Cutaneous T-cell dysplasias are chronic, premalignant, lymphoproliferative disorders. If their evolution is not prematurely terminated by death secondary to sepsis, treatment, or unrelated diseases, they progress naturally to cutaneous tumors and disseminate to lymph nodes and extracutaneous sites.

The concept of primary cutaneous T-cell dysplasia, leukemia and lymphoma includes disorders classified clinically as mycosis fungoides, parapsoriasis, poikiloderma atrophicans and Sézary syndrome. In each of these disorders, erythematous or atrophic lesions, whose patterns dominate much of the clinical life history, may give way to indurated lesions or tumors. These alterations in basic patterns are clinical markers of progressive disease.

Correlates for the clinical markers are found in cytologic and histologic alterations of the lymphoid infiltrates (histologic progression). Histologic progression is manifested by increasing degrees of cytologic atypism and by an increasing proportion of atypical cells at the expense of reactive cells. In late stages discontinuous growth is manifested by involvement of regional lymph nodes and by disseminated disease.

The visceral infiltrates often are diffuse, or leukemic in quality, and may be associated with a dermatopathic leukemia (hematogenous dissemination).

Historical Aspects

The concept of a primary, cutaneous, malignant lymphoma is intertwined with the clinical concept expressed by the archaic term mycosis fungoides. Clinically, mycosis fungoides is defined by the following characteristics:

I. Primary, chronic, cutaneous disease.
II. Evolutionary clinical stages (evolve in sequence to plaques and tumors or directly to tumors):
   - Localized erythema;
   - Plaques;
   - Nodules or tumors.
III. Clinical progression:
   - Dissemination in the skin;
   - Dissemination to lymph nodes;
   - Hematogenous dissemination to other extracutaneous sites.
IV. Unpredictable rate of progression:
   - Hematogenous dissemination closely related to lymph node involvement.
   - Evolutionary stage IIc (tumor stage) and clinical stages IIIb and IIc equate with a poor prognosis.

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The concept of mycosis fungoides has evoked controversy.\textsuperscript{7,13-28} Alibert's description of mycosis fungoides provides the model for the Alibert variant.\textsuperscript{11} In addition, the concept has evolved to include erythrodermic, and d'emblée or de novo variants.\textsuperscript{15} The erythroderma may be a dominant and persistent clinical feature or an episodic complication of the Alibert variant. (Fig. 1.) By definition, the d'emblée variant is lymphomatous from its inception and lacks the quality of histologic progression. The features that it shares with disseminated B-cell lymphomas have compromised the concept of mycosis fungoides.\textsuperscript{7} Many of the cases erroneously reported as mycosis fungoides d'emblée represent cutaneous manifestations of B-cell, or follicular center cell, lymphomas.\textsuperscript{3}

Three other disorders share features with mycosis fungoides. One of these, the Sézary syndrome,\textsuperscript{16,29,30} has been identified as a T-cell dysplasia with a dermatopathic leukemia.\textsuperscript{4,31-37} It is defined as an erythrodermic, premalignant T-cell dysplasia, in which abnormal lymphocytes (Sézary cells) circulate in the peripheral blood,\textsuperscript{8} and it shares features with erythrodermic variants of mycosis fungoides.\textsuperscript{34} Erythroderma is a non-specific reaction of the skin.\textsuperscript{29} It may be a feature of disseminated, malignant B-cell lymphomas and Hodgkin's disease, but need not be associated with specific cutaneous infiltrates. Lutzner et al. have questioned the nature of some of the cases reported as chronic lymphocytic leukemia with an erythroderma.\textsuperscript{4} They propose that erythroderma is a manifestation of T-lymphocytes that preferentially reside in the dermis.\textsuperscript{34}

The clinical patterns in progressive stages of parapsoriasis\textsuperscript{4,12,38} and poikiloderma atrophicans\textsuperscript{39} are difficult to distinguish from patterns in the progressive stages of mycosis fungoides (Alibert).\textsuperscript{4,36,39} Dermatologists cannot agree on a definition of parapsoriasis\textsuperscript{39} or on the distinctions between parapsoriasis and poikiloderma atrophicans.\textsuperscript{7} Those who accept parapsoriasis as a cutaneous, premalignant reticulosis rely on clinical features shared with poikiloderma atrophicans (parapsoriasis-poikiloderma complex).\textsuperscript{3,39}

\textit{“Dermatologists cannot agree on a definition of parapsoriasis or on the distinctions between parapsoriasis and poikiloderma atrophicans.”}

