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CHRONIC MYELOCYTIC
(MULTIPOTENT-STEM-CELL) LEUKEMIA

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CHRONIC myelocytic leukemia is a disease in which
biomedical research efforts have paid substantial divi-
dends in recent years. Both laboratory and clinical
investigators have found that this disease, first de-
scribed as "splenic leukemia" over 100 years ago, con-
tains some important lessons for the astute observer.
An early, notable example of the value of careful labo-
ratory observation was the demonstration of the Phila-
delphia (Ph¹) chromosome in patients with this dis-
ease.¹ Subsequent cytogenetic analyses using banding
techniques demonstrated that in most cases of chronic
myelocytic leukemia, the Ph¹ chromosome arises from
a balanced translocation between the long arms of
chromosomes 9 and 22, with break points in bands
q3+ and q11, respectively.² Studies using molecular
probes³ now suggest that a cellular gene, termed *c-abl*,
which is structurally related to the murine Abelson-
leukemia-virus-transforming gene, *v-abl*, is located in
the fragment translocated from chromosome 9 to chro-
mosome 22. Several laboratory groups are currently
investigating a mechanism by which chromosomal
translocation could be associated with activation of a
cellular gene or genes capable of inducing malignant
transformation — e.g., *c-abl* or another oncogene.

Chromosomal studies have paid further dividends
by demonstrating that all the various cell lines in-
volved in the disease (granulocytic, erythrocytic, meg-
akaryocytic, and lymphocytic) contain the character-
istic chromosome. These data strongly suggest that all
the malignant cells in chronic myelocytic leukemia are
derived from a single multipotent-stem-cell clone.
Further evidence that the disease arises from a single
clone is supported by studies of glucose-6-phosphate
dehydrogenase isoenzymes.⁴

The nature of the clonal abnormality or abnormali-
ties in chronic myelocytic leukemia has been of great
interest to recent investigators. Studies demonstrating
the involvement of lymphocytes in the disease have
greatly aided this analysis. Early evidence implicating
lymphocytes came from data indicating that progres-
sion of the disease resulted in blast crises that often
had lymphoid morphology. The B-lymphocyte lineage
of some lymphoid blast crises was demonstrated in
studies indicating that the malignant cell contained
immunoglobulin mu heavy chains in the cellular cyto-
plasm; these cells were thus characteristic of pre-B
lymphocytes.^{5,6} Not all lymphoid blast crises showed
evidence of cytoplasmic immunoglobulin, however,
and thus the possibility existed that cells could be ar-
rested at an even earlier stage of B-lymphocyte devel-
opment. Studies of the structure of DNA have been
extremely useful for analysis of these early steps in
B-cell development. They indicate that rearrangement
of immunoglobulin genes precedes immunoglobulin
synthesis in B-lymphocyte maturation; an arrest in
early B-lineage differentiation is observed in most
cases of acute lymphoblastic leukemia.⁷ The results

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appear to be very similar in chronic myelocytic leukemia, as reported in the elegant study of Bakhshi et al. in this issue of the *Journal*.¹ Their studies of DNA rearrangement in immunoglobulin genes indicate that the vast majority of lymphoid blast crises of chronic myelocytic leukemia involve cells of B-cell lineage. Together with data from another group,² the work of Bakhshi et al. demonstrates that additional subclones at various levels of B-cell maturation may evolve during the course of the disease. The origin of these clones within clones remains unknown.

The demonstration that the major clone in chronic myelocytic leukemia involves cells capable of lymphocytic, granulocytic, and erythrocytic differentiation has led to the conclusion that the transformation event occurs at a very early multipotent-stem-cell level. This conclusion has several theoretical and practical implications. It appears that arrested maturation does not necessarily occur at the level of the transformed cell, since transformed cells can produce very mature progeny, such as granulocytes. The therapeutic implications of the multipotent-stem-cell hypothesis are illustrated by studies using intensive chemotherapy, which demonstrate the difficulty in eliminating the abnormal clone. There are probably only very subtle differences between normal multipotent stem cells and the multipotent stem cells in chronic myelocytic leukemia^{3,4}; therefore, it has been difficult to eradicate the leukemic population selectively, without causing major destruction of normal stem cells. This problem has been circumvented by giving the patient intensive chemoradiotherapy followed by allogeneic-bone-marrow transplantation.^{11,12} Current investigations are directed at the appropriate timing of transplantation in the course of the disease, comparisons of various intensive treatment regimens, and the importance of matching donor with recipient.

I am hopeful that the rate of progress in identifying the pathogenesis of chronic myelocytic (multipotent-stem-cell) leukemia will continue to accelerate in the coming years. An understanding of the origin of the 9;22 translocation and the relation of this translocation to genes located at the break points will be important. Further therapeutic success in this formerly fatal disease is likely to be achieved with allogeneic-marrow transplantation and other innovative treatment methods. Continued cooperation of the laboratory and clinical investigator will be essential in this process.

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EDITORIAL RETROSPECTIVE

SERUM ACID PHOSPHATASE AND SCREENING FOR CARCINOMA OF THE PROSTATE

IN 1977 Foti et al.¹ described a new radioimmunoassay for prostatic acid phosphatase in patients with carcinoma of the prostate, including a large number with disease in Stages A and B. (In Stage A, foci of tumor are found incidentally at prostatectomy for presumed benign obstruction. Stage B refers to biopsy proved intracapsular tumor, usually detected by rectal examination and without evidence of metastases.) The previously available colorimetric or enzymatic assays for acid phosphatase had yielded values within normal limits in patients with localized prostatic cancer, but Foti et al. reported increased levels found by radioimmunoassay in 33 per cent of patients with Stage A disease and 78 per cent of patients with Stage B. In an accompanying editorial² I expressed the hope that if the sensitivity of the test were confirmed, it might permit the use of radioimmunoassay for mass screening and detection of prostatic cancer in the curable stages. Six years later, it is now clear that the radioimmunoassay did not and indeed could not live up to that hope. The two reasons for that outcome are worth reviewing.

The first and more instructive reason was analyzed by Carroll³ and by Watson and Tang,⁴ who pointed out that in the original results of Foti et al., the specificity of only 94 per cent (204 negative tests among 217 patients without cancer of the prostate) undermined the potential of the test for screening purposes. The reported elevation of prostatic acid phosphatase in 2 of 36 patients with benign prostatic hypertrophy was particularly noteworthy. Nearly all men over 55 have some degree of benign prostatic hypertrophy, but no more than 1 in 100 has clinically impor-

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