# Differentiation-Linked Leukemogenesis in Lymphocytes

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**Most human lymphoid malignancies preserve a pattern of gene expression reflecting their proliferative activity and the developmental level of clonal expansion and maturation arrest. Characteristics of leukemia and other cancer cells frequently considered to reflect aberrant differentiation may more often reflect clonal selection of cell types that are normally infrequent and transitory. The differentiation status of progenitor or mature lymphoid cells influences which genetic elements are at risk of being exploited, via mutation, recombination, or deletion, for clonal advantage. These alterations may frequently arise spontaneously as a consequence of the unique developmental and functional programs of lymphoid cells and have as a major phenotypic consequence the stabilization of transitory cellular phenotypes.**

THE IDEA THAT ABERRANT CELL DIFFERENTIATION IS A consistent and important characteristic of malignant cells has been a recurrent theme in cancer research. The frequent use of the terms dedifferentiation, retrogressive differentiation, neodifferentiation, transdetermination, misprogramming of differentiation, as well as de-repressed, ectopic, or oncofetal gene expression, testifies to the prevailing view that malignant transformation usurps the normal program of cell development in a substantial or anarchistic way (*1, 2*). Not only may transformed cells fail to differentiate and thus appear to be frozen in maturation arrest but, it is claimed, they may express 1000 or more "new" genes (*3*). With their inevitable evolutionary progression, malignant cells may also acquire independent assortments of phenotypic traits which defy classification and portray no discernable relationship to the cells or tissues from which they originate (*4*).

Although some acutely transforming animal viruses may use a strategy involving such gross genomic dysregulation, it is difficult to believe that this represents a general mechanism for the development of most spontaneous tumors of animals and humans, even if cellular genes homologous to viral oncogenes are causally involved. An alternative view is based on the premise that most human cancers originate in tissue stem cell or progenitor populations and share many of their characteristics. Comparison of malignant cells with these numerically infrequent normal cells as appropriate controls reveals that the former may deviate only minimally from the normal differentiation program as reflected in cellular phenotype (*5–8*). This latter view is well reflected in Potter's term of "blocked ontogeny" (*6*) and Pierce's reference to neoplasms as caricatures of tissue renewal (*5*).

The recent applications of monoclonal antibody and molecular probes to the analysis of cancer cells and their putative normal counterparts has had an enormous impact on the precision with which particular cell types and salient or unique phenotypic characteristics can be identified, isolated, and characterized (*9*). This has been particularly so in the case of hematopoietic cells, lymphocyte subsets, and their corresponding neoplasms where multiparameter flow cytometry and sorting and immunoenzyme staining of tissue sections has provided a detailed characterization of single cell phenotypes (*10*). In this article I review some of these studies that have been particularly concerned with lymphoid malignancy in humans and its relationship to the normal developmental biology of lymphocytes. These data lead me to conclude that the dysregulation of differentiation in malignancy can be extremely subtle and, moreover, that the molecular events with selective advantage in the development of clones of lymphoid cancer cells are, paradoxically, subservient to the normal differentiation program.

## Origins of Phenotypic Diversity in Lymphoid Malignancy

**Subsets of leukemic cells and their normal counterparts.** In the human lymphoid lineages, we now have a reasonably clear, though still incomplete, picture of sequential changes of membrane antigenic phenotype (*11*) and rearrangement and expression of immunoglobulin and T-cell receptor genes (*12, 13*) that accompany normal B and T lymphocyte maturation (*11*). Rearranged genes are of exceptional interest in the study of differentiation since they may identify lineage affiliation prior to or independent of its expression at the protein level. Additionally, they are by their nature clonal markers and therefore reveal monoclonal selection in neoplasia.

On the basis of these phenotypic parameters and some enzyme characteristics (*14*), it is possible to identify subsets of lymphoid neoplasms (leukemias and lymphomas) and align them with their approximate normal counterparts in lymphopoiesis (*7, 15*) (Fig. 1). Broadly speaking, the various lymphoid malignancies correspond to either lymphocyte precursor populations or to mature (immunocompetent) lymphocyte subsets.

*Acute lymphoblastic leukemia.* Table 1 summarizes the predominant antigenic and enzymatic phenotypes of leukemic cell populations of childhood acute lymphoblastic leukemia (ALL). Effectively all cells have composite phenotypes corresponding to either B or T lymphocyte precursors (*16*), with only partial assembly of the cell surface heteropolymeric antigen receptor molecules that characterize mature, immunocompetent lymphocytes. These cells appear to be frozen in the act of receptor gene assembly and expression. Thus both major subtypes express the nuclear enzyme terminal transferase (TdT) which is involved in increasing diversity in the DJ (diversity,

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joining) segments of receptor genes and show only incomplete and frequently aberrant pattern of rearrangement of their respective immunoglobulin (Ig) and T-cell receptor (α/β) genes. Protein products of these genes (μ protein or TCR β protein) may nevertheless be synthesized along with associated protein structures (J chain in B-cell precursors and T3 proteins in T-cell precursors) (Fig. 2). In the absence of Ig light chain protein or TCR α chain the other receptor components fail to be processed, transported, and inserted into the surface membrane. They can, however, be detected in the cytoplasm, often in association with the perinuclear envelope (Fig. 2). Approximately 20% of T and B precursor cell leukemias also show clonal rearrangement of at least one allele of the "inappropriate" receptor genes (that is, IgH in T cells, TCRβ in B cells) (*17*). When analyzed in more detail these rearrangements, as described earlier for IgH in murine T cells (*18*), are partial (DJ) or aberrant with sterile transcripts (*17*). Such alterations are probably a component of normal lymphocyte differentiation and reflect the utilization of common recombination mechanisms in T- and B-cell precursors (*19*).