In 1966, Reed and Cummings proposed that the term mycosis fungoides be discarded.\textsuperscript{7} Misuse of the term by clinicians and pathologists had engendered confusion and had handicapped efforts to define a clinicopathologic entity. The d'emblée variant of mycosis fungoides proved to be a hodgepodge, with most cases expressing the cutaneous dissemination of a nodal or visceral lymphoma.\textsuperscript{7} Some clinicians have ignored the inconsistent use of the term mycosis fungoides and have misinterpreted the proposed changes in the classification of cutaneous lymphoreticularoses.\textsuperscript{3} Reed and Cummings clearly identified a primary cutaneous lymphoreticulosis.\textsuperscript{7} It was characterized by a distinctive monocytoid cell and evolved slowly with histologic progressions heralding disseminated or fatal disease.\textsuperscript{7} The identification of the Sézary cell and the mycosis cell as derivatives of T-lymphocytes has restored order to a mishmash of clinical concepts. The casual manner in which the early evolutionary stages of cutaneous T-cell dysplasias are classified as lymphomas and leukemias is a current source of conceptual confusion.\textsuperscript{4} It is difficult to apply cytologic criteria to the classification of T-cell and B-cell immunoblastic processes. The morphologic spectrum of T-lymphocyte modulations in reactive processes has not
been defined. If the dysplastic cells retain the capacity to react to antigenic stimuli, variations in cytologic patterns may express immune responses rather than progressive dysplasia.

Definition of the Dysplastic T-Lymphocyte

In each of the above clinical disorders, a distinctive lymphoid cell with a hyperchromatic, convoluted, or cerebriform nucleus has been identified. Cells with these qualities have been described as Lutzner cells, mycosis cells, or Sézary cells. They have surface characteristics of thymic-derived (T-cell) lymphocytes. In the circulation the atypical lymphoid cells contain both diastase-sensitive and diastase-resistant PAS + granules. Ultrastructurally the dysplastic T-lymphocyte has a deeply convoluted nucleus and marginated heterochromatin. Its cytoplasm has relatively few distinctive organelles, but it contains occasional dense bodies and clusters of glycogen granules. The cytoplasm is relatively scanty and may have surface pseudopods or a uropod. Intracytoplasmic fibrils or filaments, mitochondria clustered at one pole of the cell, and prominent nucleoli are found frequently. Small and large variants of Sézary cells have been described: their diameters average 8μ and 15 to 20μ respectively.

The T-lymphocyte has specific markers—lymphocyte-transformation tests, T-cell antigens, rosette formation with erythrocytes, and the like—but morphologically, some dysplastic T-lymphocytes have such distinctive nuclear characteristics as dense chromatin and a convoluted nuclear membrane. Small lymphocytes with these nuclear characteristics may be identified in the dermal infiltrates of inflamed keratoses, such as inflamed seborrheic keratoses or lichenoid actinic keratoses. Ultrastructurally they have been identified in the inflammatory infiltrates in lichen planus, solar keratoses and basal cell carcinomas. Cytologically these reactive lymphocytes share features with dysplastic T-lymphocytes (mycosis or Sézary cells). In reactive processes, the convoluted nucleus of some lymphoid cells may be a histologic marker of the transformed T-lymphocyte (effector cell). It may express a modulation in the transformation of the T-lymphocyte that is comparable to the cleaved nucleus of the transformed B-lymphocyte. Ultrastructurally the dysplastic T-lymphocyte is similar to the normal T-lymphocyte that has changed in response to blastogenic agents.

Cells with the ultrastructural characteristics of mycosis cells have been identified in some examples of pityriasis lichenoides (lymphomatoid papulosis). The association between mycosis cells and lymphomatoid papulosis has prompted Lutzner et al. to classify the latter disorder as a variant of cutaneous T-cell lymphoma. Although lymphomatoid papulosis occasionally has been associated with or has evolved into mycosis fungoides, the bulk of the evidence would not warrant the interpretation that lymphomatoid papulosis is a lymphoma.

