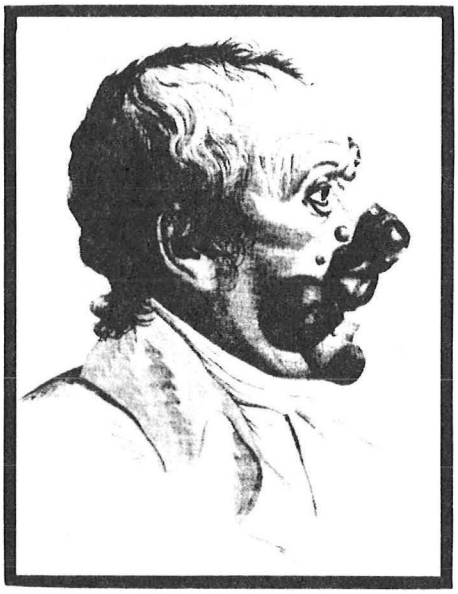
Medical Grand Rounds

CUTANEOUS T CELL LYMPHOMA

from

ALIBERT



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ARGUMENT

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CUTANEOUS T CELL LYMPHOMA

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I. INTRODUCTION

In 1806 the French physician, Alibert described a 56 year old man who after having a branny, desquamating rash for a period of several months developed small skin tumors resembling mushrooms over various parts of his body; some were smooth and initially flesh colored, but then became reddish brown. Some of these tumors would shrink and even disappear, while others enlarged and ulcerated. After five years of these waxing and waning skin lesions, the patient began to lose weight, and after languishing in bed for seven months, died of a "hectic" fever. Mycosis fungoides was the name Alibert used for this condition; the term described the mushroom-like tumors that the patient had so strikingly exhibited. Since that original description, our knowledge of various aspects of this disease has expanded greatly. Particularly in the past ten years, a tremendous amount of new information has been gathered about this disease which falls into the broad category of what is now being called cutaneous T cell lymphoma, or CTCL. The increased attention to this group of diseases is attested to by the fact that since 1979, there have been at least six major reviews or workshop proceedings devoted to the subject.

RECENT REVIEWS OF CTCL

Broder S and Bunn PA, Seminars in Oncology 7:310, 1980

Edelson RL, J Am Acad Dermatol 2:89, 1980

Edelson RL, J Dermatol Surg Oncol 6:358, 1980

Lamberg SI and Bunn PA, Cancer Treat Rep 63:561, 1979

Vonderheid EC, Int J Dermatol 19:182, 1980

Zackheim HS, Arch Dermatol 117:295, 1981

The purposes of this review today are 1) to summarize the clinical and pathological features of CTCL; 2) to review the pertinent immunopathobiologic features of CTCL; 3) to review some of the epidemiologic features of CTCL and consider some of the pathogenetic schemes which have been proposed; 4) to discuss the important prognostic variables in CTCL in the context of the results derived from various staging procedures utilized in several recent large studies; 5) to consider some of the more recently described techniques which may facilitate the pathologic diagnosis of very early stage disease both in the skin and extracutaneous sites; and 6) to summarize the various therapeutic options which can be considered in the management of CTCL.

The single most important concept which this review will attempt to convey, is that the majority of patients with CTCL who appear to have disease confined to the skin with more careful scrutiny will be found to have evidence for extracutaneous disease. The dilemma facing us today is that all this "knowledge" has yet to be matched by the development of the

ideal treatment(s) for these diseases. The ideal treatment would be a management plan which allows the patient a life span shortened neither by the disease nor by the treatment of the disease. Equally as important, the ideal treatment is one in which the quality of the patient's life is least affected by either the disease or the treatment of the disease.

While there is as yet no single ideal treatment for CTCL, there are nevertheless many therapeutic options. A patient has a right to expect his physician(s) to have very carefully weighed these therapeutic options before suggesting one plan as opposed to another. To do this in the most rational way two things are required: first, to understand as much as possible about the disease process and its natural history; and second, to get as much clinical, pathological, and laboratory information about the specific patient as is necessary to design an appropriate treatment plan.

II. CLINICAL FEATURES

Paradoxically, one of the most consistently observed features of CTCL is the extreme variability of the clinical presentation and subsequent course. Although in general the disease is characterized by slow progression from minimally symptomatic skin lesions without extracutaneous symptoms to one in which progressive involvement of both the skin and extracutaneous sites is seen, the time frame in which this progression occurs can vary from weeks to several decades. The clinical and pathological findings frequently progress from lesions which can closely resemble a number of nonmalignant skin diseases with histopathology which is either nondiagnostic or only suggestive of a malignant process, to more clearly diagnostic infiltrated plaques and tumors. However, it is clear that some patients never progress beyond clinically and pathologically nondiagnostic lesions, while others present with diagnostic skin lesions and follow a rapidly progessive downhill course. In light of this rather overwhelming variability in the natural history of CTCL, the importance of accurate identification of prognostic variables becomes obvious; i.e. the elucidation of those risk factors or clinical characteristics which may allow one to differentiate the patient whose disease is more likely to pursue a more rapidly progressive course from the patient whose disease is more likely to behave in a biologically less aggressive fashion.

A. ALIBERT - BAZIN FORM ("CLASSICAL MYCOSIS FUNGOIDES")

In 1870 Bazin described the three "classical" cutaneous stages that have been given the eponym "Alibert - Bazin" forms: 1) the premycotic, erythematous or eczematous stage, 2) the infiltrative plaque stage, and 3) the tumor stage.

1. Premycotic Stage

The premycotic or erythematous stage is one of either localized or widespread areas of erythema or "dry eczema" (i.e. without obvious vesiculation, oozing, or crusting). The eruption may therefore look somewhat like dermatitis, psoriasis, ichthyosis, or other superficial

inflammatory skin conditions. The appearance of the skin lesions may vary in the same patient at different periods of time. Lesions can vary in color from yellow-red to reddish violet. They can be variable in shape, and can have either diffuse or relatively sharply demarcated borders. Most commonly the lesions appear on the trunk and extremities, but may be seen on the face as well. Not infrequently individual lesions are transitory in nature; they may disappear leaving no residua, but then may recur in the same place or other previously uninvolved sites. Pruritis may be marked in individual cases and completely absent in others. The result of this rather marked heterogeneity of presenting signs in the premycotic phase is that it is not uncommon for patients records to bear a lengthy list of discarded diagnoses before the correct diagnosis is ultimately made. But while the initial eruption frequently may be diagnosed as e.g. eczema or psoriasis, generally in retrospect the clinical appearance in these cases was never completely typical of these benign skin conditions. Although a skin biopsy of the premycotic lesion can usually be distinguished histopathologically from typical eczema or psoriasis the early histopathology is nevertheless frequently non-diagnostic. We will return later both to the histopathologic findings in the later more definitive stages of the disease (see pp 10-11) as well as to the issue of the usefulness of additional criteria that may be used for more unequivocally establishing a diagnosis in the earliest stages of skin involvement (see pp 41).

2. Plaque Stage

The premycotic stage may last for months to many years before evolving into the plaque stage. This stage is characterized by rather sharply marginated, slightly elevated lesions which are oval or circular in shape. The plaques may develop in areas of previously uninvolved or involved skin. Once they appear, plaque lesions tend to be more stable and uniform than the premycotic lesions, but changes clearly do occur with time. The individual lesions may gradually increase in both size and number and may coalesce so that very extensive areas of the skin are involved. Central clearing may give rise to annular lesions. Very commonly lesions in the plaque stage show evidence of significant epidermal involvement demonstrated by the presence of scaling. Any plaques that develop in hair-bearing areas of the body can be associated with focal hair loss. Infiltrated palpable plaques often coexist with flatter patches of the premycotic phase. It is during the plaque stage of disease that the incidence of extracutaneous signs, such as lymphadenopathy, increases.

3. Tumor Stage

In the tumor stage, enlarging masses may appear in infiltrated plaques, premycotic lesions or previously uninvolved skin. They may occur anywhere, but have a predilection for the face and body folds. The neck, axillae, breasts, and groin are the commonest locations for tumors to develop in women. Individual lesions may attain sizes up to several inches in diameter, although smaller masses seem to be more common. While spontaneous resolution of tumors has been reported, this is a relatively uncommon event. Instead these lesions tend to become generalized in

distribution and grow with a variable rate. They may coalesce into large unsitely masses which at some point in time ulcerate. Tumors are usually painless. If itching was a prominent symptom earlier in the course of the disease, it may either diminish or even disappear in the tumor stage.

It must again be stressed that the time frame for the sequential development of these classical stages can be extremely variable. Whereas the completely typical patient may evolve through each of these stages over a period of years, cutaneous nodules and tumors may develop in individual cases within a period of weeks to months. In 1885, Vidal and Brocq (1885) described the d'emblee tumor variant in which tumors arouse de novo without preceeding premycotic or plaque lesions.

B. SEZARY SYNDROME

Hallopeau and Besnier (1892) first described the erythrodermic variant in which localized scaling patches and infiltrated plaques evolved into a generalized erythema with and scaling. Sezary and Bouvarain (1938) described a series of patients with generalized (exfoliative) erythroderma, severe pruritis, generalized peripheral lymphadenopathy, and abnormal, hyperchromatic, hyperconvoluted mononuclear cells in the peripheral blood. These atypical cells appeared morphologically similar to the atypical cells found in skin biopsies of both erythematous scaling skin and typical infiltrated plaques. The characteristic cerebriform, highly convoluted or serpentine ultrastructural appearance of Sezary cells was described by Lutzner and Jordan in 1968. Essentially identical cells were identified by electron microscopy in the skin and lymph nodes in patients with mycosis fungoides and the Sezary syndrome in the 1970's (Brownlee, 1970; Lutzner, Hobbs, and Horvath, 1971). Although the classic Sezary cell is fairly large (15-20 mμ), a small cell variant, about 8 mμ, has also been identified (Lutzner, Emerit, Durepaire, et al, 1973). Since mixtures of large and small variants can be found in the same patient (Zucker-Franklin, 1976), the importance of the size of the Sezary cell remains uncertain.

In their 1971 report, Lutzner and Jordan also found hyperconvoluted lymphocytes in skin biopsies of two patients with typical lichen planus, a relatively common benign dermatosis. Numerous studies since that time have confirmed the relative nonspecificity of the Sezary-type cell when less than extremely stringent criteria are applied to defining the degree of hyperconvolution (see also pp 41-42). Cells with relatively hyperconvoluted nuclear appearance have been found in the dermal infiltrate of a variety of nonlymphomatous dermatoses (Flaxman et al, 1971), in cultures of normal human skin (Flaxman et al, 1974), in mitogen-stimulated cultures of normal human peripheral blood lymphocytes (Yeckley et al, 1975), in cord and peripheral blood from normal individuals (Meyer et al, 1977), and in rheumatoid synovial fluid (Van Leeuwen et al, 1976). It has been suggested that cells with hyperconvoluted nuclei are therefore clearly not pathognomonic for mycosis fungoides/ Sezary syndrome , but rather represent activated T lymphocytes which may have nothing whatsoever to do with malignant transformation. Nevertheless, the presence of such cells in significant numbers remains one of the most characteristic pathological features of these classical variants of CTCL (Clendenning and Rappaport, 1979).

It should be pointed out (see also p 31) that while it is now generally accepted that the Sezary syndrome represents the overt leukemic variant of classical mycosis fungoides, patients who have more localized plaque involvement of the skin may also show variable numbers of circulating atypical, hyperchromatic, hyperconvoluted mononuclear cells.

CTCL is a relatively uncommon disorder. The relative difficulty in firmly establishing a diagnosis early in the course of the disease further complicates the question as to just how common it is. Current best estimates suggest an age - adjusted incidence of about two cases per million per year in the United States. Thus, there are approximately four hundred new cases and about one to two hundred deaths from CTCL per year in this country (Greene et al, 1979). The average age at diagnosis is fifty-two. It is relatively uncommon for the diagnosis to be made prior to age twenty, and some patients do not get lesions until over age seventy. CTCL occurs slightly more frequently in males than in females (a ratio of about four to three). The incidence is similar in blacks and whites (Broder and Bunn, 1980).

In several series the duration of skin lesions before a definitive diagnosis of CTCL was made was 4-10 years, with an average of 6.1 years (range, one month to 48 years). While older reports suggested that median survival after diagnosis (4-5 years) was shorter than the interval between the onset of symptoms and diagnosis, in more recent studies the median survivals (9-10 years) are longer than the interval from initial symptoms to diagnosis (reviewed in Carney and Bunn, 1980). It is not known whether this apparent lengthening of survival represents earlier diagnosis (with a subsequent shortening of the interval from first signs to diagnosis), improved survival with newer treatment modalities, or both.

III. IMMUNOPATHOBIOLOGY OF CTCL

A. Cell Surface Markers and Functional Studies

Contemporary cellular immunology has been nurtured and has fed on the concept that the immune system is comprised of a complex network of interacting cell subpopulations, each of which has not only a discrete and limited functional repertoire, but also unique phenotypic characteristics. Within the past ten to fifteen years is has been possible to characterize mononuclear cells on the basis of cell surface determinants, thus assigning cells to one of four major categories. By determining the presence of such phenotypic markers as cell surface immunoglobulin, Fc receptors, complement (C_3) receptors, E rosette formation with sheep erythrocytes, and unique differentiation antigens, one can identify the spectrum and relative proportions of T cells, B cells, K cells, and monocyte/macrophages both under normal circumstances and in a variety of lymphoreticular malignancies. This review will concentrate on the phenotypic and functional characteristics of normal and malignant T lymphocytes.

Normal T cells bear on their surface unique cell surface receptors and antigenic determinants which separate them from non-T cells. Some of these membrane markers are shared by virtually all T cells such as the ability to form rosettes with sheep erythrocytes and the expression of antigenic

determinants such as HTLA (which has been identified by heterologous antisera raised by conventional methodologies) (Smith, Terry and Buell, 1973). In the past three years the incredibly powerful technology of monoclonal antibodies (See also Capra,1981) has revolutionized the field of identifying T cell surface antigens. "Pan-T" antigens (i.e. those which bind to determinants expressed on the vast majority of E-rosette forming peripheral T cells) include OKT-3 (Reinherz, Kung, Goldstein et al, 1979a), Leu-1 (Engleman, Warnke, Fox et al, 1981), and 3AI (Haynes, Eisenbarth, and Fauci, 1979).

T cells have a variety of distinctive functional activities. Some are initiator cells for delayed-type hypersensitivity (DTH) reactions. Others are cytotoxic (killer) cells which can lyse, e.g., virus-infected target cells. Perhaps most importantly T cells exert powerful regulatory functions. Most B cells require helper/inducer T cells to differentiate into antibody producing cells. Similarly, some T cell activities (e.g. cytotoxicity) may be helped by helper/inducer T cells. Another major subpopulation of T cells have exactly the opposite function - i.e. they act as suppressor cells to down-regulate either B cells or other T cells. The rather incredible complexity of these regulatory T cell networks has been illustrated by the observation that a helper/inducer T cell may be required to activate a T suppressor precursor cell, which then suppresses antibody formation by B cells by somehow inhibiting the action of the T cells responsible for helping B cells become antibody-forming cells (Broder, Uchiyama, Muul et al, 1981)!

Recently monoclonal antibodies have been prepared which identifiy antigens expressed on the two major functionally discrete subpopulations of human peripheral T cells. OKT-4 and Leu-3 are antigens expressed on approximately 60% of peripheral T cells; these determinants identify cells which functionally behave as helper/inducer cells (Reinherz, Kung, Goldstein et al, 1979b). OKT-8 (and OKT-5) and Leu-2 are antigens expressed on approximately 30% of the peripheral T cells which act as suppressor or cytotoxic cells (Reinherz, Kung, Goldstein et al, 1980; Evans et al, 1981).

Malignant lymphoid cells often retain many of the membrane properties and even the functional activities of the normal cells from which they were presumably derived. The abnormal cells seen in the skin, blood, and other extracutaneous sites in classic mycosis fungoides/Sezary syndrome (MF/SS) have markers which in the vast majority of cases have identified them as T cells of the helper/inducer phenotype (Kung et al, 1981; Boumsell et al, 1981; Haynes, 1981). These recent studies support previous studies which have shown that in approximately 40% of cases, malignant T cells in the blood of patients with Sezary syndrome, from extracutaneous tumors,or from involved lymph nodes of patients with non-leukemic mycosis fungoides can act as pure populations of helper cells for mitogen-stimulated normal B lymphocytes (Broder, Edelson, Lutzner et al, 1976; Lawrence et al, 1978; Berger, Warburton, Raafat et al, 1979).

Clinicoimmunopathologic correlation. The above observations provide a reasonable explanation of the observation that many patients with MF/SS have polyclonal elevations of serum immunoglobulins, especially IgE and IgA (both of which depend heavily on helper T cells for their production)

(Blaylock et al, 1966; Mackie et al, 1976). Moreover, there have been several reports of patients with the Sezary syndrome who developed monoclonal abnormalities of IgM, IgG, and IgA (Kovary et al, 1977; Dupre et al, 1977; Joyner et al, 1979). It is conceivable that such examples of restricted excess B cell activity could represent the in vivo expression of overactive helper T cell function. It is possible that while some malignant helper T cells function to augment B cell activity in a polyconal (nonrestricted) fashion, other malignant helper T cells are much more restricted in their activity, i.e. they will only help specific B cell clones (so-called idiotype-specific helper function)(Broder and Bunn, 1980).

B. Migratory Properties and Patterns of Localization

1. Extracutaneous sites

Normal T and B cells have characteristic areas within the body where they tend to compartmentalize or migrate. Some areas such as primary lymphoid follicles in the lymph nodes and spleen are composed primarily of B cells, whereas the interfollicular (paracortical) areas of lymph nodes and the periarteriolar sheaths in the spleen contain mainly T cells. Furthermore, mature T cells comprise a very small proportion of the cells in the bone marrow; this is despite the fact that T cells in general have greater capacity than B cells to rapidly recirculate through body tissues and organs.

Very recently, studies have demonstrated that the two major subpopulations of normal T cells have distinctive patterns of migration/localization within a given tissue such as lymph nodes, tonsil, gut lamina propria, and rheumatoid synovium. OKT-4 + (helper/inducer phenotype) cells tend to localize around dendritic macrophage-like cells which express Ia (immune response-associated) antigens or Ia-like determinants on their surface. OKT-8 + (suppressor/cytotoxic phenotype) cells do not as frequently localize around these Ia-bearing cells (Janossy, Duke, Poulter et al, 1981). The significance of this observation relates to the role of Ia-bearing cells in presenting antigen to T cells. It has become increasingly apparent that for T cells of the helper/inducer type to be triggered by antigen, the antigen must be seen in the context of appropriate Ia determinants on the antigen presenting cell (Dausset and Contu, 1980). On the other hand, for suppressor/cytotoxic cells to be triggered by antigen, such Ia-bearing antigen-presenting cells may not be required. Secondly, the relatively small numbers of mature T cells normally found in the bone marrow are not proportionally representative of the T cells in the peripheral blood. Thus, while the proportion of OKT-4+ (helper/inducer) to OKT-8+ (suppressor/cytotoxic) cells in the peripheral blood is approximately 2:1, the ratio of OKT-4:OKT-8 cells in normal bone marrow has been found to be approximately 1:3 (Janossy, Tidman, Papageorgiou et al, 1981).

Clinicoimmunopathological Correlations:

1. The major areas in which early pathologic involvement of extracutaneous lymphoid tissues can be seen in patients with CTCL is in the T cell zones. It is in these areas that pathologists now focus their attempts to find small but distinctive clusters of atypical cells (see also p 39).

2. The bone marrow is rarely involved in early or even in advanced stages of classical MF/SS, even when other extracutaneous tissues may be heavily involved. This was shown dramatically in a recent study from the NIH of 18 patients with Sezary syndrome. At the time of staging all 18 patients by definition had light microscopic evidence of involvement of the peripheral blood. All 18 also had lymph node biopsies showing significant replacement in the T cell zones by malignant cells. Yet only 3 of these 18 patients, or 16%, had bone marrow biopsies which showed involvement. This observation is not unexpected in view of the facts that the phenotype of MF/SS cells is OKT-4 +, and that normal bone marrow T cells tend to be of the OKT-8 + phenotype. The clinical implication of this observation is that routine bone marrow biopsies for the purpose of staging patients with classic forms of CTCL, especially non-leukemic patients, is a very low yield procedure.

The observations noted immediately above not withstanding, virtually any extracutaneous tissue or organ can become infiltrated with malignant T cells during advanced stages of CTCL. Given the striking capacity of normal T cells to recirculate, this fact is not particularly surprising.