The relative incidence rate of T versus B precursor ALL is linked to age, sex, geographic region, and, possibly, ethnic groups, but in the United States, Europe, Taiwan, and Japan is markedly biased toward B precursor subtypes (5B:1T). A small proportion of ALL (~2%) have a mature B-cell phenotype ($TdT^-$, cell surface $Ig^+$) and may be classified as B-ALL (*16*). These are usually Burkitt-like in morphology and are probably more correctly regarded as disseminated B-cell lymphomas than as ALL.

When normal tissue is analyzed at a single cell level with the same markers as in ALL, then similar composite phenotypes are detectable (*20*). They are, however, usually associated with relatively infrequent and transitory cell types. Thus, although T-ALL cells show a range of antigenic phenotypes, their dominant antigenic, enzymatic, and molecular profile corresponds to cortical thymocytes or to the proliferating blast cell populations in the subcapsular thymic cortex. The latter correspond to no more than 2% of the total cell population of a pediatric thymus. Similarly, in normal bone marrow there is a rare (1 to 3%) population of lymphoid cells that have nuclear TdT and the same monoclonal antibody–defined cell surface characteristics as the common (B-cell precursor) form of ALL (Fig. 2). Significantly, these latter, rare, cell populations are present at higher relative frequencies in fetal tissue and in regenerating marrow (*20–22*).

