Quinacrine banding of leukemic cells from nine patients with chronic myeloid leukemia (CML) revealed that the material from the Philadelphia (Ph¹) chromosome (no. 22) was translocated to chromosome 9, not deleted. This translocation was present in chronic and acute phases of CML and was absent from peripheral lymphocytes. [The *SCI*® indicates that this paper has been cited in over 750 publications.]

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After a very rocky start, my paper on the nature of the Philadelphia (Ph¹) chromosome in chronic myeloid leukemia (CML) has led to scientific as well as personal success. I had spent a year's sabbatical (1970-1971) in Oxford learning the new chromosome banding techniques. When I returned to the University of Chicago, I applied them to my major research interest, the marrow cells of leukemic patients. In the 1960s many chromosome abnormalities had been noted in these cells, but they had not been precisely identified with banding techniques, except for the identification of the Ph¹ chromosome as involving chromosome 22, not 21.

I submitted a paper to *Nature* on January 5, 1973, describing a recurring translocation between chromosomes 9 and 22 in five patients with CML. Imagine my dismay when I received a letter, dated January 23, stating that the editors could not publish the manuscript and hoping that the "referee's report will be helpful." The reviewer was concerned that I had not investigated lymphocytes or fibroblasts, therefore violating a "golden rule" in cytogenetics. Moreover, since some patients were in or approaching the acute phase, I could not exclude the possibility that the chromosome change was related to the acute and not the chronic phase of CML. Fortunately, I had been hard at work rectifying just those deficiencies, so that, when the rejection letter arrived, I could write a revision that included nine patients, with successful lymphocyte cultures from two. Two of the patients were newly diagnosed. For another patient

I studied sequential samples in the chronic and acute phases and could show a change in karyotype with disease evolution. A revised paper was submitted February 5 and accepted on February 27.

My laboratory and others subsequently discovered a number of recurring translocations in various forms of acute leukemia and non-Hodgkin's lymphoma and, more recently, in sarcomas and some benign tumors.[1] Appreciation of the great significance of consistent chromosome rearrangements was very slow in coming, because the tools for identifying the genes involved were not available. Thus, one was left with a phenomenon—namely, translocation—but no way to relate it to either clinical medicine or basic cancer biology.

That was the situation until the fall of 1982, when two groups[2,3] reported independently on the cloning of the 8;14 translocation in Burkitt's lymphoma that had been identified in 1976 by Lore Zech.[4] These reports started a revolution in cancer biology that continues with increasing momentum. Analysis of the 8;14 translocation led to the paradigm (supported now by analysis of translocations in other leukemias/lymphomas) that the effect of translocations is to move a gene that is centrally involved in growth regulation adjacent to a gene that is actively expressed in the particular type of cell in which the translocation occurs.

With regard to CML, a group of Dutch investigators working in The Netherlands and the US was able to show that the 9;22 translocation results in the movement of the *ABL* proto-oncogene on chromosome 9 next to a gene called *BCR* on chromosome 22.[5] This gene was discovered only because of the translocation. The translocation results in a fusion mRNA and a fusion protein that is larger than the *ABL* protein in normal cells and has somewhat stronger tyrosine kinase activity. These discoveries have been translated into new diagnostic tests for CML, because the DNA from leukemic cells can be analyzed with specific probes from the *BCR* gene and DNA rearrangements are regularly detected on Southern blot analysis. With this technique, however, one cannot detect other chromosome abnormalities; thus, it does not replace cytogenetic analysis, but it offers a useful diagnostic test for physicians who do not have ready access to a competent cytogenetics laboratory.

The ultimate goal is to understand how the altered function of the chimeric protein is related to leukemogenesis and to use that knowledge to treat the genetic defect in these cells more specifically, in the hope that this will lead to less toxic and more effective therapy.

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