It has been recognized for many years that extracutaneous disease in CTCL is extremely common at autopsy. The frequency of such extracutaneous involvement in series reported between 1940 and 1974 was 72% (reviewed in Carney and Bunn, 1980). This frequency is significantly higher than that expected from clincial symptoms exhibited prior to death. As the next table illustrates, although lymph nodes are the most common site of extracutaneous disease, almost any organ may be involved. The number of organs with lymphomatous infiltrates varied from 1-25, with an average of 6.3 per patient. In general, patients with more advanced cutaneous disease had more extensive extracutaneous involvement (Epstein, Levin, Croft et al, 1972).

Sites of Dissemination of CTCL in Autopsy Studies

Reference	Lymph Nodes	Spleen	Liver	Lungs	Bone Marrow	Gastro-Intestinal Tract	Kidneys	Heart	Central Nervous System
Cawley et al.	7/10	4/10	2/10	2/10	5/10	–	2/10	4/10	–
Farber et al.	4/7	6/7	6/7	–	0/7	2/7	2/7	2/7	–
Cyr et al.	4/23	6/23	5/23	4/23	–	2/23	5/23	2/23	–
Epstein et al.	51/86	43/86	35/86	37/86	23/86	30/86	23/86	15/86	17/86
Rappaport and Thomas	24/32	19/32	17/32	21/32	12/31	–	14/32	12/32	4/28
Long and Mihm	15/15	12/15	13/15	8/15	7/15	6/15	2/15	1/15	–
Total	105/173 (61%)	90/173 (52%)	78/173 (42%)	72/166 (43%)	47/149 (32%)	40/131 (31%)	48/173 (28%)	36/173 (21%)	21/114 (18%)

Carney and Bunn: J Derm Surg Oncol 6:5, 1980

Clinically apparent disease in organs other than the skin and lymph nodes is much less commonly detected, but as the following table shows, there have been reports of clinical involvement of nearly every organ system.

EXTRACUTANEOUS MANIFESTATIONS OF CTCL

Organ System	Manifestation
Pulmonary	1. Parenchymal nodules 2. Pulmonary infiltrates 3. Pleural effusion 4. Mediastinal and/or hilar adenopathy
Skeletal	1. Solitary or numerous osteolytic lesions 2. Diffuse osteoporosis 3. Arthritis
Ocular	1. Intraocular disease—optic nerve, retina, choroid 2. Extraocular disease—Lid, conjunctiva, cornea
Oral	1. Infiltrated lesions, manifested as raised or eroded areas, on lips, buccal mucosa, tongue, larynx
Nervous	1. Intracerebral tumor mass 2. Leptomeningeal disease 3. Peripheral neuropathy 4. Cerebral hemorrhage 5. Progressive multifocal leucoencephalopathy
Gastrointestinal	1. Diarrhea 2. Ascites 3. Hemorrhage
Cardiovascular	1. Congestive cardiac failure 2. Cardiac arrythmias
Renal	1. Progressive renal failure
Hematological	1. Eosinophilia 2. Monocytosis 3. Monoclonal paraproteinemia 4. Cryoglobulinemia

(From Carney and Bunn: J Derm Surg Oncol 6:5, 1980)

Cause of Death. In a very recent study of the septicemic complications of CTCL, Posner and coworkers (1981) reviewed the records of 60 consecutive patients with CTCL. Overall, 15 patients (25%) with CTCL died during the period of study. 8 of these deaths (53%) were due to the underlying lymphoma, and 4 (27%) were due to sepsis. 14 (23%) patients had 26 septicemias; patients with advanced disease (e.g. known viceral involvement, generalized erythroderma, palpable lymphadenopathy, and peripheral blood involvement) were at greatest risk for developing sepsis. All initial episodes of sepsis were due to gram positive cocci, S. aureus being the organism identified in all but one of these cases. Sepsis was correlated with locally infected sites in 77% of the episodes. All initial episodes were "successfully" treated, but in 5 cases, 4 of which were fatal, these initial infections were followed by secondary gram-negative bacillary superinfections. As a result of their experience, these authors have suggested that the most appropriate treatment in a susceptible patient with sepsis may be a combination of antimicrobials, one of which is effective against colonizing bacteria.

There have also been several recent reports of fatal disseminated herpes simplex infection in patients with advanced CTCL (Taulbee and Johnson, 1981; Segal and Watson, 1978).

2. Cutaneous Involvement

a. Classical CTCL (mycosis fungoides/Sezary syndrome)

As we have already discussed (p 2), early and predominantly cutaneous involvement is the rule in the classical forms of CTCL. In the premycotic stage of MF, the clinical picture may be more suggestive than is the histopathologic picture, which usually shows chronic dermatitis. The identification of occasional larger, atypical cells scattered through a rather polymorphous inflammatory infiltrate may be an early clue to the diagnosis (see also below). Sanchez and Ackerman (1979) have recently stressed the importance of the presence of mononuclear cells either singly or in small clusters within an epidermis which does not exhibit the spongiosis (intercellular edema) and microvesiculation characteristically seen in benign forms of dermatitis.

In the plaque stage a diagnostic microscopic picture characteristically is seen. In the upper dermis, one finds a dense cellular infiltrate that may be patchy, band-like, or both. The infiltrate contains a mixture of cell types, but features a variable number of atypical appearing mononuclear cells that are larger than normal lymphocytes and usually have irregularly contoured nuclei. Cytoplasm is usually scant. Larger cells often exhibit deeply indented or hyperconvoluted nuclei, and a classic cell of mycosis fungoides (mycosis cell) has an irregular densely hyperchromatic nucleus. Other atypcial cells may have paler nuclei with course and irregularly clumped chromatin. In addition to these abnormal cells, the typical plaque of mycosis fungoides usually shows a variable inflammatory infiltrate of normal appearing lymphocytes, histiocytes, plasma cells, and eosinophils.

Very characteristically, this infiltrate does not spare the upper most dermis; i.e. there is no "grenz" zone. Epidermal involvement is particularly characteristic of mycosis fungoides/Sezary syndrome. Epidermal invasion by atypical hyperchromatic, hyperconvoluted cells can be as single cells diffusely invading the epidermis with small spaces about individual cells. Even more characteristically this invasion takes the form of groups of cells lying within round spaces (Pautrier microabscesses). This phenomenon of malignant T cells showing a particular affinity for the epidermis has been termed epidermotropism, and remains perhaps the most identifiable characteristic of the disease.

A number of investigators have documented by electron microscopy the intimate association in the epidermis of these atypical T cells with epidermal Langerhans cells. (Rowden and Lewis, 1976; Rowden et al, 1979). These bone marrow-derived dendritic cells express large amounts of Ia-like antigens on their surface (Rowden et al, 1977; Klareskog et al, 1977). Furthermore, very recent studies of the dermal infiltrates in MF/Sezary syndrome have also revealed a frequent association of the malignant T cells with cells bearing the surface markers (Ia antigens, OKT-6 antigen) of Langerhans cells (Chu, Kung, and Edelson, 1981). Remembering that the malignant cells in mycosis fungoides/Sezary syndrome belong to the OKT-4 + (helper/inducer) phenotype, and that there is a tendency for normal T cells of the OKT-4 + phenotype to localize in areas rich in Ia-bearing cells, the tendency for malignant T cells in the skin to migrate into or localize in areas where such Ia-bearing cells are found is perhaps not unexpected.

In the tumor stage of classical CTCL the infiltrate becomes more massive and usually occupies the full thickness of the dermis with frequent extension into the subcutaneous tissue. In addition, epidermal invasion may cause extensive ulceration. The proportion of atypical cells increases, and inflammatory cells may disappear completely. The morphology of the neoplastic cells at this stage may be quite variable with patterns occasionally resembling one of the other malignant lymphomas (e.g. diffuse histiocytic, immunoblastic sarcoma, lymphoblastic, etc.).

That the malignant cells found in the peripheral blood of patients with the Sezary syndrome clearly have an affinity for the skin has been recently verified. Two different groups of investigators have obtained Sezary cells from the peripheral blood, labeled them either in vitro with Indium-111, or in vivo with 3H-Thymidine following a single intravenous bolus injection of the radioisotope, and then reinjected them back into the same patients. The distribution of the injected cells was then followed by either whole body scans (Indium-111) or by sequential skin biopsies processed for autoradiography (3H-Thymidine). In both studies the radiolabeled cells could be shown to gradually accumulate in the skin, with maximal accumulation being seen 24 hours after injection (Miller et al, 1980; Bunn et al, 1981).

b. Non-Hodgkin's Lymphoma/Leukemia (other than MF/SS)

There is no published data which directly speaks to the issue of the incidence of specific skin lesions in patients with non-Hodgkin's lymphoma/leukemia other than classical mycosis fungoides/Sezary syndrome. However, it is the general consensus of opinion that such diseases are not commonly characterized by skin lesions. At the University of California, San Francisco, patients with skin lesions having a non-T cell pattern histologically (see below) comprise less than 10% of the total number of patients with cutaneous lymphomas seen at that institution (Zackheim, 1981). In a recent study from Japan of 44 cases of non-Hodgkin's lymphoma, skin lesions occurred some time in the course of the disease in just eight (18%) of patients (Yamanaka et al, 1981).

The clinical appearance of the skin lesions in non-Hodgkin's lymphoma/leukemia is commonly that of rapidly growing papules, nodules, or tumors, often reddish-purple in color. It is notable that the location of the initial skin lesions is very commonly on the head or neck. Tabulating data from three separate series reveals that 37 of 78 patients. (47%) presented with skin lesions confined to the head and neck (Long, Mihm, and Qazi, 1976; Evans, Winklemann, and Banks, 1979; Burke et al, 1981).

Furthermore, when such skin lesions do appear, it is usually relatively late in the natural history of the disease. The majority of patients with non-Hodgkin's lymphoma/leukemia other than mycosis fungoides/Sezary syndrome do not have skin lesions as the sole presenting sign of their disease. Rather, when such patients are staged at initial evaluation the majority are found to have readily detectable extracutaneous disease. Combining the data available from four separate series of patients with non-Hodgkin's cutaneous lymphoma, 92 of 145 patients, or 63%, were found to have readily detectable extracutaneous disease at their

initial staging evaluation (Wolk, 1977; Saxe et al, 1977; Evans et al, 1979; Burke et al, 1981).

Even in the cases in which non-Hodgkin's lymphoma is initially found to be apparently confined to the skin, progressive appearance of extracutaneous disease frequently occurs in spite of therapy. Thus 10 of 16 patients in the Canadian study developed extracutaneous disease within six months to twelve years (mean, 27.5 months) (Wolk, 1977).

The most consistent histopathologic finding in non-Hodgkin's cutaneous lymphoma is the presence of tumor-free "grenz" zone in the most superficial dermis, with virtually complete sparing of the epidermis. The malignant infiltrate tends to involve the middle and deep dermis and not infrequently the subcutaneous tissue. The malignant cells can be arranged in either a patchy or diffuse pattern. Thus, the finding of malignant cells within the epidermis in areas other than regions of obvious necrosis of the overlying epidermis with secondary extension of the tumor cell mass into this necrotic epidermis is extremely uncommon.

There is one relevant exception to this generalization; namely the extremely rare entity of the specific skin lesions in Histiocytosis X. In some cases the malignant cells do show epidermal invasion. However, these malignant cells have been shown to bear membrane markers characteristic of macrophage/ monocytes, and characteristic intracytoplasmic inclusions identical to those seen in Langerhans cells, i.e. the antigen processing, dendritic, bone marrow-derived cells which are a normal constituent of the epidermis (Basset and Turiaf, 1965; Nezelof et al, 1977).

It is important to keep in mind that the preceding discussion of non-Hodkin's lymphoma/leukemia has been based on morphology and not on definitive identification of the immunologic phenotype of the malignant cells. That is, many of the skin lesions, particularly those classified as diffuse histiocytic, undifferentiated, or lymphoblastic, could be of T cell origin (see below).

c. Other Variants of CTCL

In addition to the striking affinity for the skin in general and the epidermis in particular displayed by the classical forms of CTCL (MF/SS), it has become increasingly apparent in the past five years that other forms of T-cell non-Hodgkin's lymphoma/leukemia also display an apparent affinity for skin. Yamanaka et al (1981) recently described the results of cell surface marker analysis of forty-four cases of non-Hodgkin's lymphoma other than MF/SS. Of the forty-four cases, twenty-six (59%) were typed as B cell, thirteen (30%) were typed as T cell, and five (11%) were classified as null-cell (non-T, non-B). In the thirty-one cases of non-T cell disease, specific skin lesions occurred during the course of the disease in only two, (6%) of the cases. On the other hand skin lesions were observed at some time in six of the thirteen (46%) of patients whose disease was classified as T-cell in origin.

Recently, the clinical and hematologic features of a previously undescribed kind of adult T cell leukemia have been described by Uchiyama

et al (1977) and those of an apparently closely related adult chronic lymphocytic leukemia of T cell origin by Brouet et al (1975). The diseases described by these different investigators have many similarities. In all of these cases the malignant cells circulating in the peripheral blood had the cell surface markers of T cells, identified by their ability to form rosettes with sheep erythrocytes or to bind rabbit anti-HTLA antiserum. The clinical features which separated these cases of T cell-CLL from classical chronic lymphocytic leukemia included: massive splenomegaly, only moderate bone marrow infiltration, high content of lysosomal enzymes and cytoplasmic granules in the leukemic cells, increased frequency of severe neutropenia, and a strikingly increased frequency of specific skin lesions. Thirteen of the twenty-seven patients in the two series, (48%) were noted to have malignant cutaneous infiltrates.

In spite of the superficial similarity of T cell-CLL with classical Sezary syndrome (including a striking frequency of generalized erythroderma, generalized lymphadenopathy, and the presence of atypical circulating T cells) the differences between these entities are striking. 1) While the circulating atypical T cells in T cell-CLL have indented or lobulated nuclei, they lack the hyperconvoluted, cerebriform appearance of typical Sezary cells. 2) The striking involvement, at initial staging, of the marrow in T cell-CLL contrasts with the previously noted sparing of the bone marrow which is usually seen in patients with Sezary syndrome. 3) The survival time noted in patients with T cell-CLL was significantly shorter than the mean survival time of patients with Sezary syndrome. 4) The histopathologic pattern of cutaneous involvement was strikingly different from than seen in classical Sezary syndrome. In contrast to the typical pattern of Sezary syndrome, i.e. a diffuse band-like infiltrate of atypical cells in the mid and upper dermis (no grenz zone) and invasion of the epidermis (epidermotropism), the histopathology in T cell-CLL revealed leukemic involvement of the mid and lower dermis and subcutaneous tissue, a striking grenz zone, and absence of malignant cells in the epidermis. In this regard T cell-CLL cutaneous histopathology resembles that seen with other non-T cell malignant cutaneous infiltrates. Thus while affinity for the skin in general appears to be a feature of T cell-CLL, the striking affinity for the epidermis seen in the classical variants of CTCL is not seen.

In vitro functional studies of the peripheral blood leukemic T cells have been examined in several of these cases (Uchiyama et al, 1978). In all the cases examined, when a regulatory activity could be found (3 of 6 cases) the activity observed was invariably suppression of mitogen-induced B cell immunoglobulin production instead of help. This observation coupled with the observation that T cell-CLL frequently exhibits moderate bone marrow involvement in the early stages, correlates nicely with recent phenotypic studies of T-CLL in the USA: in 1 of 2 reported cases the malignant cells were OKT-8+ rather than the OKT-4+ (helper/inducer) phenotype exhibited by the classic epidermotropic variants of CTCL (Boumsell et al, 1981).

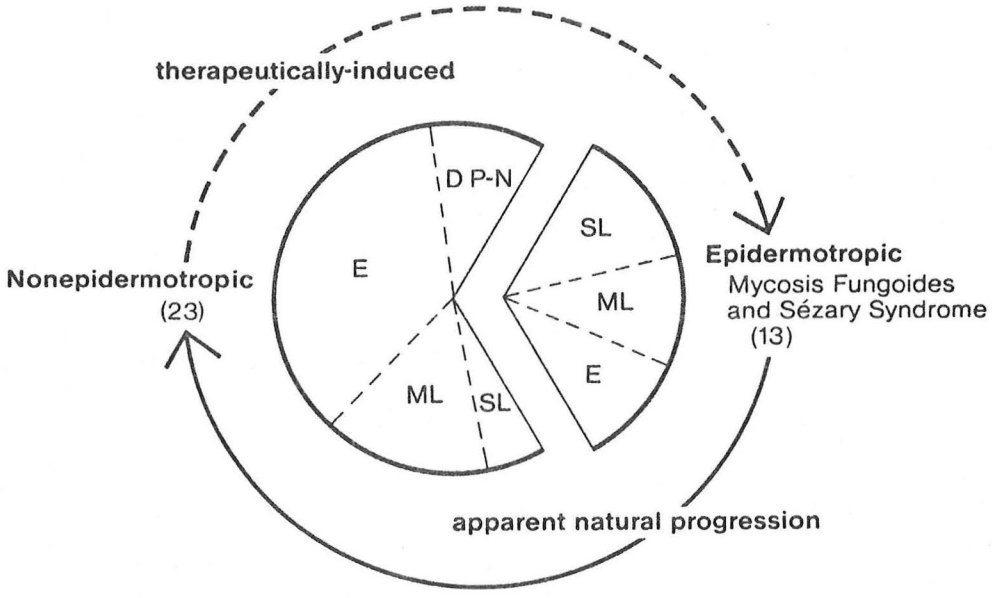
The table on the next page summarizes the patterns of involvement in lymphoreticular neoplasms which involve the skin:

CUTANEOUS INVOLVEMENT IN HUMAN LEUKEMIA/LYMPHOMA

Cell Type	Incidence of Skin Lesions	Skin Involved	Phenotype	Functional Activity	Histopath
NON-T CELL	RARE	LATE	LACK T-CELL MARKERS; OTHERWISE VARIABLE	VARIABLE	EPIDERMIS SPARED
T CELL	COMMON	EARLY	T CELL (e.g. E-ROSETTE+, HTLA+		
1) MF/SS	COMMON	EARLY	OKT4+	HELPER/ INDUCER	EPIDERMIS INVOLVED (EARLY)
2) T CELL-CLL	COMMON	EARLY	?OKT8+	SUPPRESSION	EPIDERMIS SPARED

Hopefully it is clear at this point why this reviewer has chosen to utilize the generic term "cutaneous T cell lymphoma" (CTCL) to classify the diseases being discussed. Edelson in 1975 first proposed that the generic term CTCL be used to umbrella a group of diseases which have differing clinical and histopathological presentations but are commonly characterized by 1) early and predominate skin manifestations and 2) the presence of T cell surface markers (Lutzner, Edelson, Schein et al, 1975). Included under this umbrella are not only classic mycosis fungoides and Sezary syndrome, but also several other entities listed on the following table. Many of the cases of non-Hodgkin's lymphoma involving the skin which on morphologic criteria have been called, e.g. reticulum cell sarcoma, immunoblastic sarcoma, histiocytic lymphoma, lymphoblastic lymphoma, diffuse poorly differentiated lymphocytic lymhoma, etc. have been found to be comprised of malignant T lymphocytes, in spite of the fact that the cells did not show the classic hyperconvoluted appearance of MF or Sezary cells. Thus the term "epidermotropic variants" of CTCL is being increasingly used to describe classical mycosis fungoides/ Sezary syndrome, and "nonepidermotropic variants" of CTCL to descibe other cutaneous lymphomas with T cell markers and a differing histopathologic pattern.

Unfortunately, but as frequently is the case, things are not quite as simple and straight forward as the classification scheme presented in the preceding table would imply. A recent study from Columbia by Edelson (1980) illustrates this fact as well as documenting that the classical clinical and histopathologic presentation of MF/Sezary syndrome, i.e. the epidermotropic variants of CTCL, are only part of the broader spectrum of cutaneous T cell lymphomas.



A schematic of the natural progression of cutaneous T-cell lymphomas in 36 successive patients. *Approximately one-third of these unselected patients appeared with lymphomas that were microscopically characterized as epidermotropic. The remainder of the patients had nonepidermotropic T-cell lymphomas without having clearly passed through an epidermotropic phase. Natural evolution from the epidermotropic to nonepidermotropic phase was observed in five patients, whereas the reverse was therapeutically induced in only one patient. Note that patients who had a single lesion at presentation were more common in the epidermotropic group, whereas those with erythroderma were more common in the nonepidermotropic group. Disseminated papulo-nodular lesions were not seen at all in the patients with epidermotropic cutaneous T-cell lymphomas. SL, single lesion; ML, multiple lesions; E, erythrodermic, and D P-N, disseminated papulo-nodular.*

[from Edelson, J Dermatol Surg Oncol 6:360, 1980]

Over a three year period 36 patients who presented with cutaneous lymphoma had their atypical cells typed as T cells. Of these 36, only 13 had multiple skin biopsies all of which fit the epidermotropic pattern of classic MF/Sezary syndrome. The other 23 had skin biopsies which revealed malignant T cells in the dermis and/or subcutaneous tissue without significant epidermal involvement. This data implies that the classic histopathologic criteria of MF/Sezary syndrome may be seen at presentation in all biopsies in only a minority of patients with cutaneous T cell lymphoma. Within this three year observation period, 5 of the 13 patients who initially presented with primarily epidermotropic skin involvement developed new skin lesions which were predominately nonepidermotropic. This observation strongly suggests that even in "classic" cases there is an apparent natural progression from epidermotropic to nonepidermotropic skin involvement.

