GENETIC MECHANISMS IN CHRONIC MYELOGENOUS LEUKEMIA

To the Editor:

The report by Kelman et al[1] that the p53 gene is rearranged in 30% of patients in the blastic crisis of chronic myelogenous leukemia (CML) is not surprising if one considers CML in the context of the observations of Land et al.[2] These investigators demonstrated that neoplastic transformation occurs when there are abnormalities in at least two genes belonging to complimentary families. Evaluation of studies of the *abl* oncogene led us to assign the *bcr/abl* fusion gene to the same complimentation group as the *ras* genes. In addition, we

predicted that blastic crisis would be associated with an abnormality of one of the genes in the protooncogene family that compliments the *ras* gene family[3]; specifically, the p53 gene, c-*myc*, or *erb* a. In favor of this hypothesis are the chromosomal abnormalities most frequently seen at the time of blastic crisis,[4] the observations of Kelman et al,[1] the evidence that *ras* mutations are not involved in either the chronic or blastic phase of CML,[5,6] and the demonstration in vitro that v-*myc* can compliment *bcr/abl* in transforming rat cells.[7]

Several implications are inherent in this model of CML. The first is that some of the between patient differences in the characteristics of blastic crisis may be due, at least in part, to different genes being involved at the time of the blastic crisis. Secondly, reversal of the abnormality in p53, *myc*, or *erb* a expression should result in the characteristics of the blastic crisis cells reverting to that of chronic phase cells. This same model can be applied to acute leukemia evolving from any preleukemic state. Hence, the association of a preleukemic state with an abnormality in either complimentary gene family indicates that evolution to acute leukemia will be associated with the appearance of an abnormality in a gene of the complimentary group.

HARVEY D. PREISLER
The Barrett Center for Cancer Prevention, Treatment and Research
Cincinnati, OH

REFERENCES

1. Kelman Z, Prokocimer M, Peller S, et al: Rearrangements in the p53 gene in Philadelphia chromosome positive chronic myelogenous leukemia. Blood 74:2318, 1989

2. Land H, Parada LF, Weinberg RA: Nature 304:596, 1983

3. Preisler HD: A hypothesis regarding the development of acute myeloid leukemia from preleukemic disorders. The role of protooncogenes. Cancer Genet Cytogenet 32:133, 1988

4. Sandberg AA: The leukemias: Chronic granulocytic leukemia, in: The Chromosome in Human Cancer and Leukemia. New York, NY, Elseirer, 1980

5. Cogswell PC, Morgan R, Dunn M, et al: Mutations of the ras protooncogenes in chronic myelogenous leukemia: A high frequency of ras mutations in bcr/abl rearrangement–Negative chronic myelogenous leukemia. Blood 74:2629, 1989

6. Rovera G, Reichard BA, Hudson S, Bittenbender S, Yamada M, Tournay O, Preisler HD: Point mutations in both transforming and non-transforming codons of the N-ras protooncogene of Ph leukemias. Oncogene 4:867, 1989

7. Lugo TG, Witte ON: The BCR-ABL oncogene transforms Rat-1 cells and cooperates with V-myc. Mol Cell Biol 9:1263, 1989