differ in several respects from that of the normal cells. The generation time of the cell in acute myelocytic leukemia may be longer or the same as that of the normal cell; as a result the fractional turnover rate is not increased but, due to the greatly expanded pool size resulting from the failure of differentiation or loss of a "death" function, the total growth of leukemic cells is greater than seen in the normal myeloblast compartment. The leukemic myeloblast or its progenitor may migrate from the marrow into the peripheral blood and proliferate in extramedullary sites, where normal myelopoiesis is not seen. This suggest changes in membrane properties and the interaction between microenvironment and the leukemic cell. Additionally, there is some data to suggest that the leukemic myeloblast may have specific antigens; these are being explored immunologically and may permit improved therapeutic strategies.

A third consideration is that the leukemic cell differentiates partially, i. e. from stem cell to myeloblast and even to progranulocyte but further differentiation usually is not observed. Using the soft agar technique it has been claimed that leukemic clones may differentiate normally under the direction of colony stimulating factor. As I mentioned in my formal presentation, however, the evidence on this point from a morphologic and functional standpoint is inconclusive. Further, it seems to me that to view, acute leukemia solely as a failure of the normal interaction between a granulopoietic regulator and the myeloblast is an over simplifaction. Failure of differentiation and as a result the lack of a "death function" of course leads to an ever increasing number of proliferative cells but the capacity for growth in extramedullary-sites is necessary for the complete evolution of the disease. It is possible of course that if we were able to switch the balance of differentiation from leukemic to normal clones, leukemia could be controlled but in my view this most likely will require manipulation of differentiation of the pluripotent stem cell not the committed myeloid cell or myeloblast.