One additional finding from this study deserves comment. When these 36 patients were all staged by careful light microscopic examination of the blood and biopsy of any palpable lymph nodes, involvement by the malignant cells in tissues other than the skin was found in just 3 of the 13 patients (23%) with epidermotropic skin involvement (all of those 3 patients had generalized erythroderma). In contrast, 20 of the 23 patients, (87%) who presented with skin lesions that were nonepidermotropic, were found to have readily detectable extracutaneous disease at staging. These observations strongly suggest that in classic cases there is an apparent natural progression from epidermotropic to nonepidermotropic cutaneous involvement. And with this progressive loss of affinity for the epidermis there is a markedly increased probability that extracutaneous disease can be found.

C. LOCALIZATION PATTERNS OF OTHER NORMAL AND MALIGNANT CELLS: A BASIC SCIENCE DIGRESSION

The patterns of cutaneous involvement in various types of lymphoreticular neoplasms have prompted the formulation of the following testable hypothesis: in their most differentiated states, the MF/SS forms of CTCL (epidermotropic variants) reflect the neoplastic amplification of a discrete subpopulation of normal T cells which have undergone proliferation/differentiation in skin and/or the peripheral lymph nodes draining the skin and whose normal recirculatory pathway involves trafficing into or through the skin in general and the epidermis in particular. Ongoing studies in our laboratory have been exploring the capacities of defined populations of normal mouse lymphoid cells to leave the blood stream and enter both the dermis and epidermis of skin undergoing various inflammatory reactions. The data obtained thus far has been consistent with the hypothesis that epidermotropism is indeed a property of such a subpopulation of normal T cells. That is, cells with T cell surface markers, especially T cells which have undergone recent stimulation/division in peripheral lymph nodes, have a significantly enhanced capacity (compared to non-T cells) to move from the dermis and migrate into/localize within the epidermis at sites of cutaneous inflammation. It has not yet been determined whether normal T cells of the helper/inducer phenotype are more "epidermotropic" than other subpopoulations of T cells.

The concept that lymphoid cells associated with the gut (gut-associated lymphoid tissue or GALT) may have a relatively selective pattern of recirculation to and from the gut and the lymphoid tissues in this region has been generally accepted for some time (Gowans and Knight, 1964; Guy-Grand et al, 1974). The reciprocal concept, that there is a skin-associated lymphoid tissue (SALT) in which lymphoid cells from, e.g., peripheral lymph nodes exhibit selective migration to/localization in the principal organ (skin) associated with these lymph nodes, has only recently been formulated (Streilein, 1978).

That the skin may be a target tissue in the migration/localization of the T cells which undergo differentiation/proliferation in the peripheral lymph nodes has been strongly suggested by a number of other studies. T lymphoblasts obtained from the mesenteric lymph nodes show a striking capacity to selectively migrate into/localize in mesenteric lymph nodes and the lamina propria of the gut when adoptively transferred into other animals. This localization is selective, i.e. mesenteric lymph node localization of these cells is significantly greater than localization in peripheral lymph nodes. On the other hand T lymphoblasts obtained from peripheral lymph nodes or the efferent lymph draining such peripheral nodes show the reciprocal pattern of localization; i.e. such cells localize in greater numbers in peripheral lymph nodes than in mesenteric lymph nodes (Guy-Grand et al, 1974; Rose, Parrott, and Bruce, 1976a, 1976b). Furthermore, the capacity of peripheral lymph node T lymphoblasts to localize in the skin at sites of inflammation (secondary to the topical application of primary irritants, such as croton oil) is significantly greater than that of mesenteric T lymphoblasts (Rose et al, 1976b). Lastly, although peripheral lymph node T blasts will migrate into inflamed gut sites (but less well than mesenteric T blasts), when given a "choice" of migrating into/localizing in two inflammatory sites, one in the skin and the other in the GI tract, of the same animal, peripheral lymph node T blasts selectively localize in the cutaneous inflammatory site (Rose et al, 1976b).

It must be stressed that antigen itself does not appear to be critical determinant for the homing of cells to GALT or SALT. The studies of Guy-Grand et al (1978) strongly suggests that the migratory behavior of T lymphoblasts is independent of the antigenic stimulus, and is heavily dependent on the microenvironment in which that stimulus to proliferation/differentiation took place. In these experiments thymocytes from normal strain A donors were injected intravenously into lethally irradiated (AXB) F_1 recipients. Some of the parental strain thymocytes localized in peripheral lymph nodes where they confronted strain B histocompatibility antigens. Other thymocytes localized in mesenteric lymph nodes where (presumably) identical strain B histocompatibility antigens were present. In both sets of lymph nodes the response to alloantigen was the proliferation of the strain A T cells. Four days later, when this T cell proliferation was at its peak, single cell suspensions were prepared of either the peripheral lymph nodes or the mesenteric lymph nodes. These suspensions were then incubated in vitro with 125IUDR in order to selectively radiolabel the proliferating cell populations. Each of these two radiolabeled suspensions was then injected intravenously into groups of normal strain A recipients, and the localization of the radiolabeled cells in peripheral and mesenteric lymph

nodes determined 24 hours later. The results of this experiment conclusively showed that the T lymphoblasts proliferating in peripheral lymph nodes in response to strain B histocompatibility antigens showed a distinct preference for localizing in peripheral lymph nodes, while T lymphoblasts responding to the same strain B histocompatibility antigens within the mesenteric lymph node showed a preference for localizing in mesenteric lymph nodes. The conclusion which must be drawn from these experiments is that if unique recirculatory pathways such as GALT and SALT exist, they do so not because of the unique aspects of the antigens in these sites which cause proliferation and clonal expansion of the cells, but because during the course of the recognition event, the cells "learn" something unique about that particular microenvironment. The end result is the expansion of a population of cells with an increased affinity for a similar microenvironment.

How this phenotypic alteration seen within populations of heterogeneous cells is expressed at the level of a single cell is at present completely unknown. At least two major possibilities exist. It is possible that a given cell with specificity for a given antigen has no particular microenvironmental tropism, and that the ultimate tropism displayed by its progeny is an event dictated by the particular microenvironment in which the antigen happened to be confronted. In this case, given more than one possible site for meeting antigen, the cell by chance alone would see antigen where it did. If it proliferated in one microenvironment, its progeny would display increased tropism for that microenvironment. If the same cell happened to first proliferate in a different microenvironment, its progeny would have an increased tropism for that microenvironment. There is virtually no experimental data to support such an "imprinting" model.

The second possibility could be viewed as a "selective migration clonal expansion" model. In this model, within a population of cells with specificity toward the same antigenic determinant there are preexisting subpopulations each of which already has a tropism for a particular microenvironment. In this case, the initial localization of a cell in one particular microenvironment where it sees antigen and undergoes clonal expansion is <u>not</u> a random event. What might appear to be "random" equal initial localization into either microenvironment X or microenvironment Y by a hetergeneous population of cells, would in reality be the selective localization of some number of cells in microenvironment X and the equally selective localization of an equivalent number of different cells in microenvironment Y. Following clonal expansion of each of these subsets in their "preferred" sites, the tissue tropism of cells obtained from microenvironment X will be for microenvironment X > microenvironment Y, and microenvironment Y > microenvironment X for cells obtained from microenvironment Y.

That <u>tumor cell</u> populations are mixtures of preexisting clones with differing capacities to invade and proliferate in distinct sites has been shown by the elegant experiments of Fidler and coworkers (Fidler, 1973; Fidler and Nicolson, 1976; Fidler and Kripke, 1977). When previously unselected B16 melanoma cells are injected subcutaneously in syngeneic mice, local growth of the tumor is followed by widespread metastases in multiple organ sites, including the lung. These lung metastases were then

isolated, single cell suspensions prepared, and reinoculated intravenously into new recipient mice. Again widespread metastases developed, including the lung, and again the lung metastases were selected for further passage. After multiple similar passages of isolated lung metastases it was observed that the high frequency of metastases in the lungs of recipient mice persisted, whereas the frequency of metastases in other sites dramatically decreased. Thus with repeated passage of an initially heterogeneous population of tumor cells, a homogeneous population with restricted organ metastatic potential was obtained. Two major possibilities for the observed results were entertained. Either the original tumor cell suspension was comprised of cells with no particular preexisting ability to invade and grow progressively in the lung, and with random localization in the lung the tumor cells were phenotypically altered in a way as to display an increased tropism for that organ; or alternatively, the original tumor cell suspension was comprised of discrete subpopulations of cells some of which had a preexisting affinity for the lung. In order to investigate these possibilities, the original tumor line was cloned in vitro. Subsequently each of these clones was tested in vivo for its capacity to produce lung metastases. The results demonstrated a wide variability in the capacity of individual clones to give rise to lung metastases: some were completely unable to do so, while others showed a striking capacity to localize and grow within the lung.

Similar experiments with normal or malignant lymphoid cells have not been attempted. One possible approach would involve establishing multiple clones, each derived from single cells from a normal lymphoid tissue such as the thymus, and then examining whether some clones would show selective migration/localization in peripheral lymph nodes while others would show selective localization in mucosal-associated lymphoid tissue.

SUMMARY

Studies of the frequency and histopathologic patterns of cutaneous involvement of human lymphoreticular neoplasms which have been characterized by their cell surface markers suggest that:

1) Skin involvement is more commonly seen with T cell neoplasms than with non-T cell neoplasms.

2) When the malignant T cells display a tendency to move into the epidermis at sites of cutaneous infiltration, cell surface marker phenotyping in the vast majority of cases has characterized the T cells as belonging to discrete subpopulation (helper/inducer) of T cells.

3) There is a striking tendency for malignant helper/inducer T cells within the epideris, dermis, and extracutaneous sites, to localize around bone marrow-derived, dendritic cells of cells of monocytes/macrophage lineage which express Ia-like antigens on their surface.

Studies of normal lymphoid cells have provided evidence that:

1) The capacity of normal and especially recently stimulated T cells to move from the dermis into the epidermis at sites of cutaneous inflammation is greater than that of non-T cells.

2) Stimulated T cells obtained from peripheral lymph nodes have a strikingly different pattern of recirculation/localization than stimulated T cells from gut-associated lymphoid tissue; this includes an increased capacity to migrate into the skin at sites of inflammation.

3) Normal T cells of the helper/inducer phenotype tend to be found in sites also inhabited by Ia-bearing dendritic cells.

4) While antigen may be a factor in the localization/migration of normal T cells, its role appears to be a secondary one; other microenvironmental factors (such as the presence of certain Ia-like molecules) may play a more fundamental role in determining the migration patterns of a specific cell.

All of these observations are consistent with the hypothesis that the epidermotropic variants of CTCL represent the neoplastic amplification of a subpopulation of normal T cells which, having undergone proliferation/differentiation in a peripheral site (i.e. skin or peripheral lymph nodes) have a special affinity for the skin in general and the epidermis in particular. Further studies of the migration patterns of characterized subpopulations of normal and malignant lymphoid cells, and the elucidation of the factors that regulate these migration patterns can be expected to further our understanding of the pathobiology of CTCL.

IV. PATHOGENESIS OF CTCL

As is the case for virtually all human malignancies, the pathogenesis of CTCL remains poorly understood. One factor contributing to our current lack of knowledge is that there are no known animal models for this group of diseases. While there has been a solitary report (Shadduck et al, 1978) of a dog who presented with skin lesions histopathologically identical to those seen in patients with classic mycosis fungoides, there was no attempt made to propagate the malignant cells either in vitro or in other animals.

A. Epidemiologic considerations

Although the etiology of CTCL is unknown, there are many studies that suggest that genetic, environmental, and/or infectious factors may be important in the development of CTCL. There are several reports of families in which more than one member had this disorder (reviewed in Shelley, 1980). The presence of other lymphomas and leukemias in family members has been reported even more frequently (Greene, 1979). It has also been reported that certain histocompatibility antigens (e.g., HLA-B8) are found with excessive frequency in patients with CTCL (Dick and MacKie, 1977).

Three independent studies have suggested a relationship between exposure to potential industrial/environmental toxins and the development of CTCL. Cohen (1977) compared patients who had CTCL with an age- and

sex-matched control group from the same geographic area, and found a statistically significant association between CTCL and exposure to industrial toxins. Two other studies did not utilize control groups, and therefore no firm conclusions can be reached. Nevertheless, these latter studies have suggested that patients with CTCL have a high frequency of employment in a manufacturing occupation, especially those related to petrochemicals, textiles, metals, or machinery (Greene et al, 1979). They also reported excessive mortality from CTCL in counties where petroleum, rubber, metal, machinery, or printing industries were located. Fischmann, Bunn, Guccion et al (1979) observed that a history of several exposures to potentially carcinogenic chemicals could be obtained from 91% of their patients with CTCL. It must be emphasized that it will take larger, well-controlled, prospective studies to clearly establish whether or not there is a positive relationship between such exposures and development of CTCL.

Tumor virologists for years have been doggedly pursuing the possibility that at least some forms of human lymphoreticular malignancies are related to infection with oncogenic RNA tumor viruses (retroviruses). Such retroviruses have previously been shown to cause leukemia in other animals including chickens, cats, rodents, cattle, and gibbons. Although some studies have suggested the presence of retrovirus information in some human tissues, including Langerhans cells in the skin and lymph nodes of patients with MF/SS (Van der Loo et al, 1979), the detection and isolation of complete, well defined particles from humans has proven exceedingly difficult. The development of continuously growing cell lines from patients with various neoplastic diseases, and in some cases from normal tissues, has led to reports of retroviruses in some of them (Gallagher and Gallo, 1975). However, most of these isolates have been very closely related to previously isolated primate viruses, making interpretation of their origin difficult.

In light of these difficulties, the recent reports of isolation of an apparently unique human retrovirus from cells of patients with CTCL in the United States (Poiesz, Ruscetti, Gazdar, et al, 1980) and in Japan (unpublished data discussed in Lewin, 1981) are being greeted with cautious optimism. Gallo's group isolated the virus from cell lines from 2 patients with CTCL; the two isolates were identical in all respects. Characterization of the retrovirus involved analysis of its reverse transcriptase, its RNA genome, and its core proteins; extensive studies have failed to reveal substantial similarity with any other known animal retrovirus (although it does have some core protein similarity with bovine leukemia virus). The virus isolated from cultures of malignant cells from patients with T cell-CLL in Japan shows striking similarity to that isolated in the United States. Furthermore, the Japanese investigators have apparently been able to transform normal human cord blood lymphocytes by cocultivating these cells with infected cells.

Gallo's lab has also been looking for the presence of antibody against the core protein of the virus in both patients with CTCL and normal individuals. Antibodies have been detected in all patients (4 at the present time) from whose cells the virus has been isolated; however, many patients with the disease in the USA have neither virus nor antibody. Perhaps the most striking observation, however, has been the finding of

antibodies in normal individuals! In the United States, antibody has been detected not only in the sister of one of the patients from whom the virus was isolated, but also in the wife of the first patient from whom the virus was isolated! Similarly in Japan investigators have found antiviral antibodies in 100% of patients with T cell-CLL. Furthermore, in the area where the disease appears to be endemic (Southwestern Japan, on the islands of Kyushu and Shikoku), approximately 30% of apparently healthy individuals also have the antibodies. These epidemiologic patterns suggest but do not prove that the retrovirus may be an infectious agent with an as yet unknown mode of transmission.

B. Pathogenetic schemes

There is now general agreement that most neoplasms arise by means of a stepwise progression that begins in normal cells and culminates in a tumor composed of genetically abnormal malignant cells. The initial ("premalignant") lesions may involve subtle functional or biochemical changes that steadily worsen or accumulate with time; cellular proliferation may be a feature required for initiation and/or promotion of this process. The duration of this entire process is extremely variable; in spontaneous thymic leukemia of the AKR mouse virtually the whole life span of the animal consists of a progressively deteriorating preleukemic state (Louis et al, 1980), whereas erythroleukemia develops within only a few weeks after inoculation of susceptible mice with the Friend virus complex.

Malignant lymphomas in humans illustrate these same general principles. In some instances there is overt evidence of functional or even genetic abnormalities of lymphocytes, and over a period of months or years these changes become superceded by neoplastic abnormalities. In certain cases the preneoplastic lesion involves inadequately controlled proliferation of lymphocytes; i.e. a chronic lymphoproliferative reaction (exemplified by the association of immunoblastic lymphadenopathy with immunoblastic sarcoma). Such cases, however, seem to represent a minority. In the majority of cases of malignant lymphoma other than CTCL, the lymphoma arises without any apparent antecedent preneoplastic disturbances. Nevertheless, the probability that these disturbances do indeed exist, but in a clinically undetected form, is an alternative being increasingly considered.

In other words, if the appropriate techniques existed, it might be possible to detect early, "prelymphomatous" states in individuals who are clinically normal. The previously mentioned AKR mouse, which almost always develops thymic lymphoma, is a case in point. Simple clinical observation of the animals reveals nothing until the late stages of the disease, yet the application of refined virologic and immunologic techniques can disclose important abnormalities almost from the birth of the mouse. The classical mycosis fungoides variant of CTCL is another case in point. In contrast to the usual forms of lymphomas/leukemia which principally express themselves in extracutaneous sites (and in which the early prelymphomatous stages would not be readily detected), this form of CTCL represents an entity in which the skin is a highly visible target organ for abnormal T

cells. The prolonged period of time during which this disease's expression may be clinically confined to the skin before eventuating in overt lymphoma/leukemia in extracutaneous sites more commonly associated with malignant lymphoma may, in fact, be presenting tumor biologists with a relatively unique opportunity to study the early stages in the evolution of a neoplasm.

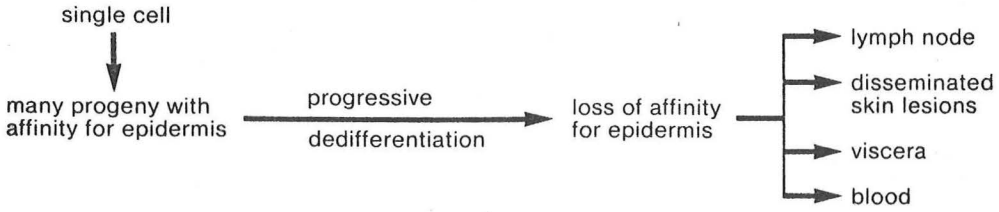
One of the more popular theories of the pathogenesis of CTCL suggests that they represent diseases of chronic antigenic stimulation (Tan et al, 1974). In this model, T cells, initially responding to some specific but unknown antigen in, or associated with, the skin, become dysplastic as a result of chronic stimulation (early eczematous or plaque stage of the disease). The further dedifferentiation of these dysplastic stimulated cells then results in the overt lymphomatous phase of the disease. Proponents of this model site the apparently increased incidence of CTCL in patients with a past and frequently long-standing history of diseases such as atopic, allergic, or irritant contact dermatitis, all of which may be conditions in which T cells are repeatedly and chronically stimulated. In order to incorporate the various epidemiologic factors which have been implicated in CTCL (see above) in such a pathogenetic scheme, one can hypothesize that a genetically susceptible individual becomes infected with a unique retrovirus (initiation). The additional presence of a persistent proliferative signal (promotion) from some environmental agent would at some point result in the overt malignant transformation of the stimulated cells, with subsequent clonal expansion of one or more subclones.

A variation on this pathogenetic scheme is that defective T cell: antigen-presenting cell interactions result in a chronic proliferative signal being delivered to the T cells which ultimately undergo overt malignant transformation (Rowden and Lewis, 1976). In this model the normally temporally-limited signal from Ia-bearing antigen- presenting cells (such as Langerhans cells in the epidermis and/or related cells in the dermis and paracortical regions of peripheral lymph nodes) is persistent and sustained. Some proponents of this model have suggested that retrovirus expression in antigen-presenting cells indirectly results in the persistent stimulus (e.g. results in an inability of the antigen presenting cells to clear other foreign antigens from their membranes) (van der Loo et al, 1979). Others have suggested that the retrovirus itself is the persistent antigenic signal (MacKie, 1981), or that some other undefined triggering signal not necessarily related to retrovirus infection is abnormally and persistently expressed by such cells (Rowden and Lewis, 1976).