Immunologic Concepts

The evidence clearly implicates the T-, or thymic-derived, lymphocyte in the pathogenesis of both mycosis fungoides and the Sézary syndrome. The T-lymphocyte is the effector cell of cellular immunity, residing in the paracortical area of lymph nodes and the periarteriolar areas of the spleen (T-cell domain). It circulates in the peripheral blood, constituting up to 70 percent of the circulating lymphocytes. In the paracortical region of lymph nodes it undergoes morphologic and functional modulations. These modulations involve the transformation of sensitized lymphocytes into blast cells, or T-im-
munoblasts, and the generation of a clone of effector T-lymphocytes, which seed the circulation. In sites of antigen localization, the effector cells leave the circulation to interact with target cells in a characteristic and intimate fashion. The requisite for a close association between effector and target cells or tissues in the efferent limb of the T-lymphocyte cycle is not shared by the ef-

### TABLE 1.
CLASSIFICATION OF CUTANEOUS T-LYMPHOCYTE DYSPALAS

| I. | Lichenoid, radial growth phase (progressive-regressive phenomena). |
|----|-----------------------------------------------------------------|
|    | Band-like infiltrate.                                           |
|    | Epidermal atrophy.                                              |
|    | Lichenoid reactions—cell-mediated attrition of epidermis and accretional fibrosis of papillary dermis. |
|    | Nonspecific inflammatory component in dermis.                   |
|    | Variable component of dysplastic cells in epidermis (mild, moderate, marked). |
|    | Foci of regression (papillary dermal fibrosis, lymphocyte depletion). |

| II. | Psoriasiform, radial growth phase (progressive-regressive phenomena). |
|-----|---------------------------------------------------------------------|
|     | Psoriasiform epidermal hyperplasia (immune stimulation?).           |
|     | Papillary dermal fibrosis.                                          |
|     | Nonspecific inflammatory component in dermis.                      |
|     | Variable dysplastic component in epidermis and dermis (mild, moderate, marked). |
|     | Focal lichenoid reactions, overshadowed by psoriasiform patterns.  |
|     | Dermatopathic leukemia ± (Sözary phenomenon).                      |

| III. | Diffuse, adventitial, radial growth phase (progressive-regressive phenomenon). |
|------|--------------------------------------------------------------------------------|
|      | Band-like infiltrates in papillary dermis.                               |
|      | Minimal epidermal involvement (uninvolved zone in papillary dermis, so-called grenz zone, often present between infiltrate and epidermis). |
|      | Three-to-four-fold or greater increase in thickness of papillary dermis.  |
|      | Variable dysplastic component (mild, moderate, marked).                 |
|      | Vascular invasion ±.                                                   |
|      | Dermatopathic leukemia ±.                                               |
|      | Disseminated disease should be ruled out.                              |

| IV.  | Malignant T-cell reticulosis in situ, radial growth phase.             |
|------|-----------------------------------------------------------------------|
|      | Cytologically malignant infiltrate confined to adventitial dermis.    |
|      | Lymphocyte depletion.                                                 |
|      | Disseminated disease should be ruled out.                             |

| V.   | Malignant T-cell reticulosis, vertical growth phase.                  |
|------|----------------------------------------------------------------------|
|      | Cytologically malignant infiltrate with tumorous involvement of reticular dermis. |
|      | Disseminated disease should be ruled out.                            |
|      | Lymphocyte depletion.                                                 |
fector and target cells in the efferent limb of the B-lymphocyte cycle.

The T-lymphocyte is a migratory, secretory cell. One of its products, the migration inhibitory factor (MIF), suppresses the movement of macrophages, and another of its products influences leukocyte chemotaxis. In part, the lytic effects of cellular immunity are mediated by macrophages. Specifical-

“In a T-lymphocyte dysplasia, the dysplastic cells recapitulate functions normally expressed in reactive or inflammatory processes.”

ly sensitized T-lymphocytes may locally activate other lymphocytes that have not participated in the immune cycle of lymph-node migration.

Several histologic patterns of cellular immunity have been defined, including a response that is invasive and destructive. The destructive pattern is characterized by:

1. Sensitization of lymphoid cells, or T-lymphocytes.
2. Migration of sensitized cells to lymph nodes.
3. Transformation of lymphocytes into effector cells.
4. Discharge of transformed lymphocytes into circulation.
5. Aggregation of effector cells in the vascular adventitia of the target organ (perivenular islands).
6. Migration of effector cells into target organ.
7. Intermingling of lymphocytes (effector cells), macrophages and target cells.
8. Stimulation of target cells (occasional), or
9. Lysis and coagulation of target cells (usual).
10. Formation of lytic defects in target organ.
11. Desmoplastic response with inlay of fibrous tissue in lytic defects.
12. Repetition of steps nine, 10 and 11.

