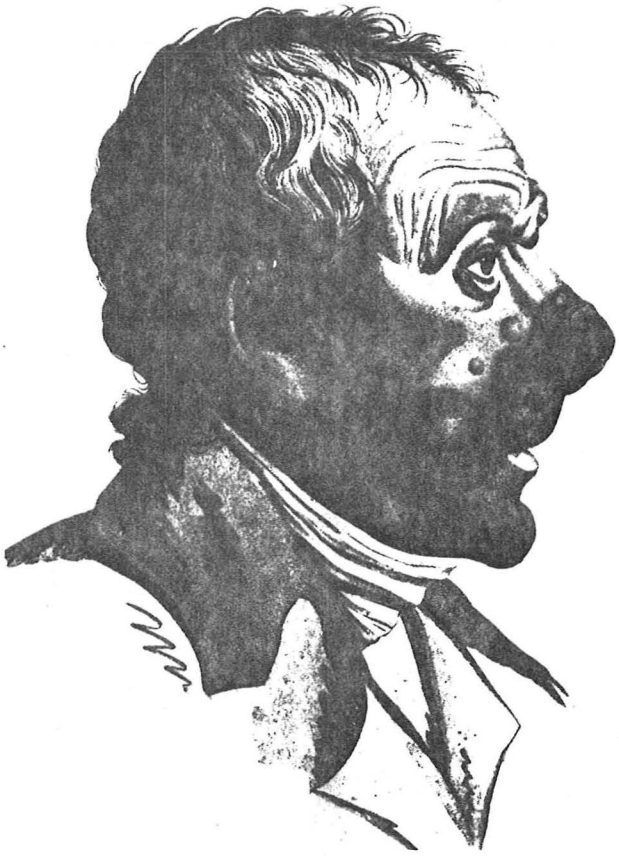
MYCOSIS FUNGOIDES AND THE SEZARY SYNDROME:

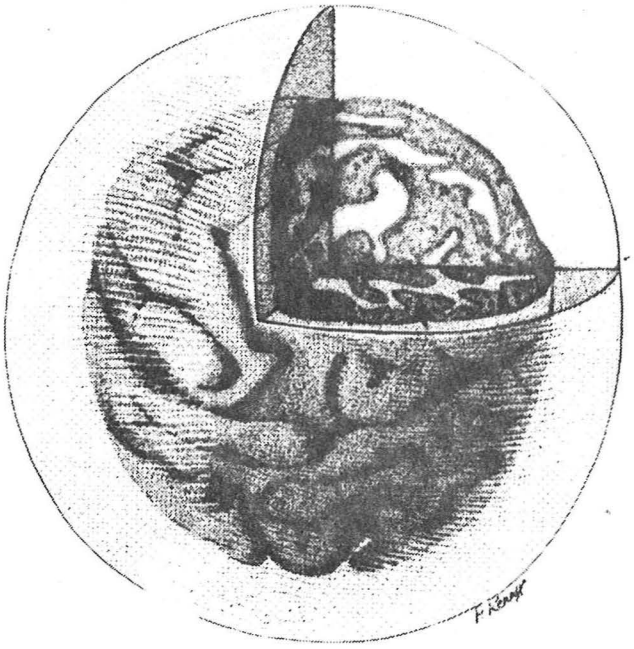
T-CELL LYMPHOMAS INVOLVING SKIN

by

JAMES H. HERNDON, JR., M.D.



The Patient Lucas. From Alibert's Atlas, 1806



A Sezary (or Mycosis) Cell

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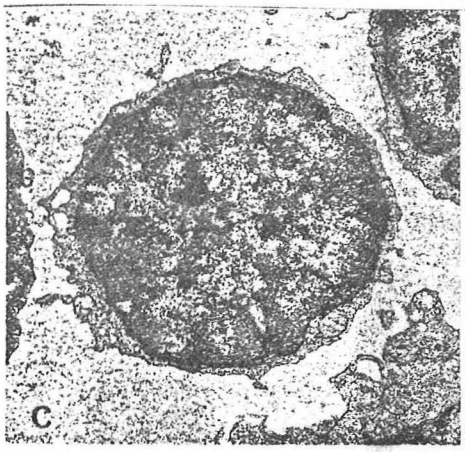
MYCOSIS FUNGOIDES AND THE SEZARY SYNDROME:

T-CELL LYMPHOMAS INVOLVING SKIN

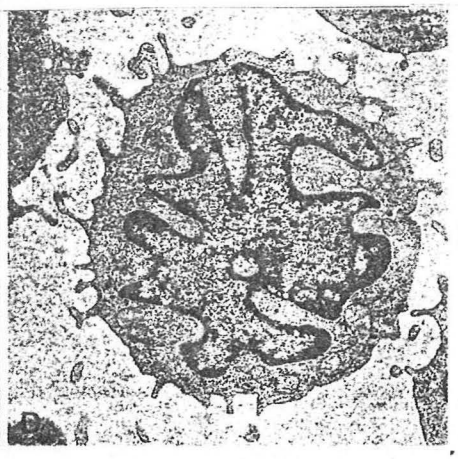
During the past five years a remarkable burst of immunologic and cytologic discovery has begun to lay bare certain basic principles concerning interactions between the human thymus and the skin. These findings have led to new views about the relations between cutaneous lymphomas and other lymphoid malignancies, and between previously empirical treatment and the control of growth and patterns of migration of populations of lymphoid cells. As a result the physician's ability to classify cutaneous and other lymphomas, to manage their treatment more rationally, and to see a little deeper into the complicated issues of neoplastic and non-neoplastic growth has grown enormously. Several reviews of the advances in this field have been published recently (1-3).