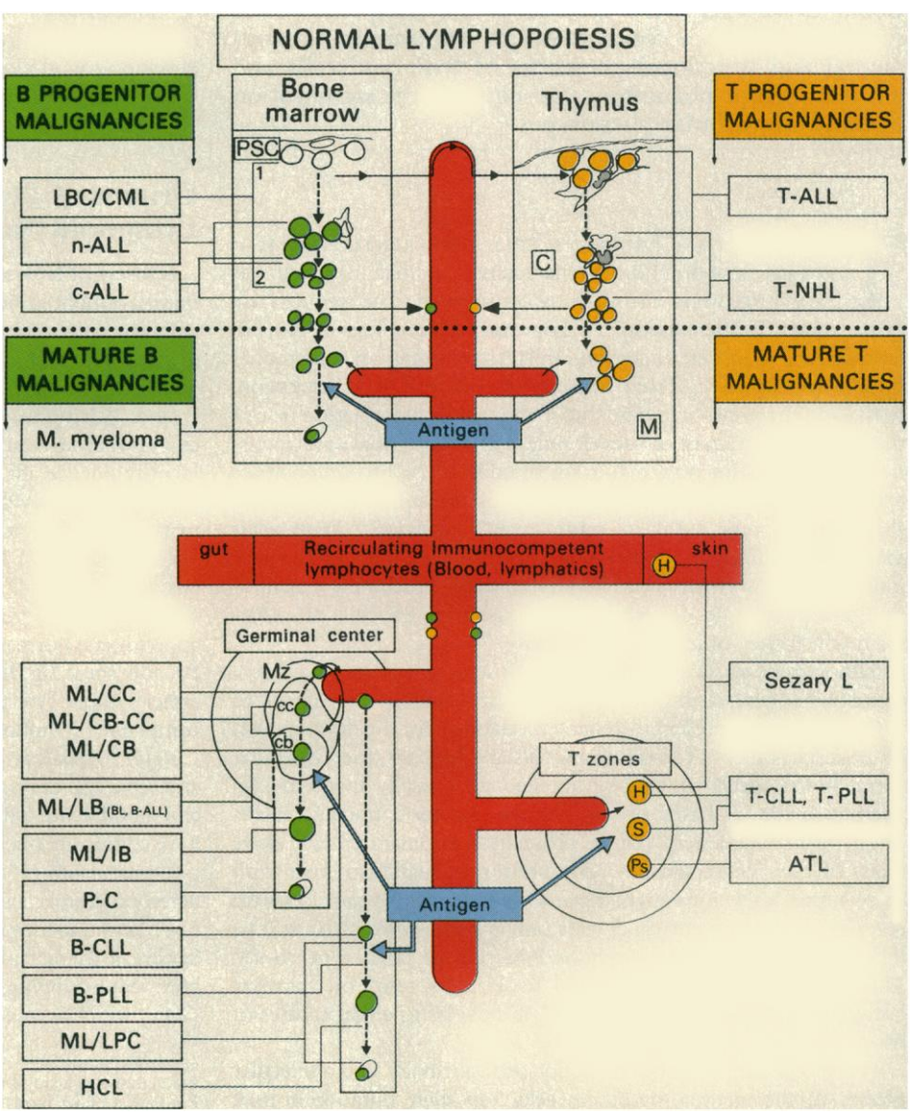


Fig. 1. Developmental levels of clonal amplification in lymphoid malignancy. Abbreviations: ALL, acute lymphoblastic leukemia; n-ALL, "null" ALL (common ALL antigen$^-$/DR$^+$ ALL); c-ALL, common ALL (c-ALL antigen$^+$/DR$^+$ ALL); T-ALL (T antigens$^+$/DR$^-$ ALL); LBC/CML, lymphoid blast crisis of chronic myeloid leukemia; Sezary L, Sezary (cutaneous) lymphoma/leukemia; T-CLL, T-cell chronic lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia; ATL, adult T-cell leukemia (HTLV-I$^+$); M. myeloma, multiple myeloma; ML/CC, malignant lymphoma/centrocytic; ML/CB-CC, malignant lymphoma/centroblastic-centrocytic; ML/CB, malignant lymphoma/centroblastic; ML/LB, malignant lymphoma/lymphoblastic; BL, Burkitt's lymphoma; B-ALL, B-cell acute lymphoblastic leukemia; ML/IB, malignant lymphoma/immunoblastic; P-C, plasmacytoid lymphoma; B-CLL, B-cell chronic lymphocytic leukemia; B-PLL, B-cell prolymphocytic leukemia; ML/LPC, malignant lymphoma/lymphoplasmacytoid; HCL, hairy cell leukemia; PSC, pluripotential (or multipotential) stem cell; 1,2 (in bone marrow), initiation of CGL(1) and emergence of lymphoid blast crisis of CGL(2); C and M (in thymus), cortical (C) and medullary (M) regions; Mz,cc,cb (in lymph nodes and spleen germinal centers), mantle zone (Mz), centrocytic cells (cc), and centroblastic cells (cb); H,S,Ps (in T-cell zones of lymph nodes, spleen, and skin), helper cells (H), suppressor cells (s), and pro-suppressor or inducers of suppressor cells (Ps). Arrows indicate maturation sequence (- - - - →) and cell traffic (——→——). Normal lymphocyte and malignant cell subset heterogeneity, anatomical compartmentalization, and precise correspondence of leukemia/lymphoma cell phenotype to normal has been considerably simplified for presentation of major relationships. Not all leukemias and lymphomas are represented (for example, diffuse lymphomas of mature T subtype). Not all cases of a given histological subtype may have the relationship to normal developmental pathways indicated. For example, the T-cell non-Hodgkin lymphomas corresponding to thymic T cells are a subset of T-NHL observed mostly in younger patients usually in association with a thymic or mediastinal mass. The nomenclature used here for lymphoma is that of the Kiel system [see (*92*)]; although this system is widely used it is not universally applied.

Within the two major subsets of B and T precursor ALL are further overlapping subgroups that differ in their antigenic phenotype and pattern of Ig or T-cell receptor gene rearrangement and expression. This subset heterogeneity is considered to parallel the normal developmental hierarchy of gene expression, for example, IgH gene rearrangement and expression prior to κ or λ light chain gene rearrangement in the B-cell lineage (*21, 23, 24*), TCRβ and T3 gene expression before TCRα (*13, 25*).

The membrane antigens associated with ALL cells (Table 1) are mainly epitopes on glycoproteins that can be solubilized by detergent extraction of cell membranes and analyzed after immunoprecipitation or affinity purification. The biochemical characteristics of these structures, including apparent molecular weight, subunit structure, glycosylation, phosphorylation, and membrane association, have in most cases been established, but their function is largely unknown.

Although the antigenic components of the leukemic cell phenotype used as discriminatory markers have a selective association with particular hematopoietic lineages or maturation compartments, they are not necessarily cell type–specific. For example, the common ALL associated antigen (gp100 or CD10), though extensively applied as a valuable diagnostic marker (*22*), is present on kidney tubules and some other nonlymphoid cells (*26*), and several other antigens expressed in leukemic subsets are shared with neural tissues or kidney epithelial cells (*27*). Other leukemia-associated antigens initially appeared to be maturation stage linked but are more properly regarded as activation or proliferation associated. Thus the monoclonal antibody–defined markers T9 and T10, described initially on T-ALL cells and normal thymocyte subsets (*21*), are not T lineage or maturation stage restricted but are regulated in concert with activation and cell proliferation. T9 has been identified as the receptor for transferrin (*28*). T10 is a chromosome 4–coded glycoprotein with a widespread expression in the hematopoietic system including multipotential progenitor populations and activated mature lymphocytes and plasma cells (*29*).

There are no convincing reports of leukemia-specific antigens in ALL or other lymphoid neoplasms in humans; those that appeared to be possibly leukemia/lymphoma specific, such as the Burkitt lymphoma glycolipid antigen (*30*) and others, have usually lost their candidature once appropriate normal tissues have been analyzed (*31*). Two interesting and special exceptions to this generalization may be as follows: (i) lymphocyte cell surface immunoglobulin or T-cell receptor idiotypes which, as clonotypic markers, are operationally tumor-specific, albeit normal gene products appropriately expressed (*32*); and (ii) protein products of altered protooncogenes, for example, mutated *ras* gene p21 (*33*) and the novel hybrid protein with kinase activity formed by the fusion of translocated c-*abl* gene and sequences (*bcr*) on chromosome 22 in $Ph^1$-positive leukemias (*34*).

The selective expression of antigenic determinants (enzymes and other markers) in ALL and other lymphoid malignancies is therefore primarily determined by lineage of origin, maturation status, and proliferative activity.

