Quinacrine banding of leukemic cells of a female patient with acute myeloid leukemia revealed a reciprocal translocation involving chromosomes 8 and 21 ([t(8;21)(q22;q22)]. In addition to the translocation, the cells also were missing one X chromosome ([45,X,-Y,1;8;21][q22;q22]). A second female patient with an identical abnormality was added when the paper was in the proof stage. [The SC° indicates that this sample has been cited 1025 times, making it the most-cited paper from this journal.]

First Recurring Translocation in Human Leukemia

Janet D. Rowley
Department of Medicine
University of Chicago Medical Center
Chicago, IL 60637

March 26, 1990

It is a widely accepted notion that new and unexpected observations often have difficulty getting published and that there is therefore a delay in making the scientific community aware of new ideas. Recurring translocations are a significant feature of the chromosome aberrations in human leukemia, lymphomas, and some solid tumors. Publication of the very first discovery of a translocation in malignant cells was not easy. Earlier studies prior to the use of banding techniques showed that leukemic cells from a number of patients had what appeared to be the loss of a C and G group chromosome and a gain of a D and E group chromosome. With banding, I could identify the chromosome rearrangements involved in this abnormality.

As a cytogeneticist interested in leukemia, I had shared the frustration of my colleagues over our inability to define the chromosome changes in malignant cells with any certainty. Chromosome banding techniques changed all of that! I will never forget the sense of exhilaration I experienced in a London pub in the spring of 1971, when I first learned of Lore Zech's new quinacrine fluorescence technique that allowed the precise identification of each human chromosome by its unique pattern of bands. 

Early in 1972, using quinacrine banding, I studied the cells of a patient with acute myeloid leukemia, whose unbanded karyotype was similar to that reported previously. I showed that the abnormality really represented a reciprocal translocation between chromosomes 8 and 21 with a break in 8q22 and 21q22. Although I was not aware of the paper by N. Kamen et al. 2 at the time, my observations confirmed their interpretation that the abnormality was a translocation.

I would have hesitated the result as being just a random translocation, except that it, together with the earlier observation on unbandecl leukemic cells, suggested that this might be a recurring abnormality. I wrote a short letter to the New England Journal of Medicine. I received a form letter of rejection; when I called to ask why, I was told that in their judgment my paper was unimportant. In November 1972, I submitted the paper to the Annales de Genetique because I knew that the editor, Jean de Grouchy, was a cytogeneticist interested in leukemia who might recognize the importance of my observation and who would be more sympathetic to my discovery. I was not disappointed. Although not mentioned in the paper for Annales de Genetique, I had preliminary evidence that the P1 chromosome in chronic myeloid leukemia (CML) might be a translocation as well. Together, these observations suggested that translocations might be an important mechanism associated with leukemia. The discovery of a second patient with a t(8;21) (added in the proof stage of the paper) provided further confirmation of this notion. An interesting and still unexplained associated chromosome abnormality in these two female patients was the loss of an X chromosome. In fact, up to two-thirds of male patients with the 8;21 translocation may lose an X chromosome and almost as many female patients may lose an X chromosome. Loss of a sex chromosome is not a common feature in other translocations.

Although the genes involved in the 8;21 translocation have not been identified yet, cloning of these breakpoints is an important problem for four reasons. First, and most important from the standpoint of cancer biology, many of the genes found at these translocation breakpoints have been previously unidentif.ied. Inad. example, BCR, BCL2, and BCL3. They would not have been discovered at this time if the translocations were not there to challenge molecular geneticists. Second, we can study the functions of these newly discovered genes in normal cells, and we can determine how their functions are altered in malignant cells. Third, the use of DNA probes has allowed the identification of these translocations in patient samples in which cytogenetic studies are difficult or unsuccessful. Fourth, an understanding of the alterations in these genes will provide insights that should lead to more specific, more effective, and less toxic treatments than are presently available.