Lichenoid Reaction as an Expression of Cellular Immunity

The cutaneous lichenoid reaction shares many features with the invasive-destructive pattern of cellular immunity. Lichenoid responses may be cell-rich or cell-poor; the reaction in lichen planus is prototypical of the cell-rich lichenoid response. On the basis of comparative morphology, the cell-rich lichenoid response satisfies most of the morphologic criteria, if not all, for the invasive-destructive pattern of cell-mediated immunity.

In lichenoid reactions, two functioning units should be emphasized. A superficial unit consists of the keratin layer, the granular layer, and cells of the stratum malpighii. In the stratum malpighii, the elongated cells are parallel to the surface of the skin and contain acidophilic cytoplasm with prominent tonofibrils. The superficial unit is concerned with the maintenance of an impervious barrier at the surface. It produces the keratin layer and obliterates the intercellular spaces. Hyperplasia of the superficial unit produces acanthosis, (thickening of the epidermis above the level of the tips of the dermal papillae), and often results in hypergranulosis and compact hyperkeratosis. Individually the cells of the superficial unit may undergo hypertrophy and show an increased cytoplasmic acidophilia. The basal unit is concerned with the replication of cells and with the maintenance of a stable interface with the papillary dermis. In the basal unit of the epidermis, elongated basophilic cells are perpendicular to the basement membrane.

Hyperplasia of the basal unit is associated with an increased prominence of basophilic keratinocytes, some of
which are in mitosis, and with elongation of rete ridges (psoriasiform pattern). Interstitial spaces are widened and mucoid.

In lichenoid reactions, the responses in the basal and superficial units are variable. The following basic patterns may be seen:

I. Primary lichenoid pattern. (Fig. 2.)
- Band-like lymphoid infiltrate in the papillary dermis.
- Psoriasiform epidermal hyperplasia, or hyperplasia of basal unit.
- Migration of lymphoid cells into epidermis.
- Intermingling of lymphoid cells, macrophages and keratinocytes.
- Lysis of keratinocytes at dermo-epidermal interface and focally within the epidermis.
- Variable changes in superficial unit, for example, focal parakeratosis.

II. Established lichenoid pattern. (Fig. 3.)
- Band-like lymphoid infiltrate in papillary dermis.
- Focal migration of lymphoid cells and macrophages into epidermis to produce lytic defects in basal unit.
- Attrition of basal unit of epidermis to produce saw-toothing or effacement of rete ridges.
- Atrophy of basal unit between remnants of rete ridges (single row of basal cells with focal lytic defects).
- Normal superficial unit (atrophic epidermis), or
- Hyperplastic superficial unit.
- Relative confinement of epidermal lymphoid infiltrates to areas of lysis.

III. Senescent lichenoid response. (Fig. 4.)
- Partial or complete resolution of lymphoid infiltrate, often with increased prominence of macrophages.
- Widened fibrotic papillary dermis (accretion).
- Atrophy of basal unit (effacement of rete ridges).
- Ectasia of vessels in papillary dermis.
- Disappearance of epidermal lymphoid component.

These patterns are not mutually exclusive, and in many lesions overlaps are common.

Application of Immunologic Concepts to T-Cell Dysplasia

The recent advances in our knowledge of the morphology and functions of lymphocytes have provided an insight into the nature of primary cutaneous lymphoreticuloses. It is possible to return fresh to archaic clinical concepts and to wonder at the apprehension of clinicians who defined and supported these concepts through years of controversy.

The lichenoid reactions serve as models for patterns commonly seen in T-cell dysplasias:

I. The primary or psoriasiform pattern is characteristic of the basic response seen in erythematous and papular lesions of the Alibert type of mycosis fungoides.

II. The established pattern may be seen in the clinical setting of parapsoriasis or the Sézary syndrome.

III. The senescent pattern is characteristic of poikiloderma atrophicans vasculare.

In a T-lymphocyte dysplasia, the dysplastic cells recapitulate functions normally expressed in reactive or inflammatory processes. In contrast to reactive lichenoid processes, those in T-cell dysplasias are distinguished by immature lymphoid cells, some of which have distinctive nuclear characteristics. The dysplastic lymphocytes infiltrate the dermis and epidermis and
are most easily identified in the latter site.8,41 If they aggregate in lytic defects in the epidermis, they produce the so-called Pautrier microabscess.8,46 In the dermis, dysplastic lymphocytes are usually admixed with a non-specific inflammatory component of histiocytes and small lymphocytes to produce a pleomorphic infiltrate. The non-specific cells may express the host's response to the dysplastic cells or be stimulated by lymphokines such as MIF, which are produced by the dysplastic cells.17