Acute myeloid leukemia (AML) parallels ALL in expressing the composite phenotypes of myeloid progenitor or precursor populations [for a review, see (*35*)]. The dominance of immature hematopoietic phenotypes reflects both the original cellular targets for transformation and the imposition of an apparent maturation arrest with a variable degree of stringency (*36*). Acute leukemia cell phenotypes, rather like the phenotype of the ostrich (*37*), can therefore be considered as ***primitive and conserved rather than degenerate***.

Leukemic cell phenotypes, though not perfect replicas of normal, may therefore only be minimally deviated (*6*), and this may be true even for acute leukemias with apparent multilineage (for example, lymphoid + myeloid) patterns of gene expression. It has been suggested that such leukemic cells have been subject to genetic misprogramming (*32*), but an alternative possibility is that the normal pattern of lineage-associated gene expression is intrinsically flexible in uncommitted progenitors. This normally transient period of "lineage promiscuity" could then be retained as a relic when cells are both transformed and arrested at the bi- or multipotential stage of hematopoiesis (*38*).

The phenotypic subtypes of acute lymphoblastic leukemia are predictive of clinical response, for example, remission duration. They also provide a rational explanation of much of the clinical and hematological heterogeneity of this disease, for example, variation in growth rates, tumor burden, compromise of marrow function, and age-associated prognosis (*39*). The routine multiparameter examination of leukemic cell phenotype therefore provides an important practical contribution to accurate diagnosis, especially since lympho-

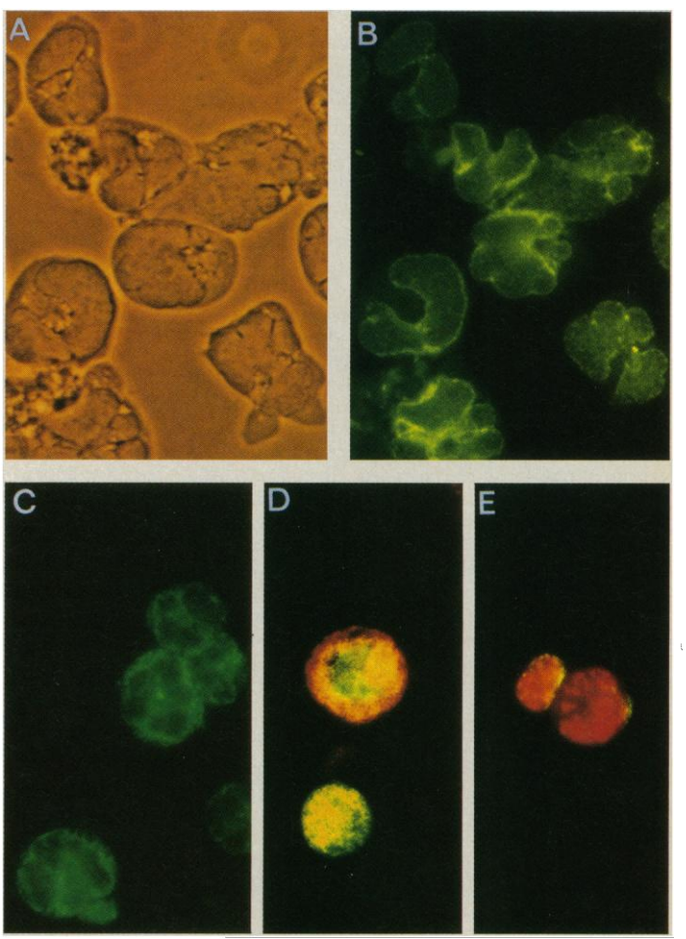


Fig. 2. Phenotypic characteristics of acute lymphoblastic leukemia cells and normal lymphoid cell precursors. (A) Acute lymphoblastic leukemia T-cell line (MOLT-3) showing highly convoluted nuclei with phase-contrast microscopy. (B) Same field as (A), with the cells stained for intracellular T3δ protein by means of monoclonal antibodies to T3δ and fluorescein-labeled goat antibody to mouse immunoglobulin. Note striking staining of the perinuclear envelope. (C) Pre-B/B-cell precursor acute lymphoblastic leukemia cell line (NALM-6); stained for intracellular μ heavy chain protein. (D) Normal bone marrow. Cells stained for nuclear TdT (fluorescein-labeled antibody) and for intracellular μ heavy chains (rhodamine-labeled antibody). Top cell contains both TdT and μ chains; lower cell contains TdT only (courtesy of G. Janossy). (E) Normal bone marrow. Cells stained for nuclear TdT (rhodamine-labeled antibody) and for the cell surface antigen CD10/cALLA. Two cells shown have same phenotype as common acute lymphoblastic leukemia cells.

cyte progenitor leukemias may occasionally be diagnosed hematologically as undifferentiated (AUL) or myeloblastic leukemia or, in the newborn, confused with erythroleukemia (*22, 40*). Additionally, the identification of normal gene products that are consistently and selectively expressed on subtypes of leukemia and lymphoma has led to their utilization as direct targets in new therapeutic strategies, for example, the use of monoclonal antibodies to cell surface antigens (*41*), or of inhibitors of adenosine deaminase (deoxycoformycin) in T-ALL (*42*).

