19 percent of those in their 20s.[10] This trend is likely to continue, since the proportion of women 30 to 34 years old who were college graduates increased by 50 percent between 1975 and 1987, and these women appear to be delaying marriage." Although the homogeneity of the patient population in the study by Berkowitz et al. lends itself to more accurate conclusions for a selected group of women, the data must be interpreted cautiously, particularly when one is considering other socioeconomic groups and more varied populations.

Nevertheless, the message is clear and highly optimistic. What should be emphasized is the fact that the few pregnancy-related problems in nulliparous women who are 35 or older are readily manageable in 1990. Given sound genetic diagnosis and counseling, together with appropriate prenatal care and the judicious management of labor and delivery, the increasing number of women postponing first pregnancies can look forward to excellent outcomes.

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CELLULAR ORIGINS OF HEMATOLOGIC NEOPLASMS

THE entire hematopoietic system in all its complexity arises from a small number of stem cells that not only differentiate but also replenish the bone marrow by a process of self-renewal. These stem cells supply the marrow with committed progenitor cells that become the main hematopoietic cell types. Cells that move beyond the progenitor stage lose their capacity for self-renewal but retain the potential to differentiate into erythrocytes, granulocytes, monocytes, megakaryocytes, or lymphocytes. The idea that a stem cell or one of its immediate descendants is the source of hematopoietic neoplasms has ramifications for all types of cancer. A lesion that renders a stem cell neoplastic may explain how a tumor consisting mainly of mature differentiated cells can continue to grow. Moreover, the issue at hand — the cellular origins of hematologic neoplasms — has potentially broad therapeutic applications: identifying the cell in which the transforming event begins could lead to treatment that would specifically target the basic abnormality.

The first and best evidence of a stem-cell defect in a cancer derives from work on chronic myelogenous leukemia. The presence of the Philadelphia chromosome (Ph^1; due to a reciprocal translocation between chromosomes 9 and 22) in all cell lineages in the bone marrow of patients with chronic myelogenous leukemia can only mean that the disease originates in a progenitor stem cell. The experiments of Fialkow et al.[1] with X-linked glucose-6-phosphate dehydrogenase isoenzymes support this conclusion. In female patients with chronic myelogenous leukemia who were heterozygous at the glucose-6-phosphate dehydrogenase locus, only one form of the enzyme was found in granulocytes, red cells, platelets, and macrophages. Thus, the root of the problem in chronic myelogenous leukemia lies in a precursor from which these diverse cells derive. More recent studies[2] have shown that the translocation in the Ph^1 abnormality moves the *c-abl* proto-oncogene from chromosome 9 to a position next to the bcr (breakpoint cluster region) gene on chromosome 22. The fused bcr-abl gene encodes a tyrosine kinase whose enzymatic activity is much greater than that of the normal tyrosine kinase product of c-abl. The importance of this genetic abnormality has been shown in the development of a disease strongly resembling chronic myelogenous leukemia in mice injected with syngeneic bone marrow cells carrying the fused bcr–ublgene (as a result of a retrovirus-mediated technique of gene transfer) (Rosenberg N: personal communication).

With such compelling evidence that chronic myelogenous leukemia begins in a stem cell, it is still not clear why myeloid cells predominate in the chronic phase of the disease. Furthermore, the molecular basis for the progression of chronic myelogenous leukemia to a blast crisis remains a puzzle. When that progression occurs, the hematologic picture of orderly myeloid maturation shifts to an overwhelming proliferation of primitive myeloid, lymphoid, erythroid, megakaryocytic, or undifferentiated blasts. The bcr–*abl* translocation is necessary for the development of the disease's chronic phase, but the blast crisis may require additional genetic changes.