**Evaluation of T-Cell Dysplasias**

An evaluation of a dysplasia is based on nuclear characteristics, on the relative proportion of dysplastic and reactive cells and on the distribution of the infiltrate.7,10 (Figs. 5 and 6) Increased cytologic atypism is manifested by increased nuclear and nucleolar size, chromatin density and mitotic rate. Increased nuclear size may reflect tetraploid cells.48 With intralesional transformation or histologic progression, there is a reduction in the population of reactive cells (lymphocyte depletion).8 If the infiltrate is confined to the papillary dermis, depleted of lymphocytes, and composed of a uniform (monomorphic) population of dysplastic cells, it qualifies as a malignant T-cell lymphoma in situ.8 If a similar monomorphic infiltrate has produced a cutaneous tumor, or nodule, and infiltrated the reticular dermis, it has progressed to a malignant, cutaneous T-cell lymphoma.8

The dysplastic T-lymphocytes probably migrate with small sensitized lymphocytes to regional lymph nodes, the afferent immune limb, and in turn may gain access to the peripheral blood, the efferent immune limb. In lymph nodes they reside in the paracortical regions, or T-cell domain. In the latter area, loosely aggregated, atypical lymphoid cells do not represent lymphomatous involvement any more than loosely aggregated mycosis cells in the dermal infiltrates qualify as malignant lymphoma. In general, the degree of lymphoid dysplasia in lymph nodes mirrors the dysplastic changes in cutaneous lesions.8 The biologic significance of dysplastic T-lymphocytes in lymph nodes may reside in their leukemic rather than in their lymphomatous potential. They may seed the circulation, to produce dermatopathic leukemia, and eventually disseminate. If numerous dysplastic T-lymphocytes gain access to the peripheral blood, the efferent immune limb, and are identified in smears, they are classified as Sézary cells. This process qualifies as a dermatopathic leukemia.9,10

Small and large variants of Sézary cells may manifest either diploidy or tetraploidy.48 In mycosis fungoides, most of the abnormal cells have chromosomes in the diploid range. Chromosome abnormalities are common and are detected in cytogenetic and Feulgen-DNA cytophotometric studies.28,48,62,63 From case to case, there are no consistent chromosomal abnormalities, but in any given patient the abnormalities are relatively constant.63

**Clinicopathic Correlations**

**Mycosis Fungoides**

The psoriasiform quality of the Alibert variant of mycosis fungoides is expressed in both histologic and clinical features. Histologically the psoriasiform pattern qualifies as a variant of a primary lichenoid reaction.59 Clinically
the erythematous, scaly papules or plaques may be confused with other psoriasiform processes such as eczema, psoriasis, neurodermatitis or contact dermatitis. Clinical progression of disease is marked by increasing induration of individual lesions. The indurated plaques are less likely to be confused with other psoriasiform processes. Some lesions may spontaneously regress, and large lesions may do so partially to produce arcuate patterns. With progression, some of the plaques may become polypoid or tumorous; tumors may also appear spontaneously in uninvolved skin. In advanced disease, cutaneous lesions may appear in an eruptive fashion. Earlier reports suggest that mycosis fungoides in the final stages may be indistinguishable from other leukemias or lymphomas. Detailed studies of autopsy material indicate that mycosis fungoides is distinctive, even in disseminated visceral lesions.

Parapsoriasis-Poikiloderma Complex

Mycosis fungoides is a clinically derived concept but the definition of the mycosis cell has contributed histologic specificity. A separation between mycosis fungoides (Alibert) and parapsoriasis is clinically possible, but in the presence of dysplastic T-lymphocytes, or mycosis cells, the distinctions are lost. Histologically, the large lesions of atrophic parapsoriasis or parapsoriasis-poikiloderma complex, exemplify the lichenoid reaction. The erythematous components show a cell-rich, established lichenoid pattern, and the atrophic areas show a senescent lichenoid pattern. The variable clinical patterns in this complex have found expression in qualifications such as lichenoides, variegata, and retiformis. Parapsoriasis en plaque embraces two distinct processes, one of which is benign and the other premalignant. The former is also classified as xanthoerythroderma perstans. The premalignant form of parapsoriasis en plaque is a primary T-cell dysplasia in the parapsoriasis-poikiloderma complex. Lesions in the complex are small or large patches of reticulated pigmentation with telangiectasia, erythema and varying degrees of atrophy, a significant component of which qualifies the process as poikilodermatous. They may progress to indurated plaques or tumors. If emphasis falls upon archaic clinical concepts, the evolved plaques and tumors precedentially qualify the process as mycosis fungoides, rather than progressive disease in the parapsoriasis-poikiloderma complex. Dysplastic T-lymphocytes in the clinical setting of the parapsoriasis-poikiloderma complex are also precedential and usually qualify a lesion as mycosis fungoides regardless of the clinical impression. Histologic progression, progressive T-cell dysplasia, may accompany the clinical progression. The concept of T-cell dysplasia avoids many of the etymologic hazards of the classic clinical concepts.