*Chronic lymphocytic leukemias (CLL) and lymphomas.* Similar immunological and molecular analyses of chronic lymphocytic leukemias and especially the non-Hodgkin lymphomas have shown that these neoplasms usually represent clonal expansions of relatively mature lymphocyte populations corresponding to immunocompetent B or T lymphocyte subsets detectable in normal lymphoid tissue (*43*) (Fig. 1).

Mature B-cell lymphoma/leukemia overall is predominant over the T-cell type by around 8 or 9 to 1 in Western countries, with lymphoid leukemia in Japan and the Caribbean region providing a revealing counterexample attributable in large part to the endemicity of the T cell–transforming virus HTLV-I (*44*). B lymphocyte neoplasms of follicular, germinal center cell origin are a common variety of lymphoma. These tumors mostly have activated B-cell subset phenotypes and, as low-grade tumors, retain much of the cellular architecture of normal germinal centers (for example, with interdigitating dendritic reticulum cell and T-cell associations) as well as the normal "homing" behavior of germinal center B cells (*45*). These features may be lost, however, with progression to high-grade diffuse malignancy. The same holds for B-cell tumors of extranodal origin. For example, those of mucosa-associated lymphoid tissue (or MALT), including perhaps Burkitt's lymphoma and lymphoma developing in α chain disease, characteristically involve follicular center cells retaining their specialized associations with epithelial cells and restricted anatomical distribution (*46*).

Some mature B-cell clonal neoplasias may show a spectrum of cellular phenotypes from small lymphocytes to Ig-secreting plasma cells (sharing a common Ig idiotype), for example, Waldenstrom's macroglobulinemia and myeloma, reflecting a lack of stringent maturation arrest. Other lymphomas, including most germinal center derivatives, may be in maturation arrest and are less often associated with monoclonal Ig in serum.

Some neoplastic cells of lymphoid tissue have had elusive lineage or subset affiliations, for example, hairy cell leukemia, B-CLL, the Reed-Sternberg (RS) cells of Hodgkin's disease, and "histiocytic" lymphoma. Recent studies with monoclonal antibodies and DNA probes indicate, however, that these tumor cells also have identifiable counterparts among the mature B lymphocyte subsets in normal tissue with RS cells having composite phenotypes similar to activated T or B lymphocytes (*47*). As in ALL, the immunological and molecular analysis of lymphoma has important practical implications in the area of differential diagnosis, classification, prognosis, and treatment strategies (*43, 48*).

**Target cells for clonal expansion in lymphoid malignancy.** Genetic events initiating or leading to clonal selection, maturation arrest, and lymphoid malignancy probably occur at three broad developmental levels of lymphopoiesis (*24, 49*): (i) the multipotential or common lymphoid-myeloid stem cell in $Ph^1$-positive (chronic granulocytic leukemia (CGL) (*50, 51*) and other acute leukemias with lymphoid and myeloid lineage involvement (*52*); (ii) the committed T or B progenitor cells (in ALL); and (iii) the mature immunocompetent T or B lymphocyte (in chronic lymphocytic leukemia, adult T-cell leukemia (ATL), most non-Hodgkin lymphomas, and myelomas). Whether these developmental levels also provide the initial target cell population for these malignancies is difficult to ascertain. The demonstration of clonality of Ig or T-cell receptor gene rearrangements in ALL, lymphoma, or myeloma, while indicating monoclonal selection at the level of lymphoid lineage (T or B) committed cells, cannot exclude a requirement for an earlier genetic event at the level of multipotential progenitors, as illustrated in the case of lymphoid blast crisis of CGL (*53*). Most ALL's probably do originate in the lymphoid progenitor compartments (*54*), although the 5 to 10% presenting with the $Ph^1$ chromosome (without a prior CGL) (*51*) may, like blast crisis of CGL, have originated in a multipotential cell.

Experimental and clinical evidence supports the notion that immunocompetent (that is, relatively mature) lymphocytes may be the primary target populations for transformation events leading to lymphoid leukemia (for example, CLL), lymphoma, and myeloma (*55*). However, other investigations raise the possibility that mature B-cell malignancies may, in some cases at least, involve clonal, genetic events at an earlier pre-B stage of differentiation. Thus Kubagawa *et al.* reported that Ig idiotypes of myeloma proteins were present in some putative pre-B cells (*56*). Tsujimoto *et al.* (*57*) have recently suggested that the chromosome 14:18 translocation commonly found in follicular lymphoma arises as an error during $VDJ_H$ joining involving the site-specific recombinases active at the pre-B stage of differentiation.

Speculations on the possible target cell populations for leukemic transformation hold more than academic interest, since a better understanding of this issue could have an impact on the design and choice of therapeutic regimes (*58*).