Additional recent data has implicated keratinocytes in the pathogenesis of CTCL. It is becoming increasingly apparent that products of normal keratinocytes can have profound effects on the state of differentiation and proliferative activity of normal T cells. Two recent studies have shown that keratinocytes elaborate a factor termed ETAF (epidermal-derived thymocyte-activating factor), which is similar if not identical to Interleukin-1 produced by peripheral blood monocytes (Luger et al, 1981). Such factors can increase the proliferation of normal thymocytes (either alone or in the presence of suboptimal concentrations of mitogens), and can also induce the production of Interleukin-2 (or T cell growth factor, TCGF) by antigen- or mitogen-stimulated mature peripheral T

cells: IL-2 in turn, enhances proliferation in mature T cells bearing receptors for this molecule. Secondly, cocultivation of normal keratinocytes with normal peripheral T cells has resulted in both blast transformation and the expression in these T blasts of terminal transferase (TdT) activity (Rubenfeld et al, 1981). TdT is normally expressed only on a fraction of bone marrow cells and thymocytes, and is felt to be an early marker for cells destined to undergo thymus-directed maturation (Gallo, 1975; Banton et al, 1976). Rubenfeld has suggested the possibility that the induction of this DNA altering enzyme in peripheral T cells may be a sign that the epidermis is a peripheral tissue with the capacity to expand the diversification of the T cell pool. Finally, Safai et al (1981) have recently reported that keratinocyte cultures from the lesional skin of patients with CTCL, but not those from normal human skin, produced a factor termed Facteur Thymique Serique (FTS) which induces differentiation of T cell precursors in vitro. While the relevance of these observations to the pathogenesis of CTCL remains speculative at present, it is intriguing to consider the possibility that products of normal (or abnormal) keratinocytes may have the capacity to alter the state of differentiation, the proliferative rate, and perhaps even the migration patterns of abnormal T cells.

Mode of Spread: **Unifocal Origin**



Edelson: J Derm Surg Oncol 6:5, 1980

Edelson (1980) proposed the above schema of cellular events in the evolution of CTCL. In this model, the neoplastic event occurs in a single, mature T cell in a single, but undefined site. This cell and its progeny have a special affinty for the skin in general and the epidermis in particular. With time there is progressive evolution or dedifferentiation of more malignant subclones. This may happen within days or decades of the original neoplastic event. But when it does happen, the affinity for the epidermis is lost, at which point the cells seem to simultaneously acquire the capacities for both widespread dissemination and progressive growth in cutaneous and extracutaneous sites, including lymph nodes and virtually any visceral organ. While this particular scheme very nicely accommodates a substantial amount of clinical data, at least two questions can be asked. First, what is the evidence that the malignant process begins with a single T cell--i.e. is clonal from its earliest time of detection? Secondly, what data speaks to the issue of the principal organ/tissue in which the malignant cells proliferate?

C. Clonality of CTCL

Cytogenetic studies of the atypical cells in the peripheral blood of patients with Sezary syndrome have failed to provide evidence that the process is a clonal one in the majority of cases (Van Vloten et al, 1980; Whang-Peng et al, 1979). In these studies abnormalities in both chromosome numbers and banding patterns were frequent, but tended to vary not only from patient to patient, but in cells from a given patient. It must be pointed out that such detectable chromosomal abnormalities are generally considered to be late events in the process of malignant transformation. Thus, the above results could mean that multiple clones are involved from the start; alternatively, one could "salvage" the clonal origin hypothesis by suggesting that an abnormal cytogenetic pattern is a late consequence of the neoplastic event and not anything related either to its cause or to the question of whether it initially occurred in one rather than several T cells.

On the other hand, Edelson, Berger, Raafat, and Warburton (1979) looked at the cytogenetic patterns of cells obtained from multiple sites of malignant involvement in the same patients, and noted a striking similarity of the abnormalities in cells from these different sites. In each instance, karyotype analysis of chromosomes in replicating malignant cells from distinct body regions revealed structural abnormalities that were identical in all examined malignant cells from each patient, but again not from the group as a whole. It must be emphasized, however, that like studies suggesting monoclonality of other neoplastic processes, the data described above for CTCL has been collected from patients with advanced disease. It is not absolutely certain that the alternative hypothesis, namely, that the disease is polyclonal at the outset but overgrowth by a particularly malignant clone supervenes, can be discarded. Nevertheless, it does appear clear that by the time the disease presents clinically as widespread disseminated visceral disease it can be characterized as having arisen from a single highly malignant clone. One obvious but technically difficult approach to this question would be to simultaneously examine multiple skin lesions in patients with early plaque or patch stage disease by cytogenetic analysis of the infiltrating cells.

D. Site(s) of proliferation of malignant T cells

At this point there is no data which address the issue of the tissue/organ site in which the first malignant T cells proliferate. Several studies have documented that, once established, the abnormal cells can migrate into and divide in the skin (Chandra et al, 1976; Bosman and van Vloten, 1976; Saglier-Guedon et al, 1977; Miller et al, 1980).

The fact is that most patients at presentation have multiple areas of skin involved, rather than presenting with a single localized lesion. If identical chromosomal abnormalities can be demonstrated in multiple different sites on the same patient (see discussion immediately above), one inevitable conclusion with far-reaching therapeutic implications would be that the disease, even at that early point in time, cannot be considered to only involve the skin. That is, the presence of cells with identical abnormalities in two or more noncontiguous skin lesions is only readily

explained by extracutaneous involvement; the abnormal cells at some point would have to be in the blood.

A slightly different question is whether the abnormal cells seen in the blood in patients with Sezary syndrome are immediately derived from proliferating precursors in the skin or in some extracutaneous site. In a technically demanding experiment, Bunn, Edelson, Ford, and Shackney (1981) recently utilized pulse labeling with ^{3}H-Thymidine in vivo to study the patterns of cell proliferation and cell migration in three such patients. Cell labeling patterns indicated that Sezary cells proliferate actively in skin and in lymph nodes, but that few, if any, Sezary cells proliferate in the peripheral blood. In two patients serial samples of skin and peripheral blood were examined. The conclusions drawn from these studies were that circulating Sezary cells originated in extracutaneous sites where cells were proliferating more rapidly than in the skin. Cells labeled in extracutaneous sites of proliferation appeared rapidly in the blood, and their transit time through the peripheral blood compartment was short. Circulating Sezary cells might then be deposited in the skin where they resume proliferation at a low rate. Thus, while Sezary cells proliferate in both cutaneous and extracutaneous sites, proliferation appears to be more rapid in extracutaneous sites such as lymph nodes. The authors concluded their discussion by making a plea for the use systemic chemotherapy and/or systemic radiotherapy in the therapy of the Sezary syndrome, arguing that while topical treatments such as nitrogen mustard, electron beam radiation, and PUVA (see also VIII. Treatment) may decrease the overall body burden of tumor cells transiently, such modalities would have no effect on the proliferation of Sezary cells at the primary site of cell production.

V. Established prognostic variables in CTCL

A. Current staging classification system

Information about the natural history of untreated CTCL is virtually impossible to obtain for the obvious reason that once diagnosed, patients almost without exception are treated in some way. We have already discussed the extremely long interval from the very first onset of symptoms to biopsy confirmation of the disease (see p 6). These considerations aside, however, it is clear that all available data points to an almost mind-boggling variation in survival of patients diagnosed as having CTCL, ranging from a few months to over fifty years. Mean survival figures from large series point to a figure of somewhere between 5 years (Epstein et al, 1972; Fuks et al, 1973) and 8-9 years (Vonderheid et al, 1979; Hoppe et al, 1979), for the average patient once he is diagnosed. This median survival for all patients with CTCL obviously is a relatively meaningless statistic for the physician and his individual patient with CTCL. The much more relevant question for that physician is what is the prognosis for a group of patients with the same stage/type of disease as the individual patient confronting the physician.

Part of the problem heretofore in obtaining such information has been the lack of a uniform, broadly accepted scheme of staging patients according to their extent of disease. In order to rectify this problem and

in order to attempt to determine the prognostic importance of various physical signs, the Mycosis Fungoides Cooperative Study Group (MFCG) in 1975 developed a modified "TNM" classification system (Lamberg et al, 1975). This system has been recently adopted with minor modifications by the 1978 Cutaneous T Cell Lymphoma Workshop (Lamberg and Bunn, 1979). The following two tables illustrate this TNM classification of CTCL and the utilization of the TNM values in order to place patients in a particular stage of disease.

TNM Classification of CTCL

Classification	Description
T: skin*	
T_0	Clinically and/or histopathologically suspicious lesions
T_1	Limited plaques, papules, or eczematous patches covering less than 10% of the skin surface
T_2	Generalized plaques, papules, or erythematous patches covering 10% or more of the skin surface
T_3	Tumors (≥ 1)
T_4	Generalized (exfoliative) erythroderma
N: lymph nodes†	
N_0	No clinically abnormal peripheral lymph nodes, pathology negative for CTCL
N_1	Clinically abnormal peripheral lymph nodes, pathology negative for CTCL
N_2	No clinically abnormal peripheral nodes, pathology positive for CTCL
N_3	Clinically abnormal peripheral nodes, pathology positive for CTCL
B: peripheral blood	
B_0	Atypical circulating cells (Sézary cells) not present (< 5%)
B_1	Atypical circulating cells (Sézary cells) present (≥ 5%)‡
M: visceral organs	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ(s) involved should be specified)

*Pathology of T_{1-4} is diagnostic of CTCL. When more than one T exists, both are recorded and the highest is used for staging, eg, $T_{4(3)}$.

†Record number of sites of abnormal nodes, eg, cervical (left + right), axillary (left + right), groin (left + right).

‡Record total white blood cell count, total lymphocyte counts, and % atypical lymphocytes (Sézary cells) observed in peripheral blood. Indicate if any special techniques are used to identify abnormal cells.

Staging Classification of CTCL

Stage	Classification		
	T	N	M
IA	1	0	0
IB	2	0	0
IIA	1-2	1	0
IIB	3	0,1	0
III	4	0,1	0
IVA	1-4	2,3	0
IVB	1-4	0-3	1

The relevance of such a uniform staging system in highlighting differences in patient populations evaluated in different referral centers is illustrated on the next page. It can be seen that many more patients with generalized erythroderma (mostly patients with Sezary syndrome) were evaluated at the National Cancer Institute than in the other centers. Conversely, relatively few patients with limited plaque (T_1) disease were

evaluated at the NCI, while nearly half the patients evaluated at Temple had T_1 skin disease.

Frequency of Skin Stages in Several Recent Series

Skin Stage	% of Patients with Stanford N = 176*	Temple N = 243	MFCG N = 336	NCI ' N = 50	Total N = 805
Lichenoid, Limited plaque (T_1)	29	49	40	10	38
Generalized plaque (T_2)	41	13	31	34	28
Cutaneous tumor (T_3)	16	18	16	20	17
Generalized erythroderma (T_4)	15	20	13	36	17

Carney and Bunn: J Derm Surg Oncol 6:5, 1980

The only factor which has consistently been shown to have prognostic significance in all major series is the extent of disease. There are, however, distinct components within this broad category, and this review will now briefly consider each of these.

B. Amount of skin involved and type of skin lesions

EXTENT/TYPE OF SKIN DISEASE AND CORRELATION WITH SURVIVAL

Extent/Type	Stage	% of Patients	Mean Survival(yr)	Alive at 5 yr (%)
Limited (<10%) plaque	T_1	38	>9	90
Generalized (>10%) plaque	T_2	28	>7	67
Cutaneous tumors	T_3	17	2.5	35
Generalized erythroderma	T_4	17	3.5	40

The extent of disease is related to both the percentage of skin involved and the type of skin lesions present. The above table shows the combined results reported by the groups from Temple University (Vonderheid, Van Scott, Wallner, et al, 1979), Stanford University (Hoppe, Cox, Fuks, et al, 1979) the Mycosis Fungoides Cooperative Group (Lamberg, Green, Byar, et al, 1979), and the National Cancer Institute (Bunn, Fischmann, Schecter, et al, 1979). It can be seen that patients with limited patches or plaques covering less than 10% of the total skin surface do quite well, with a mean survival of greater than 9 years, with 90% of such patients alive at 5 years. When patients presented with generalized patches or plaques (> 10%), however, only 67% were alive at 5 years. Patients with generalized erythroderma do much worse, with only 40% surviving 5 years and a mean survival of about 3½ years. In addition, the specific type of skin lesions present are also important. If a patient has either limited or generalized patches or plaques, but in addition has tumor formation on the skin, his prognosis is much worse, and similar to erythrodermic patients, with a mean survival of only approximately 2½ years.

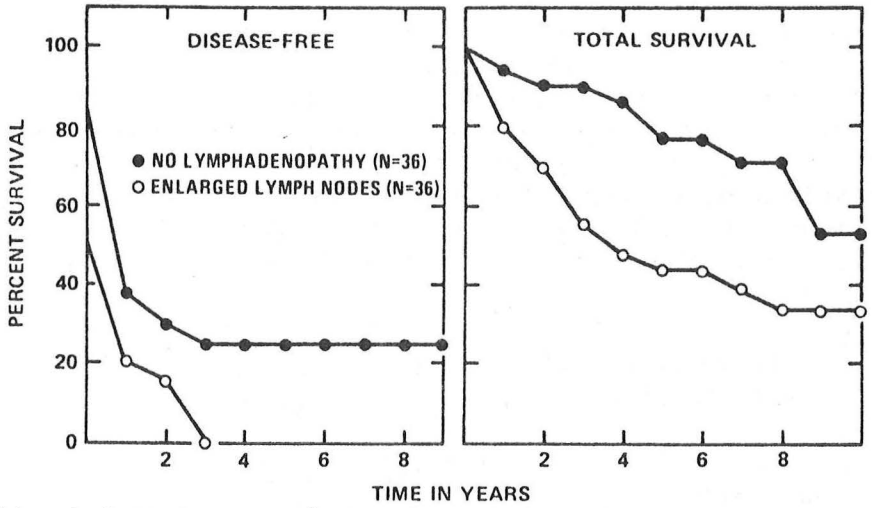
C. Lymphadenopathy

The overall frequency of palpable adenopathy in the above series is approximately 45%, and is related to the extent of skin disease.

ASSOCIATION OF LYMPHADENOPATHY WITH EXTENT OF SKIN DISEASE

Skin Involvement	% Adenopathy
Limited plaque (<10%)	17
Generalized plaque (>10%)	44
Cutaneous tumor	56
Erythroderma	83

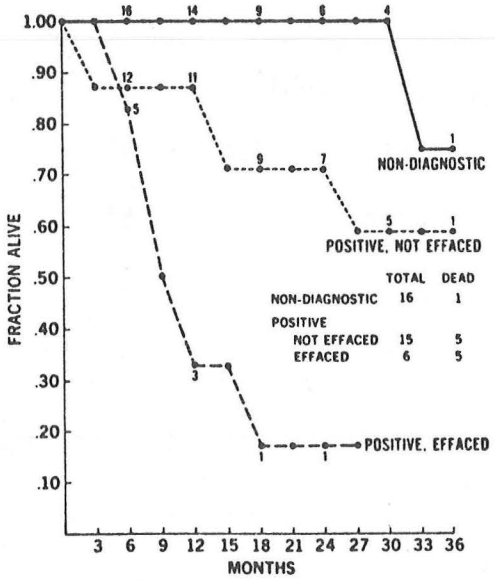
The relevant question is whether or not the presence or absence of lymphadenopathy is of prognostic significance in an individual patient with a given extent/type of skin involvement. That is, whether the two variables of extent/type of skin disease and lymphadenopathy each independently contribute to how that patient's disease may be expected to act. As shown on the next table from the Stanford study (Hoppe et al,1977), if you restrict analysis to a group of patients with a more or less similar type of skin disease (in this case generalized plaque (T_2) disease), then the patients without adenopathy have a better survival than patients who do have adenopathy.



Actuarial analysis (Berkson–Gage)[2] of survival and disease-free survival after the first course of electron beam therapy in patients with generalized plaque phase of mycosis fungoides; correlation with pretreatment peripheral lymphadenopathy.

Not only is the presence or absence of any palpable lymph nodes important, the number of sites with enlarged nodes is also important. The

next table, derived from data from the MFCG study, shows the correlation between the number of nodal sites involved and the death rates for patients grouped with either limited or generalized plaque skin disease. One can see the tendency for patients with a given extent of skin disease to show not only an increased death rate if only one site shows adenopathy compared with similar patients with no adenopathy at all, but also that within given stage as the number of involved nodal sites increases from 1, to 2 or more, the death rate continues to increase.



Bunn et al: Ann Int Med 93:22, 1980

The type of involvement seen when the palpable lymph nodes are biopsied is also relevant. The following figure from the NCI study shows that patients with nodes read as either normal or nondiagnostic (usually read as "dermatopathic lymphadenopathy") by conventional light microscopy have a significantly better survival than patients whose nodes showed early malignant involvement by virtue of having large clusters of atypical cells in the T cell zones of the node. These patients, in turn, survive significantly longer than patients whose nodes are more completely effaced by malignant cells.

DEATH RATES* BY CLINICAL CATEGORY
AND NUMBER OF NODAL SITES INVOLVED

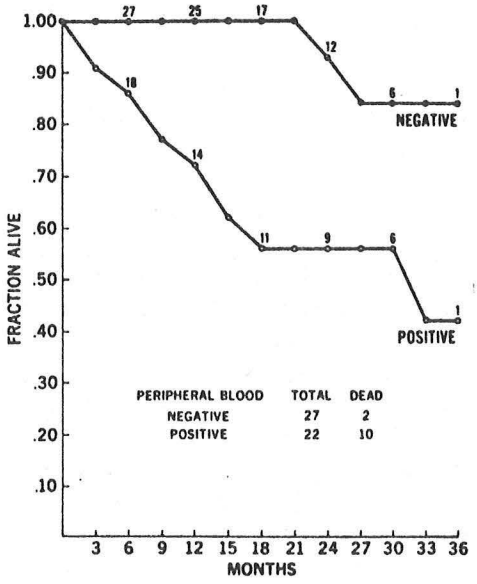
Nodal Sites Clinically Involved	CLINICAL CATEGORY T_1 (Limited Plaque)	T_2 (Gen'lized Plaque)
0	0.19	0.53
1	0.24	0.70
2+	0.68	2.11

*Deaths per 100 patient-months follow up

That the presence of palpable adenopathy in which the pathology by conventional light microscopy is nondiagnostic is an adverse prognostic sign has been previously shown by Epstein and coworkers (1972). In this NIH series of 144 patients, the overall median survival was 48 months. However, the survival of patients with palpable adenopathy in which the histopathology was not diagnostic of malignant lymphoma was only 34 months. This observation strongly suggests that routine light microscopy may be under diagnosing very early extracutaneous disease. (see also p 40).

D. Peripheral blood involvement

Large numbers of readily detectable (by conventional light microscopic techniques) atypical circulating T cells are most commonly seen in patients with generalized erythroderma, i.e. patients with the Sezary syndrome. 100% of the 18 patients with erythroderma studied at the NCI (Schechter, Bunn, Fischmann et al, 1979) had significant numbers (> 5%) of Sezary-type cells on Wright-Giemsa stained peripheral blood smears. Other workers have detected circulating Sezary cells in approximately 70% of patients with generalized erythroderma (Vonderheid, Van Scott, Wallner et al, 1979). As illustrated in the next figure, patients with readily detectible peripheral blood involvement had a significantly shorter survival than patients who did not have this finding. However, it must be pointed out that since the vast majority



Bunn et al: Ann Int Med 93:22, 1980

of patients with peripheral blood involvement in this NCI series were patients with Sezary syndrome,(i.e. generalized erythroderma and generalized lymphadenopathy as well as circulating Sezary cells), this study does not address the issue of whether the presence of detectable numbers of circulating atypical cells in the blood of patients who are not erythrodermic is also an unfavorable prognostic sign. Moran and coworkers, et al, (1977) have suggested that the presence of small

numbers of atypical T cells in the peripheral smears of patients with classic plaque or tumor stages of mycosis fungoides indeed does correlate with a poorer survival in those patients, particularly if such cells are demonstrable on several different occasions. Clearly more data on this specific point is necessary before any definitive conclusions can be drawn. Furthermore, clarification of the most appropriate methodology for looking at the peripheral blood in such patients is also needed. In the NCI series it was possible to observe Sezary type cells in 13% of 31 patients with plaque or tumor stage disease utilizing Wright-Giemsa stained smears; however, utilizing special techniques such as cytogenetic analysis, electron microscopy, and analysis of T cells using a spontaneous sheep cell rosette/cytologic method, circulating abnormal cells were found in approximately 65% of these same patients (Schechter et al, 1979).