Sézary Syndrome

Clinically the Sézary syndrome is characterized by erythroderma, edema and pruritus. Leonine facies and fissures of the palms and soles are common. The erythroderma may be preceded by an eczematous dermatitis or by erythematous, indurated plaques. The demonstration of circulating, atypical T-lymphocytes, or Sézary cells, conforms the diagnosis. The leukocyte count is variable, ranging from less than 10,000/mm³ to 200,000/mm³ or more. Atypical lymphocytes may account for 80 percent or more of the circulating leukocytes. Lymphomas may evolve from the cutaneous lesions, but reports of Hodgkin's disease or myelomonocytic leukemia as a complication of Sézary syndrome are difficult to interpret. The lymph nodes usually show dermatopathic lymphadenitis,
but histologic progression to a lymphoma has also been documented.4

Lymph Nodes and T-Cell Dysplasias

Many of the recent reports of mycosis fungoides have placed emphasis on histologic rather than clinical patterns.3,4,64,69 In these reports, the mycosis cell, when present, is a prime determinant in the classification of a cutaneous, lymphoid infiltrate. The histologic diagnosis is correlated with clinical characteristics: eczematous or lichenoid plaques; erythroderma; limited or disseminated, indurated plaques; and tumors.70 Of these clinical features, tumors clearly indicate a poor prognosis;1,64 they may monitor the same biologic parameters as palpably enlarged lymph nodes. Progression of the disease in lymph nodes has the same prognostic significance as progression in cutaneous disease. Lymph nodes that are sufficiently enlarged to provide a clinical indication for biopsy are prognostic determinants.2,3 They correlate with disseminated disease and with rapid clinical progression. In some reports, clinically enlarged lymph nodes with the histologic pattern of dermatopathic lymphadenitis have proved to have a biologic influence.2 Lymphomatous infiltrates in regional lymph nodes are an ominous sign.3

The requisites for diagnosing mycosis fungoides in regional lymph nodes are not clearly defined. In most reports, clusters of immature lymphoid cells in the T-cell domain of the lymph node are required for the diagnosis of mycosis fungoides.49 There are other reports indicating that the identification of isolated, rather than clustered, atypical lymphoid cells is adequate documentation of regional lymph-node involvement.48,63 Even in advanced lymph-node disease, the B-cell domain may be focally preserved.7 The usual requisites for the diagnosis of lymphoma in a lymph node — that is, diffuse aggregates of tumor cells, complete obliteration of nodal architecture and infiltration of perinodal tissue — are not uniformly applicable in the evaluation of lymph-node disease in mycosis fungoides. The leukemic potential of the infiltrate overshadows the histologic progression of an evolving lymphoma.

In patients who die of mycosis fungoides, the distribution of infiltrates at autopsy implicates the blood vascular system in a role of hematogenous dissemination.5,65 The involvement of the lymph nodes predisposes to hematogenous dissemination of disease in a manner that is comparable to the role of the spleen in Hodgkin's disease.71,72 Early and repeatedly in T-cell dysplasias, mycosis cells may gain access to the circulation but colonize other sites only when immune surveillance is exhausted late in the evolution of the disease. Lutzner et al. demonstrated cyclic migrations between the skin and the peripheral blood in one patient.4 In dermatopathic leukemia, vascular in-
Fig. 2: Primary lichenoid reaction showing psoriasiform pattern. Atypical cells have clustered in the epidermis to produce Pautrier's microabscesses (mycosis fungoides).

Fig. 3: Established lichenoid reaction showing a band-like infiltrate of mononuclear cells in a widened papillary dermis. The overlying epidermis shows hyperkeratosis and effacement of rete ridges with liquefaction degeneration at the dermo-epidermal interface (established lichenoid reaction: parapsoriasis-poikiloderma complex).

vasion may be an occasional feature of the cutaneous lesions.