Irrespective of the outcome of this issue, lymphocytes should be

Table 1. Summary of the major phenotypic characteristics of acute lymphoblastic leukemia cells. CD indicates cluster of differentiation; CD numbers are for the cell surface antigens of leukocytes detected by monoclonal antibodies (*93, 94*). For details of the enzymes, see (*14*). The level of insulin receptors and transferrin receptors on ALL cells is extremely variable and related to proliferative status. T-ALL cells usually have a higher growth fraction (or cells in cycle) than B precursor ALL cells (*95*) and have a higher density of transferrin receptors (*96*). In contrast, insulin receptors appear to be inversely related to growth rates and are found in greater density on B precursor ALL cells compared with T precursor ALL cells (*97*). Cytosolic corticosteroid receptors are found in both major subtypes of ALL but are present at higher levels (five to ten times) in the common variant of B precursor ALL cells compared with T-ALL cells; the more immature "null" variant of B precursor ALL cells usually has intermediate values (*98*).

| Characteristic | T-cell precursor | B-cell precursor |
|---|---|---|
| Membrane antigens | | |
| CD7 | + | − |
| CD19 | − | + |
| CD2,CD5 | Usually + | − |
| CD9, CD10, CD24 | Usually − | Usually + |
| CD1, CD3, CD4, CD8 | Variable | − |
| CD20, CD21 | − | Variable |
| Cytoplasmic CD3 | + | − |
| Cytoplasmic CD22 | − | + |
| HLA ABC | + | + |
| HLA DR/DP | − | + |
| Enzymology | | |
| Nuclear TdT | + | + |
| Lysosomal hydrolase isoenzymes | − | +* |
| Adenosine deaminase | +++ | ++ |
| Purine nucleoside/phosphorylase | + | ++ |
| 5′ Nucleotidase | + | +++ |
| Focal acid phosphatase | + | − |
| Receptors | | |
| Transferrin | +++ | + |
| Insulin | + | ++ |
| Corticosteroid | ++ | + |
| Antigen | Mostly cell surface receptor negative† | |

*Common (B-cell precursor) ALL's usually express a relatively high level of particular electrophoretic (and size) variants of lysosomal hydrolases such as hexosaminidase and mannosidase (*14*). †See text.

considered a special case in comparison with the mature cells of other tissues, which are probably seldom targets for malignancy. Lymphocytes retain extensive proliferative or self-renewal potential, longevity (inter-mitotic periods of 10 years or more in humans), and capacity for further maturation (in the case of B cells) to plasma cells.

**Aberrant phenotypes in other cancers: Lessons from leukemia?** An appreciation of the likely cell of origin, variable stringency of maturation arrest, and predominantly normal pattern of expression of leukemia-associated phenotypes is important in a more general sense for cancer biology. Without access to appropriate normal tissue or some understanding of cell lineage hierarchies and proliferation-associated changes, leukemic phenotypes could readily be interpreted as aberrant, dedifferentiated, oncofetal, or ectopic. This would be incorrect in most cases because, as emphasized here, the apparently abnormal phenotypes are usually the result of clonal selection of numerically rare cell types. This situation probably holds true for several other commonly cited aberrant phenotypic features that are associated with more common cancers and may also arise in numerically infrequent progenitor or stem cell populations (*5*), for example, under-glycosylation of membrane structures in epithelial carcinomas (*59, 60*), dedifferentiation (for example, of astrocytoma to glioblastoma) (*51, 61*), and ectopic synthesis of neuropeptides (*62–64*).

## The Essential Lesion in Lymphoid Malignancy

**Stabilization of normal transit phenotypes.** The overall consistency with which lineage phenotypic fidelity appears to be conserved in human lymphoid leukemia and lymphoma, as well as the partial reversal in vitro of maturation arrest of these cells in some instances (*65*), accords with the view that the primary lesion is regulatory in nature. It has also prompted the idea that the uncoupling of differentiation and proliferation, while permitting the retention of relatively unaltered cellular phenotypes, might be both essential and sufficient for leukemogenesis (*7, 8*). This strikes me as being rather like the dilemma posed by the Queen to Alice: "Now, here, you see, it takes all the running you can do, to keep in the same place" (Lewis Carroll, *Through the Looking Glass*).

Sachs developed a similar and more detailed concept based primarily on studies of murine myeloid cell lines in which he incorporated alterations associated with specific growth factors regulating proliferation and maturation (*66*). Studies by Graf *et al.* on the reversibility of maturation arrest in chicken erythroid cells transformed with temperature-sensitive mutants of avian erythroblastosis virus (*67*) and the effects of different viral oncogenes on differentiation and growth factor dependence (*68*) provide perhaps the clearest support for this type of model.

If the normal pattern of gene expression of lymphoid precursor cells is, as it appears, conserved in leukemia then one can entertain a novel view of the essential abnormality. Rather than being merely a permissive expression compatible with leukemic cell behavior, perhaps the transit cell phenotype is in itself the key feature or abnormality in these disorders.

The normal rules governing the balance of self-renewal and maturation of hematopoietic progenitor cells appear to be flexible and subject to environmental demands (*69*). As a consequence, hematopoietic regeneration can mimic leukemia by temporarily favoring cell renewal and expanding the numbers of cells in transit compartments. Thus, lymphoid progenitor populations expanded in regenerating marrow and in neonatal lymphocytosis may be phenotypically indistinguishable from ALL cells, aside from clonal markers (*20–22*). Similarly, persistent lymphadenopathy or dysregulated immune responses may be difficult to distinguish from lymphoma. In these circumstances, however, the amplified transit populations are usually polyclonal and not, as in leukemic clones, endowed with a constitutive alteration in growth properties with associated karyotypic abnormalities.