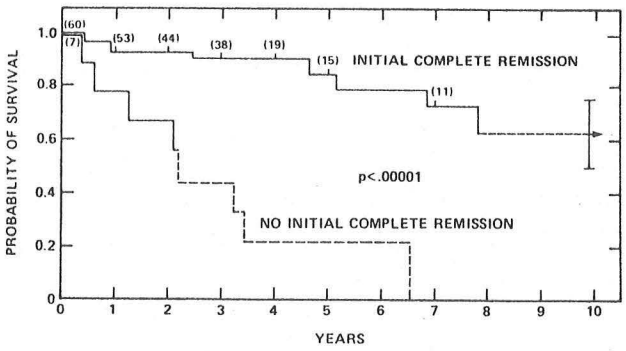
E. Malaise, Chills, etc.

In a recent study , Green, Byar, and Lamberg, (1981) analyzed the prognostic importance of various factors for 347 CTCL patients registered by the MFCG. Patients with chills at the time of registration had a signigicantly worse prognosis than patients without this symptom. Adjustment for skin stage and lymph node stage markedly reduced the differences in survival between those with and without chills, but the difference was still statistically significant. Furthermore, although patients with erythroderma had the greatest frequency of chills, the prognostic effect of chills was not confined to these patients.

As one might anticipate, malaise, as a symptom of debility, also showed a relation to survival. Survival curves revealed that the presence of malaise was associated with a markedly poorer prognosis.

F. Therapeutic induction of a complete remission

While it might seem intuitively obvious that patients whose malignant cutaneous disease disappears completely following treatment directed at the skin would have a more favorable prognosis than patients whose disease does not disappear completely, the fact is that until relatively recently no definitive data was available on this point. As can be seen from the following figure from the Stanford study utilizing whole body electron beam therapy as initial treatment, patients with T_2N_0 disease who attained an initial complete remission indeed survived longer than patients who attained a partial emission only.

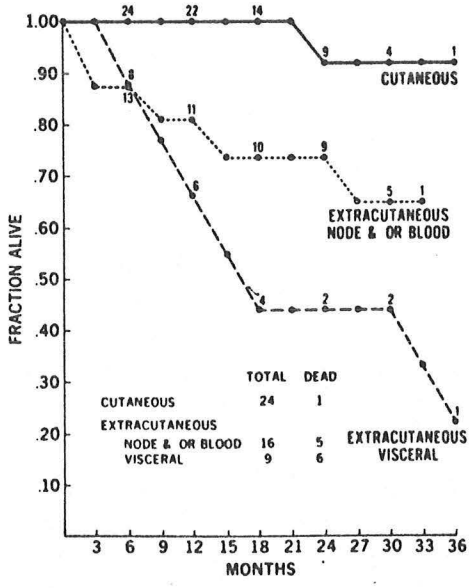


Hoppe, et al.
Cancer Treat Rep 63:697, 1979

VI. Possible Prognostic Variables in CTCL

A. Extracutaneous disease in sites other than peripheral lymph nodes and/or blood

As is shown on the following figure from the NCI series, patients with extracutaneous disease had a significantly shorter survival than did those with disease confined to the skin ($p < 0.001$). Although patients with extracutaneous disease in visceral sites had the worst prognosis, their survival was not statistically shorter than that of patients with extracutaneous disease in nodes and/or blood. The overall shape of the two lower curves in the above figure would suggest that if a larger number of patients in these categories were evaluated, that the presence of e.g., liver involvement in the presence of documented nodal and/or peripheral blood involvement would indeed be a statistically significant prognostic factor.



Bunn et al: Ann Int Med 93:22, 1980

Recent data from the NCI suggests that there is a very low probability of finding pathological involvement in visceral organs such as the liver in patients who do not already have pathologic involvement of the peripheral lymph nodes and/or blood (Huberman et al, 1980). In this study 43 patients with CTCL underwent multiple routine staging procedures prior to initiation of therapy. Evaluation of the liver included physical examination, liver function tests, liver-spleen scans, percutaneous liver biopsy, and peritoneoscopy with multiple liver biopsies. 7 patients (16%) had biopsy-documented hepatic lymphoma, histologically defined as focal aggregates of atypical convoluted lymphocytes in portal zones or hepatic lobules. All patients with hepatic involvement had documented peripheral blood and peripheral lymph node involvement. Thus, the presence of extracutaneous disease is unlikely to be confirmed only by documented pathologic involvement of visceral organs. Several other observations were made in this study.

First, peritoneoscopy with multiple biopsies was significantly more sensitive than percutaneous liver biopsy in documenting hepatic involvement; liver involvement was documented in only 3 patients by percutaneous liver biopsy, while an additional 4 patients (2 with negative and 2 with inadequate percutaneous biopsies) had hepatic lymphoma documented by peritoneoscopy. Physical examination, liver function tests, and liver-spleen scanning were not useful in predicting hepatic involvement. Physical examination revealed hepatomegaly in only 4 patients, 3 of whom had hepatic involvement. None of the patients in this series had elevated serum bilirubin, and only 1 of the 7 patients with hepatic lymphoma had an elevated SGOT. Increased alkaline phosphatase was found in 7 patients, 4 of whom did not have hepatic lymphoma. Elevated LDH levels were present in 19 patients; 6 of these had hepatic involvement, while 13 did not (most of these 13 did, however, have generalized lymphadenopathy). Focal defects were not present in any of the liver-spleen scans. Hepatomegaly and/or patchy defects were seen in the liver scans of 11 patients, only 1 of whom had lymphoma on liver biopsy.

The incidence of bone marrow involvement in post mortem series ranges from 18% - 29% (Long and Mihm, 1974; Rappaport, and Thomas, 1974). As we discussed previously, antemortem studies generally show a remarkable sparing of bone marrow. In a review of the literature, Carney and Bunn (1980) found bone marrow involvement in only 11 of 443 (2.5%) bone marrow biopsies. Furthermore, (see p 8) the finding of significant bone marrow infiltration in only 16% of patients with Sezary syndrome in whom the peripheral blood was clearly involved, is a striking one. Thus, the relative sparing of the bone marrow may be useful in differentiating classic MF/SS from other lymphoproliferative disorders with skin involvement: patients with T cell-CLL demonstrate a much higher incidence of marrow involvement. While the finding of marrow involvement in the classic MF/SS forms of CTCL is an uncommon event, it is unknown at the present time if its presence is of prognostic importance. Marrow involvement clearly is important in the staging of several other types of non-Hodgkin's lymphoma/leukemia. Furthermore, there may be other indications for obtaining a bone marrow biopsy in a patient with CTCL: e.g., if any form of systemic therapy is being considered, it is advisable to evaluate the status of the marrow.

Lymphangiography has been an extremely useful staging technique both in patients with Hodgkin's disease and some forms of non-Hodgkin's lymphoma/leukemia. However, this technique does not appear to be of very much practical utility in evaluating patients with CTCL. There are several reasons for this conclusion. Overall, lymphangiograms are abnormal in about half of the patients, a proportion similar to the finding of clinically detectable peripheral lymphadenopathy. Castellino and coworkers (1979) showed that abnormalities on lymphangiograms paralleled clinical extent of disease, so that patients with limited or generalized plaque disease had more normal-appearing studies than those with either tumors or erythroderma. This study also noted that the incidence of lymphangiographic abnormalities also paralleled the presence of palpable peripheral lymphadenopathy. Whereas 50% of patients with normal or minimally abnormal lymphangiograms had palpable adenopathy, 81% of patients with moderately or markedly abnormal

lymphangiograms had palpable adenopathy. Similarly, the study by Hamminga et al, (1981) revealed a high positive correlation of lymphangiography with advanced disease; 89% of patients with lymphoma-pattern lymphangiograms had documented extracutaneous CTCL, and conversely, 80% of patients with pathologically documented extracutaneous CTCL had moderately or markedly abnormal lymphangiograms. The fact is, however, that clinical and histopathologic evaluation of the patient's peripheral lymph nodes and peripheral blood will have already given you as much information about the probability of readily detectable extracutaneous disease. In this same study, 20% of the patients with normal or only minimally abnormal lymphangiograms had pathologically documented extracutaneous disease, i.e. there was a substantial "false negative" rate. Finally, the above two studies as well as two additional studies (Tallroth et al, 1977; Escovitz et al, 1974) have all shown a significant "false positive" rate which has varied from 15-67%; i.e., the finding of moderately or markedly abnormal lymphangiograms in patients with disease clinically limited to the skin. While it is possible that these cases are not false positives, but rather are patients who indeed do have early internal lymph node involvement, would tend to be ruled out by the observations of Hamminga et al, (1981), who noted no correlation between the presence of abnormal lymphangiograms in patients with disease clinically limited to the skin and the subsequent clinical course of such patients. Whether lymphangiograms will prove useful in following the response to systemic chemo- or radiotherapy remains a matter for additional clinical investigation.

There are no published studies in which abdominal CT scans have been utilized in the staging evaluation of patients with CTCL. However, it seems unlikely that in this particular situation, in which lymphomatous involvement may be focal and not necessarily accompanied by striking enlargement of lymph nodes, that this procedure will prove to be of significant benefit in such staging evaluations.

B. Age

Data from earlier series strongly suggested that patients under 50 years of age had better prognoses than those over 50 (Epstein et al, 1972). A more recent study by Green, Byar and Lamberg, (1981) compared survival for three age groups: those younger than 40, those between 40-60, and those older than 60 years of age. Examination of survival curves for these three groups indicated that younger patients have better survival than older patients. Although this trend was consistently seen, pairwise comparisons were significant only in comparing those under age 40 with those over age 60 ($p=0.015$). The test for trend was significant at the $p=0.004$ level. However, because any cause of death was used as the end point of this particular analysis (rather than just CTCL-related deaths), no definite conclusion could be drawn that age was a prognostic factor for death specifically related to CTCL. In fact, the preliminary analysis presented earlier (Lamberg, Green, Byar et al, 1979) did not give a significant result when confined to CTCL deaths.

C. Race

This same study also compared the survival of black versus white patients with CTCL. Although the observed survival was better for whites than for blacks, the survival curves crossed twice and the difference between the two curves was not significant. The difference was further reduced when adjusted for TN stage, suggesting that blacks presented with somewhat more advanced disease. For this particular variable, it was also thought to be important to look at age-adjusted comparisons. When the survival of blacks was compared with that of whites, adjusting for age in the three categories outlined above, the difference was significant, showing better survival for whites ($p=0.03$). However, the authors concluded that the results of these three analyses did not allow a certain conclusion that whites have a better prognosis than blacks; furthermore, the small number of black patients under study limited the final conclusion. They suggested that the role of race could only be resolved by further collection of data.

D. Allergic history

Because of the hypothesis that CTCL may result from continuous antigenic stimulation, an allergic history was obtained from all patients registered in the study by Green, Byar, and Lamberg (1981). The specific conditions reported were: food allergy, drug allergy, contact dermatitis, hay fever, asthma, eczema, and hives. Patients were classified into two groups, one with no allergic history, and the other reporting one or more allergic conditions. Survival curves constructed for these two groups revealed a significantly better prognosis for those with a positive allergic history ($p=0.03$). After adjustment for TN stage the patients with an allergic history still showed a better prognosis, but the result was no longer statistically significant. The authors postulated that this was because patients with an allergic history presented at registration with lower TN stages; they also suggested the alternative explanation that the ability to mount an allergic reaction keeps the patient in a lower TN stage. This interesting observation suggests that the ability to make a immune response of any kind in CTCL may be important, and that further studies of the relationship between allergic phenomena and both stage of disease at presentation and prognosis should be carried out.

E. Cytomorphology

Recently, the degree of differentiation of atypical lymphoid cells was assessed in pretreatment cutaneous biopsy specimens from 248 patients with CTCL, and the findings were correlated with the subsequent therapeutic results (Vonderheid, Tam, Johnson, et al, 1981). Overall, patients with a predominance of cells with hyperchromatic nuclei (well-differentiated lymphoid cells) in cutaneous infiltrates responded better to treatment, with improved survival rates, than patients with infiltrates composed predominantly of cells with pale vesicular nuclei (poorly differentiated lymphoid cells). Infiltrates with a predominance of poorly differentiated lymphoid cells were observed primarily in

patients with advanced (tumor) stages of disease. Comparison of the therapeutic results achieved for the two cytomorphologic patterns in patients at comparable stages of advanced disease did not reveal significant differences, suggesting that the presence of large numbers of poorly differentiated cells did not have additional prognostic implications beyond those obtained from usual staging procedures. It must be pointed out, however, that these investigators did not analyze whether there was a difference in survival between patients with one or the other of these two cytomorphologic patterns who had only plaque-stage disease.

F. Other signs/symptoms

1. Pruritus

The MFCG study (Green, Byar, and Lamberg, 1981) showed that patients with pruritus at the time of registration had a significantly worse prognosis than patients without this symptom ($p=0.04$). However, when this comparison was adjusted for TN stage, most of the effect disappeared, indicating that this symptom was highly correlated with TN stage. Thus, this data would suggest that when the TN stage is known, the presence or absence of pruritus does not increase the knowledge of a given patient's prognosis.

2. Burning

The MFCG study also indicated that the symptom of burning at the time of registration into the study was associated with a poor prognosis. Again, however, after this comparison was adjusted for TN stage the result was no longer significant when all patients were considered. However, in those patients with TN stage III-IV, burning was still associated with a significantly worse prognosis ($p=0.02$).

3. Ulcers

This same study indicated that the presence of cutaneous ulcerations at registration was associated with a much poorer prognosis ($p < 0.0001$). Adjusting for TN stage revealed that most of this difference was accounted for by patients in TN stage I, even though ulcers were much more common in patients with higher TN stages; this suggests that ulcers are of greater prognostic significance when they occur in the absence of tumors or generalized erythroderma.

4. Alopecia

This same study indicated that hair loss at the time of registration was associated with a poorer survival ($p < 0.001$), but again the overall importance of this finding was markedly reduced (to $p=0.07$) when the analysis was adjusted for TN stage. Although alopecia was more commonly seen in patients with more advanced disease, it would appear that this physical sign might be of greater prognostic value in patients with lower TN stages.

5. Lymphopenia

Early data from the Stanford study suggested that patients with lymphopenia (< 1000/mm^3) had a poorer prognosis than those with normal lymphocyte counts (Fuks, Bagshaw, and Farber, 1973). Later studies from this same group, however, suggested that the previously observed differences were primarily related to the stage/extent of the cutaneous disease (Hoppe, Cox, Fuks, et al, 1979); i.e. this sign was not an independent variable separable from the TN stage.

G. Presence of abnormal cells by other than routine qualitative light microscopic criteria

In their recent staging evaluations of 49 patients with CTCL, Bunn and coworkers (1980) observed the following association of the extent/type of skin disease with the frequency of extracutaneous disease in the blood, peripheral lymph nodes, bone marrow, and viscera as assessed by routine qualitative light microscopy:

ASSOCIATION OF SKIN TYPE WITH FREQUENCY OF LIGHT MICROSCOPIC EVIDENCE OF EXTRACUTANEOUS DISEASE (PBL, LN, VISCERA)

Skin Involvement (N)	Frequency
Limited plaque (5)	0%
Generalized plaque (16)	18%
Cutaneous tumors (10)	40%
Erythroderma (18)	100%

[from Bunn et al. Ann Int Med 93:226, 1980]

In addition to these routine analyses, these investigators also looked at these same tissues with a variety of additional studies including electron microscopy, cytology of E-rosetting T cells, and cytogenetic analysis. As shown below, the incidence of "probable" extracutaneous disease in patients with skin stage T_1 or T_2 disease increased from 15% to 81%!

INCIDENCE OF EXTRACUTANEOUS DISEASE AT STAGING OF PATIENTS WITH LIMITED OR GENERALIZED PLAQUES OF CTCL

Staging Procedures	No. Positive/ No. Examined (%)
Routine light microscopy of PBL, LN, BM	3/21 (15%)
Special studies (EM and cytogenetics) of PBL, LN, BM	17/21 (81%)

[from Bunn et al: Ann Int Med 93:226, 1980]

These results strongly suggest that by the time the diagnosis of CTCL is made, malignant cells are not confined to the skin alone, but in the majority of cases have already "spread" to extracutaneous sites. These extracutaneous sites may contain only relatively small numbers of abnormal cells, and hence the fact that such early involvement is almost always asymptomatic is not surprising. These findings may also explain why treatments directed principally at the skin disease alone appear to be curative in only a small percentage (10-20%) of cases (see p 55).

Whether or not the additional 14 patients with probable early extracutaneous disease uncovered by these special studies have a poorer prognosis than patients in whom no abnormalities were detected has yet to be determined in this particular study. However, there is suggestive evidence that this will be the case. All the patients in this study were treated in a similar manner, utilizing a combined modality therapy schedule of whole body electron beam irradiation followed by combination chemotherapy (Bunn, Fischmann, Schechter, et al, 1979). All of the patients without any detectable extracutaneous abnormality achieved a complete remission, while only 40% of the patients in the group with abnormal special studies had a complete response ($p < 0.05$). While a longer follow up period is clearly necessary before any definitive statement can be made, it is worth reiterating the observations (see p) showing that the failure to achieve a complete remission with initial therapy is associated with poorer prognosis.

It must be pointed out that, with the exception of cytogenetic analysis (which revealed abnormalities in 62% of cases read as normal by routine analysis), the "special" studies employed in this study were based on qualitative or at best semi-quantitative criteria. In two more recent studies, attempts were made to use the NIH group's criteria for analyzing lymph node biopsies (based on the presence of "small clusters of atypical cells") to 1) subclassify CTCL patients to see if the presence of such features correlated with poorer survival and 2) compare the "dermatopathic" nodes of CTCL patients with "dermatopathic" nodes of patients with a variety of benign skin diseases (Colby et al, 1981; Burke and Colby, 1981). In the first study, no significant differences in survival were found among the various grades of dermatopathic lymphadenopathy, and in the second study small clusters of aytpical lymphocytes were found to be equally as frequently among dermatopathic nodes of both CTCL and non-CTCL patients, without any statistically significant differences in quantitation or distribution. These studies underscore the current difficulties in confidently distinguishing by routine qualitative light or electron microscopy small numbers of atypical malignant T cells from stimulated normal T cells. These difficulties extend both to the confident early diagnosis of CTCL in the skin in patients with clinically and pathologically nonspecific (i.e. "suspicious but not diagnostic") lesions, and to the confident diagnosis of early extracutaneous disease in patients with diagnostic skin lesions. Clendenning and Rappaport (1979) neatly summarized this dilemma in their Report of the Committee on Pathology of Cutaneous T Cell Lymphoma: "The pathology of T cell lymphoma remains a difficult and problematic field in which reasonable experts may have profound differences..... This state of affairs may be distasteful to the purist and more or less disturbing to the scientist, but it reflects reality

and will not change until a definitive marker of the disease is found". The possibility that such markers may be available is discussed below.

1. Quantitative DNA analysis

Cytogenetic analysis, Feulgen microdensitometry and, more recently, flow cytometry (FCM) have been used for quantitative DNA analysis of normal and malignant human cells. In some lymphoma/leukemias, including CTCL, cytogenetic analysis provides prognostic information; abnormal cytogenetic profiles were associated with transformation in the clinical course to a more aggressive disease with a poorer prognosis (van Vloten et al,1980). Cytogenetic analysis, however, is limited by the requirements for single cell suspensions of living cells with a relatively high proliferative rate; furthermore, relatively few cells can be conveniently analyzed. DNA cytophotometry and FCM, relatively newer techniques, are based on the intensity of nuclear staining with a DNA stain in order to quantitate the DNA content of a cell, do not have the same limitations.

Recently, van Vloten and coworkers (1979) utilized Feulgen-DNA cytophotometry of lymph node imprints from patients with mycosis fungoides in an attempt to obtain objective criteria for the early diagnosis of nodal involvement in patients with CTCL. They first established criteria which allowed them to confidently discriminate between tissues clearly invaded by malignant T cells and those involved with clearly benign processes. Measurements of cell imprints from control tissues showed diploid and tetraploid DNA values. Hyperdiploid DNA (2N-4N) values present in these tissues were regarded as representing proliferating cells in S phase. On the other hand, tissues from patients with known CTCL demonstrated a significant (> 5% of cells) aneuploidy and polyploidy; the DNA values in these cases ranged from the hypodiploid to beyond the octoploid region. After establishing criteria for distinguishing benign from malignant lymphoid cells, they then examined the lymph nodes of 22 patients with CTCL which had originally been read as dermatopathic lymphadenopathy by conventional criteria. They subdivided the nodes into two groups - ones that looked like nodes from patients with nonmalignant skin diseases and whose cells had a normal DNA content, and another group with significant numbers of cells with an abnormal DNA content. After subclassifying the nodes into these two groups, the patients' clinical responses to treatment were followed. The next table shows that the response to treatment and survival of patients whose nodes showed no abnormalities was substantially better than that of patients whose nodes contained cells with an abnormal DNA content.