Disseminated Disease
There is convincing evidence of widespread dissemination of tumor cells in the final stages of T-cell dysplasias.\textsuperscript{5,6} This feature was not noted in earlier reports. The discrepancies between earlier reports and recent ones may be explained in part by the improved survival related to control of sepsis. Paradoxical survival rates from studies in which the group of patients without disseminated disease have experienced a shorter clinical course, have been reported.\textsuperscript{5} This paradox may reflect the selection of cases in which infections rather than leukemic progression terminate the disease.

The visceral lesions of disseminated T-cell reticuloses are often diffuse and mimic leukemic infiltrates.\textsuperscript{5} Localized and nodular lesions may also occur, but they should not obscure the leukemic qualities of disseminated disease.\textsuperscript{5} The lungs are usually involved; infiltrates are often interstitial but may accumulate within alveoli. In the liver, infiltrates may be either sinusoidal, portal or both; in the spleen, they are diffuse or nodular. In minimal splenic lesions, they may be confined to the periarteriolar sheath (T-cell domain). In the kidney, infiltrates are interstitial but may penetrate tubular epithelium to produce a remarkable pattern of epitheliotropism. The visceral infiltrates mimic the patterns of the cutaneous and nodal infiltrates. Bone-marrow infiltrates are common but seldom extensive, and they rarely com-
promote the hematopoietic component.\textsuperscript{34}

With few exceptions, the visceral infiltrates of T-cell dysplasia are histologically distinctive.\textsuperscript{3,6,5} In advanced disease, the infiltrates may be monomorphic and frankly lymphomatous.\textsuperscript{7,8} The histologic pattern in lesions of the latter type may be difficult to distinguish from B-cell lymphomas, particularly poorly differentiated lymphocytic lymphoma (Rappaport)\textsuperscript{9} or the lymphoma composed of small follicular center cells with cleaved nuclei (Lukes).\textsuperscript{34}

\textbf{“There is convincing evidence of widespread dissemination of tumor cells in the final stages of T-cell dysplasias.”}

The convoluted or cerebriform nucleus of the dysplastic T-lymphocyte remains as a marker, but it may be difficult to identify histologically. Anaplasia may occasionally be a feature of T-cell lymphomas, and it may produce a pattern easily confused with Hodgkin’s disease.\textsuperscript{5,7,34} We have recently seen a cutaneous T-cell dysplasia in which characteristic infiltrates of Hodgkin’s disease developed in regional lymph nodes nine years after the original diagnosis of T-cell dysplasia.

In advanced disease, there is evidence of an increasing proportion of circulating null cells at the expense of T-cells.\textsuperscript{75} Surface markers on the dysplastic T-lymphocytes may be blocked or may disappear in advanced disease.\textsuperscript{44,75} The null cells may be circulating dysplastic T-lymphocytes.\textsuperscript{75} In some patients with advanced disease, anergy may be related to lymphokines (MIF) that are secreted by the dysplastic T-cells.\textsuperscript{4}

\textbf{Survival}

The survival of a patient with a cutaneous T-cell dysplasia depends primarily on the stage of the disease at the time of the initial histologic diagnosis. In staging a patient’s disease, the following findings are significant: \textsuperscript{3,70}

- Age at time of initial histologic diagnosis.
- Cutaneous tumors and ulcers.
- Palpably enlarged lymph nodes.
- Hepatosplenomegaly.
- Lymphocytopenia.
- Histology of skin and lymph nodes.

The significance of the patient’s age at the time of the initial histologic diagnosis has not been adequately defined. Patients whose age is less than 50 years at the time of histologic diagnosis survive longer than patients whose age at diagnosis is more than 60 years.\textsuperscript{3} The historical duration of disease prior to initial histologic diagnosis is not a significant factor. During the early evolutionary stages, the histologic picture is likely to be non-specific or borderline. The progression of the disease to an easily diagnosed, histologic stage is a significant correlate. Recognition of a diagnostic histologic pattern is a marker for a predictable sequence of tumor progression. Much of our information regarding the significance of historical duration of disease and of initial histologic diagnosis is derived from material at the National Institutes of Health (NIH).\textsuperscript{3} The bulk of this material represents cases in which the diagnosis had been established prior to referral to NIH.

Once the baseline of a histologic diagnosis has been established,\textsuperscript{3,70} three clinical findings influence the rate of progression. Cutaneous tumors correlate with a relatively short survival and also with advanced histologic progression, often signaling an evolution to a monomorphic lymphoma or malignant T-cell lymphoma. Cutaneous ulcers correlate with rapidly progressing disease.\textsuperscript{3} Tumors and ulcers are complementary; the clinical course is shorter if both are present than if either occurs without the other.\textsuperscript{3} Finally, pal-
pable lymph nodes correlate with a short survival and similarly complement the effect of tumors and ulcers. This triad—tumors, ulcers, palpable lymph nodes—is a measure of progressive disease and heralds the appearance of disseminated disease.

