Editorial

With many genetic conditions, insights are only now beginning to be attained through molecular approaches. Fanconi anemia (FA), probably better called Fanconi pancytopenia is an autosome recessive condition and was described by Guido Fanconi in 1927 (1). Pancytopenia is probably a more appropriate descriptor because all marrow elements are affected and result in anemia, leukopenia and thrombocytopenia preceding the development of acute myeloid leukemia in many instances. Associated features include pigmentary skin changes, malformations of the heart and kidney, aplasia of the radius, and thumb deformities. Although the condition is rare, it has received considerable scientific attention since its initial discovery.

Among earlier attempts to identify the genetic defect in Fanconi anemia, Löhr (1965) found reduction of hexokinase activity not only in red blood cells but also in white blood cells and platelets in some patients (2). Duckworth-Rysiecki (1985) first demonstrated the presence of two complementation groups in this condition through the use of somatic cell hybridization analysis (3). Similar studies by Strathdee et al. (1992) found at least four complementation groups (4) with a fifth described by Joenje et al. (5), indicating significant genetic heterogeneity. The first four complementation groups have been given letter designations A through D.

In 1992 Strathdee et al. used the characteristic of hypersensitivity of Fanconi anemia cell lines to mitomycin C and diepoxybutane to isolate the gene related to the complement type C Fanconi anemia (6). This gene was subsequently found to be mutated in patients with the group C disorder. The predicted protein controlled by the gene does not contain any characteristics similar to other proteins and its basic function still remains to be elucidated. Several steps to this end have been already achieved. In 1995 Youssoufian et al. (7) noted in relation to genetic heterogeneity, "Although the FA phenotype may result from distinct pathogenetic mechanisms, the overall similarity in phenotypes suggests a biochemical mechanism characterized by a shared molecular defect, such as lesions in a multimeric complex or in a multistep metabolic pathway whereby the failure of any single component could lead to a similar dysfunction." One might add that a combination of these mechanisms could also be operative given our current understanding. Studies of these authors also indicate that the C protein is present in most cells and it complexes with at least three cytosolic polypeptides. They also found that the cytoplasmic location appears to be necessary for preventing or correcting hypersensitivity to chromosome damaging agents. Joenje et al. (5) indicate that the proportion of Fanconi anemia patients belonging to complementation group C is estimated to be 8%. Gene mapping and linkage analyses showed the C group gene is located at 9q22.3 (4, 8).

Joenje et al. (5) emphasized the importance of complementation analysis for genetic classification of affected patients. Such studies could estimate the different subtypes in human populations even before the responsible genes have been isolated. Thus, genes for the non-C types could be determined in affected families through linkage analysis which potentially could permit positional cloning of these genes. They go on to emphasize, "Furthermore, complementation analysis can be a critical tool in ascertaining the pathogenic status of sequence alterations found in FAC by mutation screening methods. Finally, in view of the upcoming clinical trials designed to correct the bone marrow failure in FA patients by gene therapy, complementation analysis is an important means to select patients who are eligible for such treatment." However, because of limitations of the complementation analysis, they suggest that screening for specific mutations in the C gene and linkage analysis using polymorphic markers flanking the C gene in a family can be used to determine whether the patient belongs to the C group or not. They also note that the complementation method is the only available method for the classification of the non-C patients at this time.

In this context, the paper by Youssoufian et al. (9) in this issue of *The Journal* expands our understanding of the nature of the defect in the complement C disorder. They demonstrate that the overexpression of the mutant protein in a wild-type cellular background produced the Fanconi phenotype by making these cells hypersensitive to mitomycin C. They also ascertained no differences in the biosynthesis, subcellular localization and protein interactions between normal and mutant proteins. These studies demonstrate the utility of an uncommonly used approach of overexpression of a mutant gene to demonstrate the effect of an otherwise recessive disorder, which may have applications to understanding other recessive disorders. This is an important step giving further insight into the nature of the type C Fanconi anemia.

A number of interesting questions still remain. First, in relation to the type C disorder, it will become important to further define the normal function of the involved protein and thus a better understanding of the pathogenesis of the disorder with the mutant protein. Although five different complementation types of the disorder have already been demonstrated, there is the possibility that others will still be found. It still remains for the non-C complementation group genes to be identified and isolated and characterized along the lines that have been used to characterize the type C gene. What mechanism(s) account for the manifestations of this disorder, including chromosome instability, the skin changes and malformations of other organs including the heart, kidney, radius and thumb and how the underlying mechanism predisposes affected individuals to develop leukemia? Gene mapping and linkage analyses should determine whether any of the complementation groups represent different mutations of the same gene locus or are mutations in different genes.

It is exciting to note the progress that has been made to date and with the increasing application of the newer molecular approaches one can expect answers to the problems posed

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in the preceding paragraph. Answers to these questions may give us further insight into understanding conditions ranging from birth defects to leukemia.

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