DNA CYTOPHOTOMETRY TO SUBCLASSIFY CTCL
PATIENTS WITH "DERMATOPATHIC" LYMPH NODES
[Van Volten et al. J Invest Dermatol 73:275, 1979]

CLASS I ("Normal" Dermatopathic Node)
11 patients
10 alive 1/2-5 years later (9% mortality)
10 free of disease (90%)

CLASS II ("Abnormal" Dermatopathic Node)
11 patients
7 alive 1/2-4 years alter (85% mortality)
2 free of disease (18%)

These results suggest that the continued application of more sophisticated examinations to extracutaneous tissues of patients with CTCL will enable us to select a subset of patients with early extracutaneous involvement whose prognoses with current treatment must remain more guarded. The use of FCM analysis of DNA content (which has the advantage of allowing the analysis of a much larger number of cells) has also been recently utilized in the study of a large number of patients with CTCL (Bunn, Whang-Peng, Carney, et al, 1980). Of 14 patients with normal FCM, 10 (70%) were in complete remission up to 30 months following treatment, and there had been no deaths. On the other hand, of the 24 patients with abnormal FCM profiles, only 8 (33%) achieved a complete remission and 4 patients (17%) had died. An important question not yet answered by this study however, is whether the presence of abnormal DNA content at presentation, in the presence of nondiagnostic light microscopic examinations of blood or lymph nodes, correlates with a poorer survival.

2. Quantitative Electron Microscopic Cytomorphometry

This review has already briefly discussed the difficulties in confidently distinguishing the hyperconvoluted malignant lymphocyte nucleus in patients with CTCL from lymphocytes with indented nuclear envelopes in a variety of other benign disorders (see p 4). As a result, the significance of any relationship between nuclear convolution and CTCL has been called into question. In an effort to improve the electron microscopic criteria for lymphocyte atypia, several laboratories have been utilizing quantitative electron microscopic measurements on lymphocyte nuclei to describe both their range of size and degree of nuclear envelope convolution, in hopes of determining which criteria can best discriminate CTCL from benign disorders (McNutt et al, 1981; van der Loo et al, 1981). Both groups quantitate the degree of nuclear convolution by calculating a nuclear contour index (NCI) by dividing the perimeter of the nuclear envelope by the square root of the area. The minimum NCI is that of a circle, with a value of 3.54. Larger NCI values indicate increased degrees of convolution of the nuclear envelope. Utilizing NCI measurements alone to differentiate benign skin lymphoid infiltrates from the infiltrates in patients with CTCL proved to be considerably better than the usual qualitative electron microscopic diagnostic assessment in reducing false-positive diagnoses of CTCL. (Low false-positive diagnosis of CTCL is considered to be of fundamental importance, since the number of patients who have benign skin infiltrates which qualitatively can mimic CTCL is very much larger than the number of actual CTCL patients in the general population). However, using NCI criteria alone, both groups of investigators were disturbed by the number of false-negatives in cases of confirmed CTCL. Both groups of investigators then utilized relatively sophisticated statistical analysis of their data to search for additional ways of using information about e.g. nuclear size, nuclear profile area, and the proportion of cells having NCI values greater than a given number, in order to generate a number of different variables. These variables were then submitted to stepwise linear discriminate analysis, which selected variables one at a time for discriminating CTCL until no substantial further improvement could be

achieved. Although the variables ultimately selected by these two groups of investigators were slightly different, they were both able to achieve a remarkable capacity to discriminate with a very high probability between cells from skin biopsies of patients with known CTCL from cells from patients with clearly benign skin disease. The Dutch investigators then applied these criteria to the examination of the skin biopsies of 29 patients in whom the diagnosis of CTCL was suspected, but had not either been unanimously agreed on either by clinicians or pathologists. By their previously established criteria, 20 biopsies were classified as malignant and 9 as benign. During the follow-up period of up to 5 years, of the 20 classified as malignant, 17 developed definite CTCL, and 1 patient was still suspected of having CTCL. Of the 9 patients classifed as benign, on follow up 8 proved to have benign skin diseases and only 1 developed clear-cut CTCL.

3. Abnormal Cell Surface Markers

The possibility that malignant cells may express antigens or other markers on their membrane which are not expressed by the normal cells from which the tumor is presumably derived (i.e. tumor specific antigens), has attracted the attention of tumor immunologists for many years. With the development of the technology of raising monoclonal antibodies to cell surface antigens, the interest in this particular sphere has increased even further. Very recently, Edelson and coworkers have reported preliminary results which suggest that they have produced monoclonal antibodies directed against antigens expressed on the surface of malignant T cells which are not expressed on normal T cells (Berger, Takezaki, De Pietro, et al, 1981). In this study splenic B cells from mice immunized with CTCL lymphocytes were hybridized with a mouse myeloma line and 4,000 hybridoma clones were screened for reactivity with CTCL cells as well as with normal peripheral blood mononuclear cells and a variety of B and T cell lines. Two monoclonal antibodies were identified which were reactive with antigens present on the surface of CTCL cells but absent from the surface of normal peripheral blood mononuclear cells. One of the antibodies was found to react with the neoplastic T cells from each of six CTCL patients tested. Further investigation revealed that this monoclonal antibody did react with an antigen expressed on an Epstein-Barr virus-transformed B cell line. These preliminary results indicate that CTCL cells express membrane antigens present on certain transformed cell lines but not on normal blood mononuclear cells. If these results stand the test of further investigation, the obvious possibility would exists for trying to use such antibodies, along with a technique such as immunofluorescence, to detect very small numbers of nevertheless clearly malignant cells in both skin and in extracutaneous tissues.

VII. Minimal Staging Workup for Patient With CTCL

In light of the major prognostic features characterized thus far in large series of patients with CTCL, the following list represents a reasonable minimal staging workup for a patient with CTCL. It does not include several of the special procedures currently under investigation

in many centers which may ultimately prove capable of providing additional important prognostic information.

MINIMAL STAGING WORKUP OF CTCL PATIENT

1. Multiple skin biopsies (1-μ plastic-embedded sections preferable)
2. Complete history and physical exam, including whole body mapping of skin lesions
3. Chest x-ray, EKG
4. CBC, absolute lymphocyte count, and % of atypical convoluted lymphocytes
5. Serum chemistries, including liver and renal function tests, uric acid (not known to be of prognostic significance)
6. Lymph node biopsy of palpable lymph node (preferably not inguinal if other sites available)
7. Further evaluation of specific organ systems when involvement is suspected or if additional information is desired prior to initiating treatment (e.g. LAG, BM bx, liver bx)

VIII. Treatment

A. Modalities Consistently Able to Effect Clinical Regression

1. Topical Chemotherapy

Haserick and coworkers (1959) first reported regression of skin lesions after topical application of mechlorethamine (nitrogen mustard, HN_2). Since that time there have been a number of published trials employing whole-body application of this agent; the largest series of patients followed for the longest period of time have come from the investigators at Temple University (Vonderheid, Van Scott, Wallner, et al, 1979; Vonderheid, Van Scott, Johnson, et al, 1977). The reader is referred to these publications for the specific details for using this agent. As with virtually all forms of topical therapy, HN_2 seems to be most useful in patients with early cutaneous stages; in patients with more advanced disease (skin stage T_3 or T_4), the response appears to be much more variable. The overall complete remission rate is in the range of 65%; 94% of T_1 and 60% of T_4 patients achieved complete responses. The overall survival following HN_2 was good: 68% of patients were alive at 5 years, and the median survival was about 8 years. However, relapses tended to occur steadily over the years, and at 3 years only 13% of patients were relapse free in spite of continuing maintenance HN_2 during that time. Furthermore, these investigators reported preliminary

results which showed that patients who have been maintained in apparent complete remission for a minimum of 3 years while on continuous maintenance treatment are still at substantial risk for developing recurrent disease when the treatment is discontinued; 32% (5 of 16) of such patients relapsed within 6 months of discontinuing maintenance therapy.

The principal advantage of the use of this modality is its convenience; patients can be easily instructed in the application of the HN_2, and usually require little or no assistance in this process. Another potential advantage of HN_2 is its ability to affect disease in sites such as the intertriginous areas not readily accessible to electron beam irradiation or photochemotherapy (see also below).

The primary complication from topical HN_2 is the development of allergic contact dermatitis, which has been seen in up to 40% of patients. While such allergic reactions most commonly are seen early after initiating treatment, they can occur at any time. Patients with earlier stages of disease are more likely to become sensitized (perhaps related to a general state of immunosuppression in patients with advanced disease); this has partially limited the utility of this topical therapy in the group of patients most likely to benefit from sustained treatment. For these patients topical desensitization beginning with very dilute solutions of HN_2, has been used with some success (Constantine et al, 1975). Other side effects include irritant contact dermatitis, generalized or localized hyperpigmentation, and most importantly, an increased incidence of malignant epithelial neoplasms. Du Vivier and coworkers (1978) reported epithelial cancers in 10.5% of 202 patients; squamous cell carcinomas appeared in areas not exposed to sunlight in two patients. This overall incidence is considerably higher than might be expected in the general population. Kravitz and McDonald (1978) also reported squamous cell carcinomas in nonexposed areas in two patients treated with HN_2; metastases to regional nodes occurred in one patient.

For patients sensitive to HN_2, topical treatment with 0.1% carmustine (BCNU) solutions may be tried since this agent does not cross-react with nitrogen mustard (Zackheim et al,1979). Nineteen of 24 patients with plaque stage disease were kept under "satisfactory control" for median follow up periods of 9-22 months. Results in 4 patients with Sezary syndrome were unsatisfactory. With single-course doses of up to 1,260 mg, reversible bone marrow depression, severe irritant dermatitis, and telangiectasia occurred in about 1/3 of the patients. Thus, the influence on cutaneous CTCL is probably similar to HN_2 but the potential for local and systemic toxicity appears to be greater because of better penetration. The long-term benefits of topical BCNU have not been established.

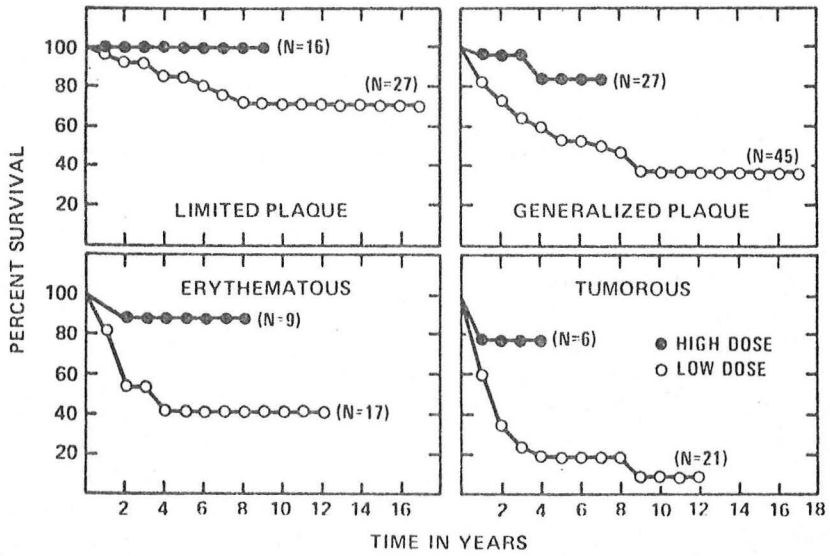
2. Superficial Radiation Therapy

Localized lesions of CTCL almost always respond to relatively low doses of superficial x-ray (i.e. 150-300 rads of superficial x-ray (80-140 kv) administered 2 or 3 times weekly to a total dose of

approximately 1,000 rads). However, only limited areas can be treated in this way because of the risk of systemic toxicity. Furthermore, given the mulifocal nature of the lesions in most patients with CTCL, a conservative approach consisting of radiotherapy only for problematic lesions would be expected to have little influence on the course of the disease. Nevertheless, the use of localized orthovoltage radiotherapy as an adjunct for localized nodules or tumors in a patient simultaneously receiving some other form of treatment is a reasonable and widely utilized modality.

Trump and coworkers (1953) first used high-energy electrons to treat disseminated mycosis fungoides. Electrons with energies of 3-4 MeV have limited penetration through the skin (50% depth-dose, approximately 1 cm) so that direct toxicity to internal organs can be largely avoided. Fuks and coworkers at Stanford have refined the techniques for applying a uniform dose to the entire skin surface (Hoppe, Fuks, Bagshaw, 1979) and have reported long-term follow-up on patients treated in this manner (Hoppe, Cox, Fuks, et al, 1979). They observed a complete remission in 84% of their patients; the median duration of these remissions was 16 months. The 5-year actuarial survival was 65%, and the estimated median survival was approximately 9 years. Overall, about 20% of patients remained relapse-free at 3 years; few patients have been reported to relapse after 3 years. Virtually all patients with relapse-free survival in excess of 3 years had T_1 or T_2 skin disease without tumors, lymphadenopathy, or obvious visceral involvement; about 40% of these early stage patients have long-term, relapse-free survival after electron beam therapy. However, equally impressive therapeutic results generally have not been achieved at other centers (van Vloten et al, 1977; Meyler, Blumberg, Purser, 1978).

The total dose of electron irradiation is a critical factor in this treatment modality. Complete response rates, relapse-free survival intervals, and actuarial survival are superior for patients receiving greater than 2,500 rads compared to patients receiving less than 2,500 rads (Hoppe, Cox, Fuks, 1979).



Actuarial analysis (Berkson–Gage)[2] of survival of patients following the first course of electron beam therapy as related to initial dose. Low dose = 800–2499 rad; high dose = 2500–3600 rad.

At the present time it is not known whether the actual technique of administering the electrons and the dose fractionation schedule are equally important. At Stanford patients are treated with a dual, six-field technique; a complete six-field treatment cycle requires 2 days, and generally patients receive 2 treatment cycles each week. The tolerance of individual patients for electron beam radiation varies, but total doses of 3,000-3,600 rads in 8-9 weeks (400 rads/week) are tolerated by most patients (see also below). The Sloan-Kettering group has reported that 400 rads can be given once weekly with good response rates (Nisce and Safai, 1979).

The advantages of whole body electron beam therapy are: 1) it produces a high frequency of initial complete responses some of which appear to be long lasting and require no maintenance treatment; and 2) these responses are achieved without undue systemic toxicity. The major disadvantages of this treatment are its limited availability and skin toxicity. Whole body electron beam therapy requires meticulous attention to dosimetry and other physical details, and thus for maximum success this technique requires extensive training and experience as well as support by trained radiation-physics personnel. The result of these requirements is that electron beam therapy is not only expensive, but is available at only a limited number of centers. The manifestations of skin toxicity include: erythema; edema of hands, legs, and ankles; occasional blistering reactions; temporary alopecia and nail loss (unless the nails are shielded with lead); temporary loss of sweating; and occasionally, gynecomastia. The most common long-term side effects include xerosis, premature aging of the skin, with superficial atrophy and telangiectasias (Price, 1978). Secondary squamous cell cacinomas have been reported (Volden and Larsen, 1977). The known long-term cutaneous side effects of ionizing radiation restrict repeated use of whole body electron beam therapy in the treatment of CTCL; this is particularly a problem in those cases treated with relatively high doses (3,000-3,600 rads) during a single course of treatment. The dilemma confronting the radiotherapist is thus whether to use intensive whole body electron beam therapy in the hopes of "curing" the disease (realizing that repeated treatment may not be possible), versus using lower doses of radiation for palliation (realizing that retreatment is possible).

Proctor and coworkers (1978) recently reported several patients in which subcutaneous nodules with the histologic appearance of CTCL appeared after whole body electron beam therapy; such tumors may have originated from deep foci not reached by the radiation.

3. Methoxsalen Photochemotherapy (PUVA)

The rationale for the use of oral 8-methoxypsoralen followed by exposure to titrated doses of long-wave (320-400 nm) ultraviolet light is based on the capacity of photoexcited psoralens to bind with pyrimidine bases and inhibit nucleic acid synthesis (reviewed in Parrish, LeVine and Fitzpatrick, 1980). The early results of treatment with this modality in the United States have been discussed by Minna, Roenigk, and Glatstein (1979); more recently, the experience in Great

Britian has been published (Briffa et al, 1980). Experience to date indicates that approximately 80% of patients will initially clear with treatment, primarily those patients with early/limited skin disease. Patients with skin tumors or erythroderma are less likely to respond completely to treatment. None of the clinical trials are of sufficient duration to accurately estimate median duration of remission or median survival of patients treated with PUVA.

The principal advantages of topical therapy with PUVA include its availability and relatively low acute toxicity (which includes mild nausea, generalized pruritus and sunburn-like changes). Patients who have failed topical HN_2 or electron beam therapy may still have high response rates to PUVA therapy. The prinicapal disadvantages of this modality include the present uncertainty of both its long-term efficacy and long-term side effects. It is apparent that maintenance therapy is required in virtually all patients who achieve an initial complete response; cessation of treatment has almost invariably been followed by recurrence of skin lesions. Furthermore, this particular modality may have more limited penetration than either HN_2 or electron beam therapy; Lowe and coworkers (1979) reported several patients in whom apparent clinical remission was associated with persistent, deep dermal, atypical cellular infiltrates. This may be the reason for the observed high relapse rate after stopping maintenance PUVA treatment. Furthermore, there is increasing evidence that long-term PUVA therapy accelerates actinic damage and photocarcinogenesis (Stern et al, 1979; Verdich, 1979).

4. Systemic Chemotherapy

a. Single Agent

A large number of systemic drugs when administered alone have been reported to produce beneficial, although in the overwhelming majority of cases, temporary responses in patients with CTCL. Reponse rates (both complete and partial remissions) between 40-100% have been reported. Response durations have not always been reported, but appear to vary from 1-14 months. Methotrexate has been the most extensively studied single-agent antimetabolite. McDonald and Bertino (1979) recently reported that approximately 2/3 of their patients achieved a complete remission (median duration, 22 months) following "high-dose" methotrexate with citrovorum rescue. Prednisone has been reported to induce partial remissions in up to 50% of patients; however, there are no reported complete remissions and remission durations have been short. The first table on the next page summarizes the data relating to single agent chemotherapy taken from a recent review of the literature by Broder and Bunn (1980). The references listed by number in the table below are from that article.

Single-Agent Chemotherapy in Cutaneous T-Cell Lymphomas

Agent	Reference	No. of Patients	CR (%)	CR + PR (%)	Duration of Response (mo)	
					Median	Range
Mechlorethamine (nitrogen mustard)	4, 62, 63	86	15	64	NR	1–12+
Cyclophosphamide	4, 64–68	86	NR	67	NR	3–14+
Chlorambucil	4, 69, 70	69	NR	57	NR	NR
BCNU	4, 65, 67	16	NR	63	NR	NR
Triethylenemelamine	4, 71	13	NR	31	NR	NR
Methotrexate	4, 72, 73	91	20	68	6	1.5–26.5
"High Dose" methotrexate	74	11	64	100	22	3–78
Azarabine	75	16	54	88	2–3	0.5–43
Bleomycin	76–81	32	22	62	3	1–8+
Doxorubicin (adriamycin)	82	13	23	62	5	3–10+
Streptonigrin	73, 83, 84	11	0	82	3	1.5–9+
Actinomycin D	4, 73	13	0	38	NR	NR
Vincristine/vinblastine	4, 73	27	NR	41	3	1–11
VP-16	85, 86	15	27	67	4	2–6+
Corticosteroids	4, 5, 73	50	NR	50	NR	0.5–24
Total		549				
Estimate from total			20%–25%	64%	<6	0.5–78

Abbreviations: CR—complete response; PR—partial response; NR—not reported.

[from Broder and Bunn, Seminars in Oncol 7:319, 1980]

Combination Chemotherapy in Cutaneous T-Cell Lymphomas

Combination	Reference	No. of Patients	CR (%)	CR + PR (%)	Duration of Response (mo)	
					Median	Range
CBL + PRED	85, 88	21	14	57	NR	NR
CTX + VP 16	89	4	25	75	6	NR
BLEO + MTX	81	10	10	90	6	NR
CVP-B	90	12	17	92	11.5	1–18+
CVP	91, 92	9	44	89	16	4–25+
CHOP/HOP	90	12	42	100	5	1.5–17
Total		68				
Estimate from total			25	81	5–16	1–25+

Abbreviations: CBL—chlorambucil; PRED—prednisone; CTX—cyclophosphamide; BLEO—bleomycin; MTX—methotrexate; CVP-B—cyclophosphamide, vincristine, prednisone, bleomycin; CVP—cyclophosphamide, vincristine, prednisone; CHOP—cyclophosphamide, doxorubicin, vincristine, prednisone; HOP—doxorubicin, vincristine, prednisone; CR—complete response; PR—partial response; NR—not reported.

[from Broder and Bunn, Seminars in Oncol 7:320, 1980]

In summary, at the present time there is no data to indicate that single-agent chemotherapy has "cured" any patient with CTCL. Furthermore, there is insufficient data to definitively say that any of these agents prolong survival (i.e. no appropriate control group).

b. Combination Chemotherapy

Compared to the extensive experience utilizing multiple-agent chemotherapy in other non-Hodgkin's lymphoma/leukemias, there is relatively little information on the use of this modality in patients with CTCL. Published data is limited to approximately 70 total patients; as can been seen from the second table on the preceding page, most individual reports have less than 15 patients.