The origin of a leukemic clone in an ancestral stem cell or committed progenitor cell implies that the precursor can, up to a point, continue to differentiate

regardless of its genetic lesion. This may explain the presence of myeloid antigens on acute lymphoblastic leukemia cells (detected with the use of monoclonal antibodies in the technique of immunophenotyping).[3] It may also explain the presence of erythrocytic and megakaryocytic antigens on leukemic cells from patients with acute myeloid leukemia.[4] In these cases, only a small percentage of cells have multilineage markers, but there are also biphenotypic leukemias in which most of the cells express both lymphoid and myeloid antigens.

These bizarre phenotypes can be compared with the unusual rearrangements of immunoglobulin and T-cell–receptor genes that occur in acute lymphoblastic leukemia. Normally, the stepwise rearrangements of these genes correlate with the stage of lymphocytic differentiation. The process begins before the lymphoid progenitor cell becomes committed to one lineage or the other, with rearrangements of both immunoglobulin and T-cell–receptor genes.[5,6] In hematopoietic neoplasms with mixed phenotypes,[5] inappropriate rearrangements have been found, such as immunoglobulin-gene rearrangement in malignant T cells and rearrangements of T-cell–receptor genes in malignant B cells. We can therefore infer that such cases originate from a malignant lesion in an early progenitor of the lymphoid line.

Recent findings in multiple myeloma, usually considered to be a monoclonal proliferation of terminally differentiated B cells, underline this point. Investigations with antiidiotypic antibody markers,[7] immunochemistry, and flow cytometry[8,9] have shown that the earliest identifiable precursor of the "myeloma cell" is an immature B cell with characteristics (plasma-cell antigen, cytoplasmic μ chains, and immunoglobulin-gene rearrangements) identical to those of the mature malignant plasma cell. These aberrant pre–B cells have a high proliferative index and are thought to make up the self-renewing population in myeloma.

A perplexing new finding complicates the story in myeloma. Both myeloid and plasma-cell antigens have been detected on fresh or cultured plasma cells from the bone marrow of patients with myeloma.[10] In this issue of the *Journal*, Epstein[11] and coworkers have taken the problem one step further with dual-Parameter flow cytometry. They identified malignant aneuploid plasma cells from patients with myeloma that expressed both myeloma-associated and nonlymphoid markers. These results — as well as those in the biphenotypic leukemias — may well reflect a transforming event in a multipotent stem cell. However, the findings could also be due to the aberrant expression of normally quiescent lineage-specific genes by the malignant cells. The latter possibility arises because, after several passages in culture, myeloma cells may switch from the expression of one monocytic antigen to the expression of a number of myeloid antigens.[10] This kind of in vitro modulation of phenotype points to the defective regulation of gene transcription as the cause,[10] and away from a precursor common to both B cells and myeloid cells.

The issue of localizing the cellular origin of multiple myeloma to either a hematopoietic stem cell or a primitive lymphocyte could be resolved by the identification of a specific genetic or chromosomal abnormality. Such chromosomal alterations are seen in human follicular lymphomas and chronic lymphocytic leukemia, and they seem to arise in pre–B cells during an early step in the process of immunoglobulin-gene rearrangement.[13] Burkitt's lymphoma involves a translocation of genes at a later stage of B-cell differentiation.[10] A characteristic genetic marker has not been identified in multiple myeloma, but there is promise in recent work describing novel alterations in the c-*myc* gene.[12] It is uncertain whether the c-myc mutations are relevant to the pathogenesis of myeloma or are an epiphenomenon.

Oncogenetic defects that lead to hematologic neoplasms can therefore occur at various points along the pathways taken by hematopoietic stem cells as they differentiate into committed progenitor cells. The genetic abnormality may become manifest in the progenitor cell itself or only after the altered precursor undergoes what appears to be normal differentiation. The new findings in multiple myeloma emphasize the complexity of self-renewal, gene expression, and cell differentiation in all neoplasms. Even so, it is now possible to believe that by joining the resources of molecular and cell biology with astute clinical research it may be feasible to discover the cellular origins of all cancers. From such knowledge will come an entirely new foundation for the rational and specific treatment of cancer.

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