Sézary's phenomenon, abnormal circulating T-lymphocytes, obviously offers an opportunity for dissemination of disease but does not appear to be a prime determinant. In early clinical stages, before one element or all elements of the prognostic triad have appeared, the circulating dysplastic lymphocytes are apparently not capable of colonizing the viscera. Palpably enlarged, lymphomatous lymph nodes are prognostically more important than similar nodes showing the pattern of dermatopathic adenopathy. In cutaneous T-cell dysplasias, tumor growth in regional lymph nodes is a measure of immune incompetence. The diagnosis of malignant T-cell lymphoma in a lymph node marks a transition from benign lymphocytosis to a leukemia. At that point, the balance in the interplay between tumor cells and the host's immune response shifts to favor the intruder. Hepatosplenomegaly indicates a poor prognosis, and a fatal process follows rapidly. Lymphocytopenia influences prognosis. If it is found initially, in a group of patients, the prognosis is worse than in a group with normal lymphocytes and comparable skin disease.

Correlations between the degree of lymphocyte dysplasia and clinical stage of disease have not been clearly defined. The initial histologic diagnosis is a significant marker of progressive disease; that observation is an indirect verification of histologic stages as prognostic determinants. Tumors and ulcers as prognostic determinants are also indirect indices of histologic progression; they herald lymphomatous transformation. Finally, the relationship between a histologic diagnosis of lymphoma and poor prognosis establishes the significance of microstaging in prognostic evaluation. Table 1 is a classification of cutaneous T-cell dysplasia microstages.

Infections are also important prognostic determinants. Their influence often overshadows or eliminates tumor progression as a prognostic factor. Staphylococcus and pseudomonas are common offenders and often affect the lungs.

The results of staging laparotomies confirm the value of the clinical prognostic determinants (palpable lymphadenopathy and splenomegaly). They also confirm a correlation between circulating abnormal lymphocytes and splenic infiltrates. The difficulties of defining distinctions between dermatopathic lymphadenopathy and nodal infiltrates of mycosis fungoides have compromised the value of staging procedures.

**Therapy**

Appreciating the leukemic nature of the disseminated tumor cells in T-cell dysplasias and lymphomas is basic to an understanding of the disease's evolution. It offers an explanation for disseminated disease at a time when the histology of the cutaneous lesions indicates a dysplasia rather than a histologically fully evolved lymphoma.

In mycosis fungoides, the chronicity of the disease and its confinement to the skin for long periods of time have tempered the therapeutic approach. The accumulated data on the life his-
In the pre-tumoral stage, it has been difficult to justify aggressive forms of therapy. Alternatives to a conservative approach in the pre-tumoral stage are designed to eliminate the cutaneous disease prior to visceral dissemination. In the pre-tumoral stage, electron-beam therapy has produced prolonged remissions. A disregard for the role of the lymph nodes is a deficiency in the rationale for electron-beam therapy. It is reasonable to assume that dysplastic T-lymphocytes participate in the migration of lymphocytes to and from lymph nodes in the immune cycle. Lutzner's observation that mycosis cells may be identified ultrastructurally in some examples of dermatopathic lymphadenitis offers support for this assumption. The results of electron-beam therapy may be improved by techniques designed to eliminate the migratory, dysplastic T-lymphocytes in the extracutaneous lymph nodes and
and the dermal infiltrates have been non-specific.46,76,81,86 Levi and Wiernik have summarized the results of various therapeutic modalities.20

Fig. 6: Marked T-cell dysplasia in which most of the cells in the infiltrate in the epidermis and the dermis are atypical. The atypical cells in the infiltrate are confined to the papillary dermis and qualify as malignant T-cell lymphoma in situ (mycosis fungoides).

the spleen and by the anticipation of the leukemic potential of dysplastic T-cells.

In the tumoral stage, with cutaneous tumors or palpably enlarged lymph nodes, the therapeutic objectives include elimination of visceral disease. Perhaps multiple-drug therapy will offer more benefits than the single-drug therapy that has been used in the past. In mycosis fungoides, there is meager evidence that therapeutic efforts have altered patient survival.20

The involvement of specific organ systems such as the heart or central nervous system may require special therapeutic procedures.73,83-84 Leukapheresis may play a role in occasional cases.4 The morphologic effects of various forms of therapy on the tumor cells

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