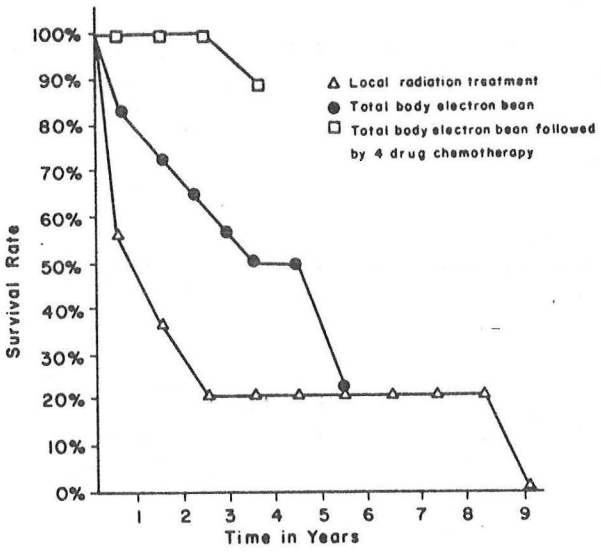
It would appear that drug combinations produce very high objective response rates (perhaps slightly higher than with single-agent chemotherapy), and complete remissions in approximately 1/4 of the cases. Unfortunately, the median duration of these remissions is only about 1 year, and appears to be shorter than the duration of remissions produced by the same combinations of drugs in some other non-Hodgkin's lymphomas. While reports of combination chemotherapy have essentially all been in patients with advanced disease, no disease-free remissions in excess of 3 years have been reported.

At the present time, therefore, there is no evidence that any patient with CTCL has been "cured" by chemotherapy alone. Although the complete and objective response rates with combination chemotherapy appear to be slightly higher than with single agents, the superiority of combination chemotherapy has not been established conclusively; there have been no published reports of randomized trials comparing single agents with combination chemotherapy. In this regard, recent randomized data from other forms of non-Hodgkin's lymphoma with "favorable histology" may be relevant; a review of the recent literature (Portlock, 1980) suggests that in terms of response rate, remission duration, and survival, combination chemotherapy may not be superior to single alkylating agent therapy.

5. Combined Modality Therapy

There is even more limited data on the efficacy of the combination of treatment directed principally at the skin plus systemic therapy in patients with either limited or advanced CTCL. Electron beam therapy followed by maintenance topical HN_2 is being investigated in a number of centers. The Stanford group has published an early trial comparing electron beam therapy alone with the combined modalities of electron beam plus topical HN_2 in patients with predominately cutaneous plaque disease (Price, Hoppe, Constantine et al, 1977). Although there appears to be a trend toward superior survival in the combined group, the difference to date is not statistically significant. Thus, while there might be a delayed in relapse as a result of maintenance HN_2 treatment, further observation is clearly necessary to validate this suggestion.

Electron beam therapy plus systemic chemotherapy has been the subject of several nonradomized trials, predominately in patients with extensive disease (Bunn, Fischmann, Schecter et al, 1979; Minna, Roenigt, and Glatstein, 1979; Griem et al, 1979). The objective response rate (98%) and complete response rate (59%) are higher than those reported for other forms of therapy in patients with comparable extent of disease. The long disease-free survivals and overall survival rates in CTCL patients treated with electron beam and combination chemotherapy (HN_2 or cyclophosphamide, vincristine, procarbazine) at the University of Chicago are noteworthy (Griem et al, 1979). The figure below suggests a striking superiority of combined modality therapy compared with electron beam treatment alone.



Griem, et al.
Cancer Treat Rep 63:656, 1979

Careful analysis of patient selection in this study uncovers a potential bias which confounds interpreting the above data. Six of 7 (86%) of CTCL patients with skin tumors and no evidence of extracutaneous disease received combined modality therapy, whereas none of the 5 patients with skin tumors and documented extracutaneous disease received the more intensive treatment. Thus, it would appear that in at least this cohort of patients, those with less extensive disease received more intensive treatment than those with more extensive disease.

The response to treatment of a more homogeneous group of CTCL patients without obvious clinical and pathological extracutaneous disease followed at the University of Washington through August, 1980, is shown below.

RESPONSE TO RX OF PATIENTS WITH DISEASE
"APPARENTLY" CONFINED TO THE SKIN (STAGES I-II)
(University of Washington, August, 1980)

Treatment	n	Mean Follow-up	Number with "Progressive" Disease (%)
Electron beam alone	14	32 mo.	4 (29%)
Electron beam + combined chemo Rx	12	25 mo.	0 (0)

During the preceding 5 years, 14 patients were treated with electron beam alone (3,000 rads) as their initial form of therapy. Twelve other patients received within 2 months of completing a similar course of electron beam therapy, several monthly cycles (up to 6) of combination chemotherapy, most commonly cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin). Mean follow-up time was comparable in the two treatment groups (32 months and 25 months respectively). "Progressive" disease was defined as the presence of more extensive cutaneous disease (or the development of documented extracutaneous disease) at the end of the study period than was present immediately prior to treatment. Of the 14 patients treated with the electron beam alone, 4 (29%) showed evidence of disease progression and 3 of these patients died with systemic lymphoma. Only 1 of the 14 (7%) remained free of disease. On the other hand, none of the 12 patients treated with combined modality therapy had more extensive disease at the end of the study period than they had prior to initiation of treatment, and 50% have remained disease free from 0-31 months after cessation of all therapy. While this data is encouraging, and suggests the superiority of intensive combined modality therapy when compared to less intensive treatment, it is clear that larger numbers of patients will have to be followed for a more extended period before any definitive conclusions can be reached concerning both its efficacy and safety. On the other hand, it is equally clear that combined modality therapy has not associated with excessive early morbidity. Equally as important, neither this study nor any of the published data (reviewed in Minna, Roenigk, and Glatstein, 1979) have provided any evidence that the rate of disease progression has been accelerated by the use of combined modality therapy.

B. Other Investigational Therapies

1. Systemic Radiation Therapy

Investigators at both Stanford University and Temple University have recently initiated limited, non-randomized trials using high-energy (supervoltage) photon irradiation as an adjunct to whole body electron beam therapy in some patients with extracutaneous CTCL apparently confined to lymph node-bearing areas. Total lymphoid radiation has been shown to be a safe and effective treatment for Hodgkin's disease and other malignant lymphomas. There have not yet been any reports on its therapeutic effects in CTCL, and therefore it is impossible to assess the potential value of this modality. Another treatment which has been recently suggested for disseminated extracutaneous involvement is fractionated total-body radiation with 4-6 MeV photons (Hoppe, Fuks, and Bagshaw, 1977). This technique has been employed in the management of patients with generalized nodular lymphomas and CLL (Chaffey et al, 1977; Johnson and Ruhl, 1976). No data is available on the efficacy of this particular form of treatment in patients with CTCL. Another modality with therapeutic potential in CTCL is sequential half-body radiation, reported as an effective palliative treatment for metastatic disease (Fitzpatrick and Rider, 1976). In this technique, 1/2 of the body is treated with a single dose of 600-1,000 rads given with high-energy photons followed by a similar dose to the other half of the body 3-6 weeks later when hematologic recovery has occurred. In view of the known radio-sensitivity of CTCL lesions to high-dose single-fractionation radiation, this approach might seem ideal for patients with extensive cutaneous and extracutaneous involvement; its use in CTCL has not yet been reported.

2. Leukapheresis

Selected patients with leukemic variants of CTCL whose disease is characterized by marked lymphocytosis (greater than 30,000/mm^3), limited bone marrow involvement, and low rates of leukemic-cell renewal, have been symptomatically improved and maintained in a clinically comfortable state for up to 3 years by this treatment alone (Edelson, 1977; Edelson et al, 1974). However, it is clear that leukapheresis by itself slows, but does not prevent eventual death from the leukemic phase of CTCL. Futhermore, other investigators have not had as much success with this particular modality (Safai, Reich and Good, 1976).

3. Anti-Thymocyte Globulin

A beneficial response was obtained in 3 of 4 patients with CTCL treated with anti-thymocyte globulin by Edelson, Raafat, Berger, et al (1979). However, beneficial responses were of short duration. One of the major limitations of the use of ATG-serotherapy in the treatment of CTCL has been the justified fear of administering large amounts of foreign serum protein to patients.

4. Monoclonal Antibody Immunotherapy

The hybridoma technique developed by Kohler and Milstein provides a method for the production of virtually unlimited amounts of pure monoclonal antibodies (Kohler and Milstein, 1975). Using this technique it is possible to produce antibodies of a defined class, avidity, and specificity. Bernstein, Tam, and Nowinski (1980) have recently shown the utility of monoclonal antibodies in the treatment of a mouse lymphoma. These investigators were able to demonstrate that a monoclonal antibodies directed against a normal T-cell differentiation antigen (Thy-1.1) could inhibit the growth of a transplantable mouse lymphoma that expressed high levels of this antigen. In some instances, these antibodies were capable of curing mice with tumor transplant doses 100-fold greater than the LD_{100}. The results of the first cautious use of mouse monoclonal antibodies in patients with lymphoid tumors, including CTCL, have been recently reported. Investigators at Stanford University have used an antibody to the human T-cell antigen Leu-1 to treat one patient with adult T cell leukemia (Miller, Maloney, McKillop, and Levy, 1981) and another with CTCL (Miller and Levy, 1981). In both cases the monoclonal antibody was given to patients with advanced disease unresponsive to other forms of therapy. The CTCL patient tolerated 17 treatment courses over 10 weeks without symptoms of toxicity. Each course of treatment caused a reduction in circulating T cells which reached a stable level after 2 weeks of therapy. Serotherapy produced a striking clinical response in the skin, lymph nodes, and blood, but complete remission was not achieved. After approximately two months of a stable partial remission, increasing inguinal adenopathy became apparent; progressive enlargment of these lymph nodes was not controlled by increasing the amount of monoclonal antibody. At this point monoclonal antibody immunotherapy was discontinued. Although the patients skin and peripheral blood disease remained stable, his progressive lymphadenopathy was unresponsive to radiotherapy and he died four months after the initiation of antibody therapy with massive lymphadenopathy, but with skin and peripheral blood disease still in partial remission.

Ritz and coworkers (1981) have recently tested the efficacy of monoclonal antibody serotherapy in four patients with acute lymphoblastic leukemia who had relapsed while receiving chemotherapeutic agents. Each patient received multiple intravenous infusions of monoclonal antibodies specific for the common acute leukemia antigen (CALLA). In the three patients with circulating leukemic cells, there was a rapid decrease in circulating blasts that began immediately after antibody infusion, but not all leukemic cells were cleared, and the remaining cells appeared to be resistant to further serotherapy.

The evidence of toxicity from monoclonal antibody serotherapy was reassuringly slight in all of the above studies; low-grade fever appeared in two of the Boston patients and the minor renal and hepatic dysfunction seen in one Stanford patient was transient and presumed to be due to immune complex formation during his weak and clinically insignificant IgM response to mouse Ig. Both groups found evidence of antigenic modulation *in vivo*, i.e. the complete or partial disappearance of the target antigen on the remaining tumor cells at a time when antibody was present in the patient's serum. *In vitro* studies confirmed that modulation made the cells resistant to the effects of the antibody.

The Stanford group also noted an increase in the level of circulating Leu-1 antigen in their patients, presumably as a consequence of tumor cell destruction. How the tumor cells were destroyed in these patients is unknown, but both the Stanford and Boston groups favor a cellular rather than a complement-mediated mechanism. Both agree that antigenic modulation contributed at least partly to the failure of the antibody to eliminate the tumor burden completely, and that this phenomenon is thus the most pressing problem to be overcome in the therapeutic use of these mouse antibodies. The Stanford group has pointed out the value of monitoring antigen release so that antibody administration can be timed to avoid the formation of circulating immune complexes. Several centers are currently designing monoclonal antibody serotherapy protocols which will utilize several different antibodies directed at distinct antigenic determinants expressed on the surface of the malignant cells, in the hope that the problem of antigenic modulation can be circumvented.

The above studies offer the promising hope of another alternative to systemic chemo- or radiotherapy in patients with advanced CTCL. Obviously the specificity of the antibodies utilized may ultimately dictate their usefulness. As long as the antibodies available for use are directed against antigens expressed not only on the surface of the malignant cells but also on the surface of at least some normal lymphoid cells, the possibility of nonspecific immunosuppression remains a potential problem. If attempts such as those described from Edelson's lab (Berger, Takezaki, De Pietro, et al, 1981) in raising monoclonal antibodies to determinants expressed on malignant T cells but not on normal lymphoid cells prove ultimately successful, the obvious possibility exists for utilizing such antibodies in the serotheraphy of CTCL.

C. Overview of the Efficacy of Therapies Directed Principally at the Skin

At this point several generalizations concerning the efficacy of any of the three major therapies directed principally at cutaneous disease in patients with CTCL seem warranted. First, with either HN_2, electron beam, or PUVA the chances of getting a continuous complete remission are inversely correlated with the extent/type of skin disease. The greater the extent of disease as determined by the staging procedures previously discussed, the less the chance that any of these therapies will result in complete disappearance of skin disease. The following table illustrates this point for electron beam therapy (Hoppe et al, 1979); however, qualitatively similar results have been seen with either nitrogen mustard or PUVA.

COMPLETE CLINICAL REMISSION RATE FOLLOWING INITIAL ELECTRON BEAM RX IS INVERSELY CORRELATED WITH EXTENT/TYPE OF DISEASE

Skin Lesions	% Complete Remission
Limited plaque (T_1)	96
Gen'lized plaque (T_2)	87
Tumors (T_3)	72
Erythroderma (T_4)	71

For any given stage of disease, if the initial therapy brings about a complete clinical remission, that patient's chances for survival are better than the patient in whom that first treatment only brings about a partial response. Data illustrating this point for patients with generalized plaque disease (T_2) who received electron beam therapy has been presented on page 32. While it seems intuitively obvious that patients whose cutaneous malignant disease disappears will do better than patients disease does not disappear, the corollary is perhaps not so obvious. That is, patients who relapse after completely responding to one modality, as well as patients who fail to completely respond to a given modality, appear to have a decreased likelihood of successfully responding to the second and all subsequent modalities employed. Recently, Wallner, Vonderheid, Brady, et al, (1979) reported on the response of 30 patients with CTCL to whole body electron beam radiation. 87% of these patients had been unresponsive to previous topical therapy with HN_2 or were unable to tolerate continued topical therapy because of skin sensitivity. In contrast to the Stanford experience (Hoppe, Fuks, and Bagshaw, 1977) in which 92% of patients with T_1 or T_2 disease who were treated to dose levels of greater than 2,500 rads demonstrated initial complete clearance of the disease, in the Temple study a complete response was seen in only 62% of the patients with similar T_1 or T_2 disease. Furthermore, an additional 25% of the Temple study group had relapsed within 4-6 months. These results suggest that electron beam radiation alone is unable to induce and maintain clearance of disease in patients who have failed on previous topical therapy.

As can be seen from the following summary table, each of the three topical modalities can produce initial complete clearing of the skin in from 64-84% of all patients with CTCL, the vast majority of whom had disease clinically limited to the skin with no obvious evidence for extracutaneous disease by routine staging procedures.

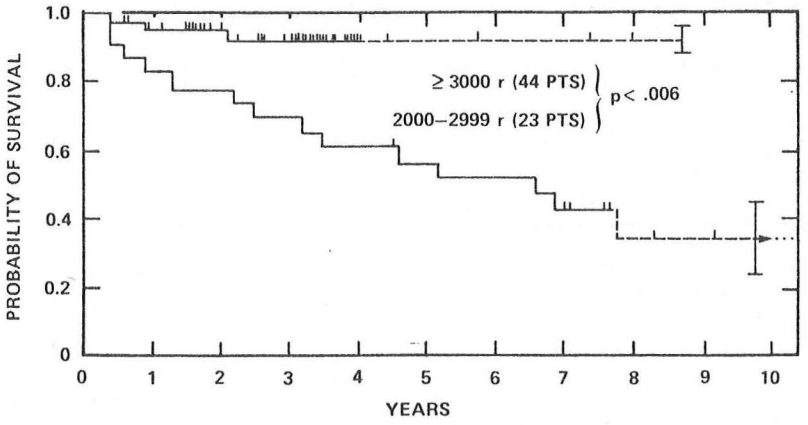
RESULTS OF TOPICAL RX IN CTCL

Modality	n	Complete Response (%)	Median Duration (mo.)	Disease-free at 3 yr (%)	Alive at 5 yr (%)
HN_2	243	64	18+	13	68
Electron beam	140	84	16	20	65
PUVA	164	70*	13+	too early	too early

*Question of residual deep dermal infiltrates in many

It can be seen that less than 20% of all patients followed for 3 years or more are free of disease. An obvious question is why so few patients are "cured" by these modalities which seem so effective in clearing the skin of the malignant infiltrates. The staging data previously discussed strongly suggests that unsuspected extracutaneous disease is present in the majority of patients with CTCL and may explain the failure of these topically effective therapies.

Finally, it is important to point out the relative paucity of data which unequivocally shows that any form of treatment for CTCL can enhance survival. The major reason for the lack of such data is the fact that virtually all patients with CTCL are treated in some way and there is therefore no untreated control group. Furthermore, until recently there have been no published trials in which patients with similar stages of disease were systematically randomized into two different treatment groups. Because of the disparity in staging procedures employed by different institutions at different times, inter-study comparisons and even historical comparisons within a single center are fraught with interpretive difficulties. Perhaps the closest one can come to good data showing that survival can be improved with any form of therapy in CTCL is the data from Stanford illustrated on the next page.



Hoppe, et al. Cancer Treat Rep 63:697, 1979

It can be seen that the survival of patients with generalized plaque (T_2) disease who were treated with 2,000-2,999 rads of whole body electron beam radiation was significantly less than the survival of apparently similar stage patients who were treated with 3,000 or more rads. Nevertheless, it is important to point out that the 2,000-2,999 rad cohort was an historically-matched group which was compared to the more recent patients at that institution, all of whom are now treated with at least 3,000 rads.

D. Restatement of Current "Dilemma" Concerning the Ideal Treatment of CTCL

The use of any form of systemic therapy for the treatment of CTCL is something that the majority of dermatologists have refused to seriously consider unless all other forms of therapy have failed. In many cases, this aversion is founded upon either ignorance or a sometimes irrational fear that to subject any patient with CTCL to systemic therapy is tantamount to "throwing in the towel." On the other hand, a modification of this basically conservative thought process can be rational. The rational conservative physician says: "It may be better to treat the patient with early stage disease with therapy which

may not be curative. I will treat my patients, only trying to control the disease, with one of the several available topical regimens for as long as they seem to work, and only use systemic and potentially more toxic therapy when the disease has obviously gotten out of control. I realize that any the responses we are likely to get at that point are apt to be partial and of short duration. I am adopting this attitude in light of the current lack of incontrovertible evidence that we can do better than that with any kind of therapy".

On the other hand, the equally rational proponents of a more aggressive approach to treatment say the following: "The bulk of experience throughout the world is that patients with internal disease ultimately do rather poorly. Therefore, more intensive and aggressive and even potentially toxic therapy should be tried in at least some patients with early stage disease in an attempt to prevent them from ever getting into the later stages, when we seem to be able to do little anyway. The available data on the efficacy of more aggressive treatment of early stage disease has suggested that it is at least as effective, and perhaps more effective than less aggressive therapy; early results do not suggest excessive morbidity following more aggressive treatment. We may be able to do significantly better in treating this group of diseases than we are currently doing. And if we don't try, we will never know."

Each physician makes a rational argument. There is a proper setting for each of them to carry out their respective appoaches to treatment. At this point in time the conservative approach is perhaps most appropriate for the physician with the occasional patient who for valid reasons is not a candidate for enrollment in one of the ongoing randomized clinical trials. If the physician and patient together have determined that the patient is not a suitable candidate for participation in such protocols, then the descision as to which form(s) of therapy is to be employed ought to take into account the following factors: extent of disease; rate of progression of disease; the age and general status of the patient's health; the response to and sequelae of previous forms of treatment; the facilities available; the previous experience of those who are to be involved in managing the patient's treatment; and other factors such as the time and dollar commitments which will be required.