The dysregulation underlying the emergence of a leukemic clone might therefore be quite subtle, and intimately linked with the target cell's program for differentiation. Recent molecular investigations of human lymphoid leukemias are compatible with this notion.

**Molecular events in leukemogenesis exploit the normal differentiation program.** Consistent phenotypic abnormalities identifiable at the single cell and clonal level in lymphoid leukemias and lymphomas (as well as in myeloid leukemias) have been defined karyotypically in terms of nonrandom chromosome alterations. These include reciprocal translocations, duplications, and deletions (*70*). These alterations in turn are postulated to precipitate changes in the expression or regulation of protooncogenes or other genes involved in cell growth or differentiation control (*70*). Although they may be causally part of the leukemogenic process, specific chromosomal alterations may paradoxically be linked to and dependent on the cell's normal program of differentiation and proliferation. The strongest evidence supporting this view derives from the striking association, in both myeloid and lymphoid malignancy, between particular chromosomal translocations and developmental compartment or cell type (*70*).

The majority of nonrandom karyotypic alterations recorded in lymphoid malignancy are found associated with particular subtypes of B- or T-cell leukemias or lymphomas (*70–73*). In many cases the genes involved have not yet been identified; some, however, involve breaks that are close to the localization of protooncogenes, other important genes in growth control (for example, insulin receptor), or inherited fragile sites (*70–73*). The most significant association to emerge from these studies is the involvement of rearranging immunoglobulin and T-cell receptor genes in B and T lineage malignancies, respectively. The t(8;14)(q24;q32) marker in Burkitt's lymphoma, and other developmentally related B-cell neoplasms, involving IgH and c-*myc* genes is the most extensively studied of these associations (*70, 71, 74*). Other B-cell lineage associated translocations involve the IgH locus with genetic regions on chromosome 11 (q13) or 18 (q21) that may have sequences recognizable by the recombinases active during the period of lymphocyte diversification (*57*).

More recent observations have implicated the rearranging T-cell receptor α and β loci in transformation events. The α gene has been mapped to 14q11 (*75*), a region involved in gross chromosomal alterations in a high proportion of T-cell leukemias of different subtypes. Breaks at 14q11 occur primarily as reciprocal translocations involving 11p13, as translocations between two number 14 chromosomes, or as inversions associated in both instances with breaks at 14q32 involving the IgH locus (*76*). Recent reports suggest that the T-cell receptor β gene at 7q32 may also be involved in a T-cell leukemia translocation—in this case in association with 9q34 (*77*).

It may be significant that the loci of these three rearranging T-cell receptor genes, γ (*78*), β (*79*), and α (*75*), are all mapped to chromosomal positions prone to breakage and occasional rearrangement in normal activated T cells and especially in patients with inherited chromosome fragility (ataxia telangiectasia) (*80*). This could indicate that the chromosomal changes associated with rearranging receptor genes in leukemia are relatively trivial. The more likely, and currently favored, explanation is that functional translocation of a growth regulating gene into such rearranging loci results in transcriptional dysregulation of the former and subsequent clonal proliferative advantage.

Whether alterations in the activity of particular protooncogenes or nonrandom chromosome changes are sufficient in themselves for leukemogenesis is another matter, as emphasized by critiques from both Duesberg and Rubin (*81*). Often only a minority of the patients with the same subset of lymphoid malignancies appear to have the same karyotypic changes, and in some cases the cell type–specific translocations are accompanied by other multiple chromosome alterations [for example, changes accompanying t(1:19) in pre-B ALL and 14q11 in ATL] or even occur secondarily to other chromosome alterations. Additionally, as exemplified by karyotypic analysis of T cells in patients with ataxia telangiectasia, nonrandom chromosomal changes can precede overt leukemia by ten or more years. Several lymphoid cell type or leukemic subtype associated karyotypic markers do occur with striking regularity, however, and since these changes are probably rare events and clonal in origin, their frequency is likely to reflect a potent selective advantage.

Similarly, whether gross karyotypic changes are ever primary or initiating events in the evolution of lymphoid tumors is also difficult to determine; in the case of the two virus-associated lymphoid neoplasias [Epstein-Barr virus (EBV) EBV and Burkitt's lymphoma; HTLV-I and ATL] they probably are not, and yet in both cases they may well be essential for the evolution of neoplasia.

It seems likely that these alterations, and other genetic events not involving chromosomal changes visible by karyotyping, for example, mutations in *ras* genes (*82*) or other developmentally regulated genes with no known viral homologs (*83, 84*), are indeed causally involved at various stages in the multistep evolution of lymphoid malignancy. The important proviso, required to accommodate available data as well as the skeptics' reservations (*81*) and, perhaps, intuitive common sense, is that although certain genetic alterations may predominate, according to cell type, no single or obligatory sequence of genetic events is required to render any one lymphoid cell type leukemic.

Whatever the genes involved, and the particular biochemical function of their products, a substantial proportion of genetic alterations in lymphoid neoplasia may have selective advantage primarily by exploiting components of the normal developmental programming of lymphocytes including stage-specific genes, recombinases, and rearranging loci. The primary consequence of these changes appears to be a partial or complete stabilization of a cellular phenotype which is *similarly expressed, though only transiently, in equivalent normal cells*. The crucial phenotypic difference between leukemic and normal cells is then a time frame shift in expression. The key product, or products, might even be present at precisely the same functional level in a leukemic cell and its normal counterpart *in a short time frame*.