A more aggressive approach for some patients is most appropriate in another setting. Many centers throughout the United States currently have the appropriate personnel and facilities either independently or cooperatively to enroll substantial numbers of patients, to stage them using all potentially useful technologies, and then to carefully follow these patients, some of whom may be treated relatively conservatively and others, with apparently similar disease, more aggressively. Ongoing clinical studies include the multicenter cooperative groups such as the Mycosis Fungoides Cooperative Group and the Southwest Oncology Groups, and individual centers such as the National Cancer Institute, Temple University, Columbia University, Duke University, Stanford University, and the University of California at San Francisco. The contributions of such clinical studies to our present knowledge of CTCL have been substantial; these contributions include the further clarification of

obvious risk factors, the identification of new risk factors, and the identification of more effective treatments.

The importance of adequate staging must be stressed for one last time. In order to rationally compare the efficacy of various therapeutic regimens it is imperative that appropriate staging be done on all patients, so that all potential prognostic factors can be examined. Then the response rate and survival for each category of disease can be assessed. This is especially important in a group of diseases such as CTCL which have such a variable natural history and in which therefore the "natural" differences in prognosis of patients entering the study could easily be of the same order of magnitude as the differences observed between two therapeutic modalities.

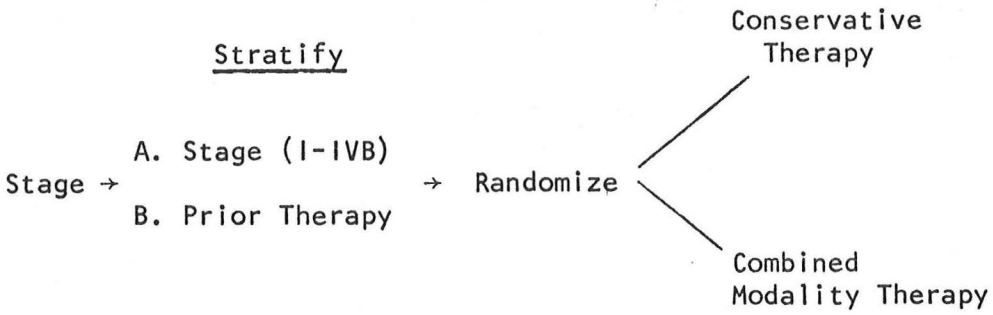
The current National Cancer Institute protocol for CTCL is outlined on the next page as an example of the stratified and randomized clinical trial.

The major problem faced by clinical centers trying to ask such therapeutic questions as outlined above is the difficulty in enrolling adequate numbers of patients with early stage disease. There is much less of a problem obtaining patients with advanced disease; referring physicians in many cases are only too happy to at least temporarily unburden themselves of such difficult patients. Clearly part of the problem in enrolling patients with early stage disease relates both to the relative rarity of CTCL and the inability in many cases to make an unequivocal diagnosis in the early stages. Equally important, however, has been the relative unwillingness on the part of physicians, particularly dermatologists, to refer such early stage patients to a center where some patients are being randomized to a more aggressive form of therapy. The importance of continuing to try to educate such physicians is obvious. No one physician in private practice sees enough cases of CTCL to be in a position to make a truly enlightened decision regarding the most appropriate treatment for a given patient. The end result is that an empirical decision is reached which based on inadequate information. If, a year later, another patient with CTCL presents to that same physician, another empirical decision is likely to be made. It is difficult to convince such a physician that randomized and stratified clinical trials are virtually our only hope for ever being able to make a truly rational decision regarding the most appropriate treatment for a patient with CTCL. Many of us can rightfully be accused of treating this disease "by flying by the seat of our pants".

E. Summary

In the past decade we have witnessed an exposion of new information concerning the natural history and immunopathobiology of the group of diseases referred to as cutaneous T cell lymphoma. We are currently witnessing some potentially important findings in the realm of the pathogenesis of these diseases. At the present time we remain uncertain of the most appropriate treatment for a given patient with a given amount/stage of disease. We remain uncertain as to how best to classify

NCI PROTOCOL



"CONSERVATIVE" THERAPY

Stages I-IVA: Sequential (i.e. use one modality until it fails, then procede to next) use of

Topical HN_2 → PUVA → Electron beam (3000 rads) → Methotrexate ($20\ mg/m^2$ p.o. twice weekly)

Stage IVB: Topical Rx <u>plus</u> Methotrexate

COMBINED MODALITY THERAPY

For all stages: Electron beam <u>plus</u> (Stages I-IVA) or 16 (Stage IVB) cycles of combination chemotherapy consisting of:

Cyclophosphamide	$500\ mg/m^2$ d1
Adriamycin	$50\ mg/m^2$ d1
VP-16	$100\ mg/m^2$ d1,3,5
Vincristine	$1.4\ mg/m^2$ d1

Repeat in 21 day cycles

patients with CTCL in relation to other non-Hodgkin's lymphoma/leukemia; while some of the characteristics of CTCL are similar to "favorable histology" non-Hodgkin's lymphoma, other characteristics seem to more closely resemble "unfavorable histology" types. What does seem clear to an increasing number of people is that cutaneous T cell lymphomas may well be offering us some unique opportunities to observe the evolution of a malignant process from a much earlier point in time than we can for other lymphomas and leukemias. These opportunities are made possible by the apparently special affinity which both normal and malignant T cells have for the skin, the most visible and readily accessible organ in the body.

REFERENCES

Banton R, Goldschneider I, and Bollum F. (1976) J Immunol 116:462-468.

Basset F and Turiaf MJ. (1965) CR Acad Sci (DP Paris) 261:3701-3709.

Bazin E. (1870) Paris, Adrien Delahaye, p. 425.

Berger CL, Warburton D, Raafat J, et al. (1979) Blood 53:642-651.

Berger CL, Takezaki S, De Pietro W, et al. (1981) J Invest Dermatol 76:311 (abs.).

Bernstein ID, Tam MR, and Nowinski RC. (1980) Science 207:68-70.

Blaylock WK, Clendenning WE, Carbonne PP, et al. (1966) Cancer 19:233-236.

Bosman F and Van Vloten WA. (1976) J Pathol 118:49-57.

Boumsell L, Bernard A, Reinberz EL, et al. (1981) Blood 57:526-530.

Briffa DV, Warin AP, Harrington CI, et al. (1980) Lancet 2(8185):49-53.

Broder S and Bunn PA. (1980) Sem Oncology 7:310-331.

Broder S, Edelson RL, Lutzner MA, et al. (1976) J Clin Invest 58:1297-1306.

Broder S, Uchiyama T, Muul LM, et al. (1981) New Engl J Med 304:1382-1387.

Brownlee TR. (1970) Cancer 26:686-698.

Brouet JC, Flandrin G, Sasportes M, et al. (1975) Lancet 2:890-893.

Bunn PA Jr., Fischmann AB, Schecter GP, et al. (1979) Cancer Treat Rep 63:713-717.

Bunn PA, Huberman MS, Whang-Peng J, et al. (1980) Ann Int Med 93:223-230.

Bunn PA, Whang-Peng J, Carney DN, et al. (1980) J Clin Invest 65:1440-1448.

Bunn PA, Edelson R, Ford SS, and Shackney SE. (1981) Blood 57:452-463.

Burke JS and Colby TV. (1981) Ann J Surg Pathol 5:343-352.

Burke JS, Hoppe RT, Cibull ML, and Dorfman RF. (1981) Cancer 47:300-310.

Capra JD. (1981) Southwestern Medical School Grand Rounds, May 21, 1981.

Carney DN and Bunn PA. (1980) J Dermatol Surg Oncol 6:369-377.

Castellino RA, Hoppe RT, Blank N, et al. (1979) Cancer Treat Rep 63:581-586.

Chaffey JT, Hellman S, Rosenthal DS, et al. (1977) Cancer Treat Rep 61:1149-1152.

Chandra P, Chanana AD, Chikkappa G, et al. (1976) Blood 48:996 (abs.).

Chu A, Kung PC, and Edelson R. (1981) J Invest Dermatol 76:324 (abs.).

Clendenning WE and Rappaport HW (1979) Cancer Treat Rep 63:719-723.

Cohen SR (1977) MPH Thesis, Yale University, pp 27-29.

Colby TV, Burke JS, and Hoppe RT. (1981) Cancer 47:351-359.

Constantine VS, Fuks ZY, and Farber EM. (1975) Arch Dermatol 111:484-488.

Dausset J and Contu L. (1980) Progr Immunol 4:573-629.

Dick HM and Mackie R. (1977) Dermatologica 155:275-282.

Dupre A, Bonafe JL, Lassere J, et al. (1977) Rev Med Toulouse 13:803-808.

DuVivier A, Vonderheid EC, Van Scott EJ, et al. (1979) Brit J Dermatol 99:61-63.

Edelson RL. (1977) Proceedings of the 4th Advanced Blood Components Seminar 4:1-7.

Edelson RL. (1980) J Am Acad Dermatol 2:89-106.

Edelson RL, Berger CL, Raafat J, et al. (1979) J Invest Dermatol 73:548-550.

Edelson RL, Facktor M, Andrews A, et al. (1974) New Engl J Med 291:293-294.

Edelson RL, Raafat J, Berger CL, et al. (1979) Cancer Treat Rep 63:675-680.

Engelman EGR, Warnke RI, Fox J, et al. (1981) Proc Natl Acad Sci USA 78:1791-1794.

Epstein Eh, Levine DL, Croft JD, et al. (1972) Medicine (Baltimore) 51:61-72.

Escovitz ES, Soulen RL, Van Scott EJ, et al. (1974) Radiology 112:23-27.

Evans HL, Winkelmann RK, and Banks PM. (1979) Cancer 44:699-717.

Evans RL, Wall WL, Platsoucas CD, et al. (1981) Proc Natl Acad Sci USA 78:544-548.

Fidler IJ. (1973) Nature New Biol 242:148-149.

Fidler IJ and Kripke ML. (1977) Science 197:893-895.

Fidler IJ and Nicholson GL. (1976) J Natl Cancer Inst 57:1199-1202.

Fischmann AB, Bunn PA, Guiccion JG, et al. (1979) Cancer Treat Rep 63:591-596.

Fitzpatrick PJ and Rider WD. (1976) Int J Radiat Oncol Biol Phys 1:197-207.

Flaxman BA, Van Scott EJ, Goldman LI. (1974) Arch Dermatol 109:577-578.

Flaxman BA, Zelazuy G, Van Scott EJ. (1971) Arch Dermatol 104:141-147.

Fuks ZY, Bagshaw MA, and Farber EM. (1973) Cancer 32:1385-1395.

Gallagher RE and Gallo RC. (1975) Science 187:350-353.

Gallo R. (1975) New Engl J Med 292:804-805.

Gowans JL and Knight EJ. (1964) Proc Roy Soc B 159:257-270.

Green SB, Byar DP, and Lamberg SI. (1981) Cancer 47:2671-2677.

Greene MH, Dalager NA, Lamberg SI, et al. (1979) Cancer Treat Rep 63:597-606.

Griem ML, Tokars RP, Petras V, et al. (1979) Cancer Treat Rep 63:655-657.

Guy-Grand D, Griscelli C, and Vassalli P. (1974) Eur J Immunol 4:435-443.

Guy-Grand D, Griscelli C, and Vassalli P. (1978) J Exp Med 148:1661-1677.

Hallopeau H and Besnier E. (1892) J Cutan Genitourin Dis 10:453.

Hamminga L, Mulder JD, Evans C, et al. (1981) Cancer 47:692-697.

Haserick JR, Richard JH, and Grant DJ. (1959) Cleveland Clinic Quarterly 26:144-147.

Haynes BF. (1981) Immunological Rev 57:127-161.

Haynes BF, Eisenbarth GS, and Fauci AS. (1979) Proc Natl Acad Sci USA 76:5829-5833.

Hoppe RT, Cox RS, Fuks ZY, et al. (1979) Cancer Treat Rep 63:691-700.

Hoppe RT, Fuks Z, and Bagshaw MA. (1979) Cancer Treat Rep 63:625-632.

Huberman M, Bunn PA Jr, Matthews MJ, et al. (1980) Cancer 45:1683-1688.

Janossy G, Duke O, Poulter LW, et al. (1981) Lancet 2:839-842.

Janossy G, Tidman M, Papageorgiou ES, et al. (1981) J Immunol 126:1608-1613.

Johnson RE and Ruhl V. (1976) Int J Radiat Oncol Biol Phys 1:387-399.

Joyner MU, Cassuto JP, Dujardin P, et al. (1979) Arch Dermatol 115:326-328.

Klareskog L, Tjernlund J, Forsum J, et al. (1977) Nature 268:247-248.

Kohler G and Milstein C. (1975) Nature 256:495-497.

Kovary PM, Niedorf H, Sommer G, et al. (1977) Dermatologica 154:138-146.

Kravitz PH and McDonald CJ. (1978) Acta Dermatol Venereol 58:421-425.

Kung PC, Berger CL, Goldstein G, et al. (1981) Blood 57:261-265.

Lamberg SI and Bunn PA. (1979) Cancer Treat Rep 63:561-736.

Lamberg SI, Green SB, Byar DP, et al. (1979) Cancer Treat Rep 63:701-707.

Lawrence EC, Broder S, Jaffe ES, et al. (1978) Blood 52:481-492.

Lewin R. (1981) Science 214:530-531.

Ledbetter JA, Evans RL, Lipinski M, et al. (1981) J Exp Med 153:310-321.

Long JC and Mihm M. (1974) Cancer 34:1745-1755.

Long JC, Mihm MC, and Qazi R. (1976) Cancer 38:1282-1296.

Louie S, Daoust PR, and Schwartz RS. (1980) Seminars in Oncology 7:267-280.

Lowe NJ, Cripps DJ, Dufton PA, et al. (1979) Arch Dermatol 115:50-53.

Luger TA, Stalder BM, Katz SI, and Oppenheim JJ. (1981) J Immunol 127: 1493-1498.

Lutzner M, Edelson R, Schein P, et al. (1975) Ann Int Med 83:534-552.

Lutzner MA, Hobbs JW, and Horvath P. (1971) Arch Dermatol 103:375-386.

Lutzner MA and Jordan HW. (1968) Blood 31:719-726.

Lutzner MA, Emerit I, Durepaine R, et al. (1973) J Natl Cancer Inst 50:1145-1162.

MacKie RM. (1981) Lancet 2:283-284.

MacKie R, Sless FR, Cochran R, et al. (1976) Brit J Dermatol 94:173-178.

McDonald CJ and Bertino JR. (1979) Cancer Treat Rep 62:1009-1014.

Meyer CJLM, van Leeuwen AWFM, van der Loo EM, et al. Virchows Arch Cell Pathol 25:95-104.

Meyler TS, Blumberg AL, and Purser P. (1978) Cancer 42:1171-1176.

Miller RA, Coleman CN, Fawcett HD, et al. (1980) New Engl J Med 303:89-92.

Miller RA and Levy R. (1981) Lancet 2:226-230.

Miller RA, Maloney DG, McKillop J, and Levy R. (1981) Blood 58:78-86.

Minna JD, Roenigk HH, and Glatstein E. (1979) Cancer Treat Rep 63:729-736.

Moran EM, Walther JR, Aronson IK, et al. (1977) Proc AACR and ASCO 18:276.

Nezelof C, Diebold N, Rosseau-Merck MR. (1977) J Pathol 122:105-113.

Nisce LZ and Safai B. (1979) Cancer Treat Rep 63:633-638.

Parrish JA, LeVine MJ, and Fitzpatrick TB. (1980) Int J Dermatol 19: 379-386.

Poiesz BJ, Ruscetti FW, Gazdar AF, et al. (1980) Proc Natl Acad Sci USA 77:7414-7419.

Portlock CS. (1980) Seminars in Oncology 7:292-301.

Posner LE, Fossieck BE, Eddy JL, and Bunn PA. (1981) Am J Med 71:210-215.

Price N. (1978) Arch Dermatol 114:63-66.

Price N, Hoppe RT, Constantine V, et al. (1977) Cancer 40:2851-2853.

Proctor MS, Price NM, Cox AJ, et al. (1978) Arch Dermatol 114:1326-1328.

Rappaport H and Thomas LB. (1974) Cancer 34:1198-1229.

Reinherz EL, Kung PC, Goldstein G, and Schlossman SF. (1979a) J Immunol 123:1312-1318.

Reinherz EL, Kung PC, Goldstein G, and Schlossman SF. (1979b) J Immunol 123:2894-2899.

Reinherz EL, Kung PC, Goldstein G, and Schlossman SF. (1980) J Immunol 124:1301-1308.

Ritz J, Pesandro JM, Sallou SE, et al. (1981) Blood 58:141-152.

Rose ML, Parrott DMV, and Bruce RG. (1976a) Immunol 31:723-730.

Rose ML, Parrott DMV, and Bruce RG. (1976b) Cell Immunol 27:36-46.

Rowden G and Lewis MG. (1976) Brit J Dermatol 95:665-671.

Rowden G, Phillips TM, and Delovitch TL. (1978) Immunogenetics 7:465-478.

Rowden G, Phillips TM, Lewis MG, and Wilkinson RD. (1979) J Cutan Pathol 6:364-382.

Rubenfeld MR, Silverstone AE, Knowles DM, et al. (1981) J Invest Dermatol 77:221-224.

Safai B, Incefy GS, Good RA, et al. (1981) New Engl J Med 303:113.

Safai B, Reich L, and Good RA. (1978) Clin Res 26:576 (abs.).

Saglier-Guedon I, Prunieras M, Durepaire R, et al. (1977) Bull Cancer 64:259-266.

Sanchez JL and Ackerman AB. (1979) Am J Dermatopathol 1:5-26.

Saxe N, Kahn LB, and King H. (1977) J Cutan Pathol 4:111-122.

Schechter GP, Bunn PA, Fischmann AB, et al. (1979) Cancer Treat Rep 63:571-574.

Segal RT and Watson W. (1978) Arch Dermatol 114:1067-1069.

Sezary A and Bouvrain Y. (1938) Bull Soc Fr Dermatol Syph 45:254-260.

Shadduck JA, Reedy L, Lawton G, and Freeman R. (1978) Vet Pathol 15:716-724.

Shelley WB. (1980) Arch Dermatol 116:1177-1178.

Smith RW, Terry WO, and Buell DN. (1973) J Immunol 110:884-886.

Stern RS, Thibodeau LA, Kleinerman RA, et al. (1979) N Engl J Med

Streilein JW. (1978) J Invest Dermatol 71:167-171.

Tallroth K, Wiljasalo M, Valle M, et al. (1977) Lymphology 10:147-150.

Tan RSH, Butterworth CM, McLaughlin H, et al. (1974) Brit J Dermatol 91:607-616.

Taulbee KS and Johnson SC. (1981) Arch Dermatol 117:114-115.

Trump JG, Wright KA, and Evans WW. (1953) Am J Roentgenol Rad Therapy Nucl Med 69:623-629.

Uchiyama T, Sagawa K, Takatsuki K, and Uchino H. (1978) Clin Immunol Immunopathol 10:24-34.

Uchiyama T, Yodoi J, Sagawa K, et al. Blood 50:481-492.

Vander Loo EM, van Muijen GNP, van Vloten WA, et al. (1979) Virchows Arch B [Cell Pathol] 31:193-203.

Van Leeuwen AWFM, Meyer CJLM, van de Putte LBA, et al. (1976) Lancet 1:248-249.

Van Vloten WA, Pet EA, and Geraedts JPM. (1980) Brit J Dermatol 102:507-513.

Van Vloten WA, Scheffer E, and Meijer CJLM. (1979) J Invest Dermatol 73:275-277.

Van Vloten WA, Vermeij J, and De Vroome H. (1977) Dermatologica 155: 28-34.

Verdich J. (1979) Arch Dermatol 115:1338-1339.

Vidal E and Brocq L. (1885) Le France Medical 2:946, 957, 969, 983, 993, 1005, 1019, 1085.

Volden G and Larsen TE. (1977) Acta Dermatol Venereol 57:341-343.

Vonderheid EC. (1980) Int J Dermatol 19:182-190.

Vonderheid EC, Van Scott EJ, Johnson WC, et al. (1977) Arch Dermatol 113:454-462.

Vonderheid EC, Van Scott EJ, Wallner PE, et al. (1979) Cancer Treat Rep 63:681-689.

Vonderheid EC, Tam DW, Johnson WC, et al. (1981) Cancer 47:119-125.

Whang-Peng J, Bunn PA, Knutsen T, et al. (1979) Cancer Treat Rep 63:575-581.

Wallner PE, Vonderheid EC, Brady LW, et al. (1979) Int J Radiat Oncol Biol Phys 5:23-27.

Wolk BH. (1977) Can Med Assn J 117:750-753.

Yamanaka N, Ishii Y, Koshiba H, et al. (1981) Cancer 47:311-318.

Yeckley JA, Weston WL, Thorne EG, et al. (1975) Arch Dermatol 111:29-32.

Zackheim HS, Epstein EH Jr, and Grekin DA. (1979) Cancer Treat Rep 63:623.

Zachkeim HS. (1981) Arch Dermatol 117:295-304.

Zucker-Franklin D. (1976) J Invest Dermatol 67:412-418.