Recent experiments on c-*myc* messenger RNA (mRNA) regulation are very instructive in this regard. Campisi *et al.* (*85*) demonstrated that chemical transformation of rodent cells led to no rearrangement, amplification, or over-expression of c-*myc*, but did lead to a loss of the normal cell cycle–linked regulation. Kelly *et al.* (*86*) have also reported cell-cycle association of c-*myc* mRNA expression in human B cells (and murine 3T3 fibroblasts) and speculated that temporal deregulation of c-*myc* expression may be far more important in B-cell neoplasia than absolute levels.

**Etiologic mechanisms.** The etiological factors initiating or promoting the genetic alterations underlying the evolution of malignant lymphoid clones are largely unknown. The functional organization of the lymphoid system may, however, favor certain types of mechanisms. As mutations, changes in genes regulating growth or differentiation can clearly have an induced, inherited, or spontaneous origin [see (*87*)]. All three mechanisms probably contribute to lymphoid neoplasia, but spontaneous mutation occurring in cells under intense or sustained proliferative stress may be predominant. In mature lymphoid neoplasms this possibility might arise as a consequence of viral infection (plus transformation in some instances, for example, EBV, HTLV-I) or dysregulated immune responses (*55, 88*). In ALL, the intrinsic developmental program of lymphocyte precursors has a number of unusual characteristics that should predispose toward spontaneous mutation. These include (i) extraordinarily extensive proliferation in the precursor compartment (*89*); (ii) rearrangement (and occasionally breaking) of receptor gene regions with the use of site-specific recombinases capable of recognizing similar sequences on other chromosomes (*57*); and (iii) the activity of an enzyme functioning as a somatic mutagen, that is, TdT (*90*). These features could provide sufficient opportunity for spontaneous mutation to account for the initiation of most (though not necessarily all) cases of the major childhood cancer in developed societies (*91*). At the same time this explanation, if correct, would resolve a long-standing enigma—the apparent lack of any clear environmental or genetic (inherited) associations that can explain the etiology of most cases of ALL [reviewed in (*91*)].

## Conclusions

Leukemias and lymphomas are the first human cancers in which phenotypic and clinical heterogeneity has been systematically analyzed from the perspective of the developmental biology and function of the tissue of origin. The results reveal the extent to which lymphoid malignancy at both the cellular and molecular level mirrors the complexity of normal lymphopoiesis involving both progenitor populations and mature immunocompetent lymphocytes. These findings have direct clinical value in differential diagnosis and in the design of novel therapeutic programs and may also serve as a paradigm for other human cancers where pathological and clinical diversity is perceived but poorly understood.

Some of the environmental agents, immunological factors, and cellular genes involved in the etiology of lymphoid neoplasia have now been identified. Most of the data are compatible with the notion that acute lymphoblastic leukemia represents a developmental lesion in lymphoid precursors, whereas mature B-cell (or more rarely T-cell) neoplasms usually evolve against a background of dysregulated immune responses and, in some instances at least, involve transforming viruses. Although the underlying cellular and molecular mechanisms, and the possible role of lymphocyte growth factors and their receptors, are still incompletely resolved, the data available accord with the view that subtle exploitation of the normal differentiation program and consequent stabilization of normally transient proliferative cellular phenotype are key events.

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# Life Cycle, Individual Thrift, and the Wealth of Nations

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**One theory of the determinants of individual and national thrift has come to be known as the life cycle hypothesis of saving. The state of the art on the eve of the formulation of the hypothesis some 30 years ago is reviewed. Then the theoretical foundations of the model in its original formulation and later amendment are set forth, calling attention to various implications, some distinctive to it and some counterintuitive. A number of crucial empirical tests, both at the individual and the aggregate level, are presented as well as some applications of the life cycle hypothesis of saving to current policy issues.**

*THE ROLE OF THRIFT AND THE KEYNESIAN REVOLUTION.* The study of individual thrift and aggregate saving and wealth has long been central to economics because national saving is the source of the supply of capital, a major factor of production controlling the productivity of labor and its growth over time. It is because of this relation between saving and productive capital that thrift has traditionally been regarded as a virtuous, socially beneficial act.

Yet, there was a brief but influential interval in the course of which, under the impact of the Great Depression and of the interpretation of this episode which Keynes suggested in the *General Theory of Employment, Interest and Money* (*1*), saving came to be seen with suspicion, as potentially disruptive to the economy and harmful to social welfare. The period in question goes from the mid-1930's to the late 1940's or early 1950's. Thrift posed a potential threat, as it reduced one component of demand, consumption, without systematically and automatically giving rise to an offsetting expansion in investment. It might thus cause "inadequate" demand—and, hence, output and employment lower than the capacity of the economy. This failure was attributable to a variety of reasons including wage rigidity, liquidity preference, fixed capital coefficients in production, and investment controlled by animal spirits rather than by the cost of capital.

Not only was oversaving seen as having played a major role in the Great Depression, but, in addition, there was widespread fear that the problem might come back to haunt the postwar era. These fears were fostered by a widely held conviction that, in the future, there would not be too much need for additional accumulation of capital while saving would rise even faster than income. This combination


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