Electron microscopic evidence: Sezary and mycosis cells

The first important advance came in 1968 when Marvin Lutzner at NIH first noticed what his predecessors had overlooked in their concern for viral inclusions (4); he found that the large atypical blood monocyte in the Sezary syndrome as well as a similar cell in the skin infiltrate of mycosis fungoides displayed a uniquely convoluted and serpentine or cerebriform nucleus (5, 6). Atypical cells from these two clinical states appeared to be identical by cytologic



An abnormal B-lymphocyte from a patient with chronic lymphatic leukemia



An abnormal T-lymphocyte from a patient with the small-cell variant of the Sezary syndrome

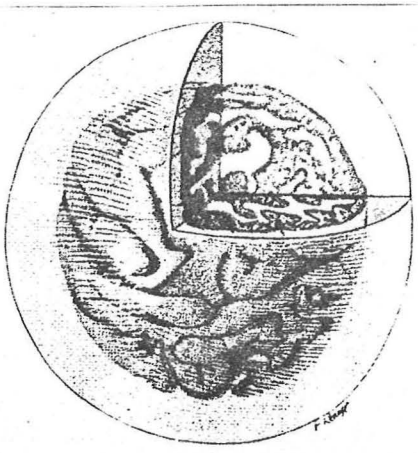
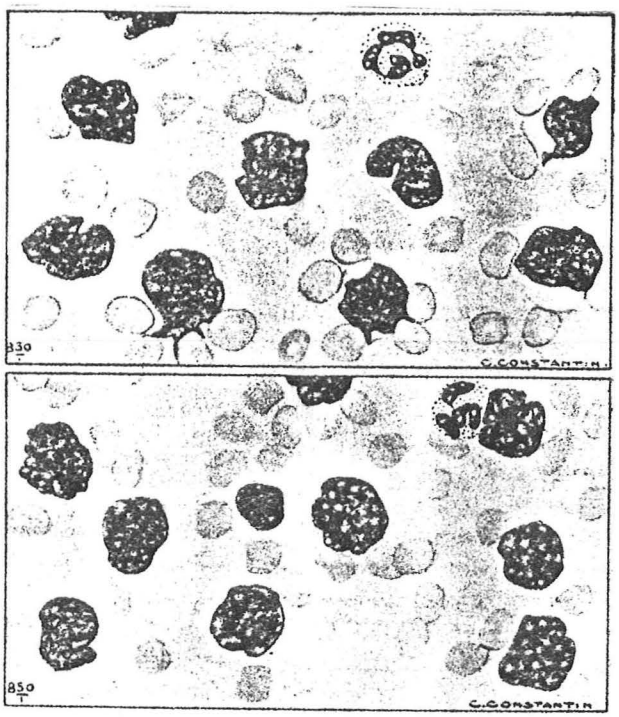


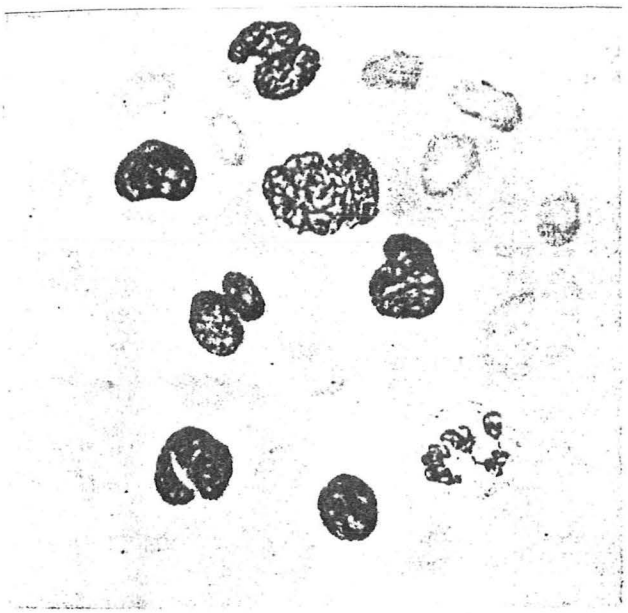
Diagram of the abnormal T-lymphocyte from the Sezary syndrome and mycosis fungoides

from Lutzner, Edelson, Schein, et al.

criteria (7), supporting an earlier view that the Sezary syndrome represents a form of mycosis fungoides in which the abnormal cells 'overflow' into the circulation (8). Both Sezary himself (9) and the earliest descriptions by Lutzner (5, 6) referred to cells that appeared large and atypical in the light microscope (15-30μ in size). But later studies showed that cells indistinguishable from small lymphocytes by the light microscope (7-12μ in size).



Cells illustrated by Sezary from his first cases.



Cells illustrated by Baccaredda from his case.

from Winkelmann (ref. 102)

could have serpentine nuclei as well (10,11), and that these cells could occur together with the larger cells in blood and pathologic sections (12).

Following the work of Lutzner the abnormal cells were detected not only in skin and nodes, but also in peripheral blood, spleen (13), and other organs of patients with mycosis fungoides. Unfortunately for didactic clarity small numbers of such cells have more recently been found in a number of other skin conditions: dermatitis, lichen planus, psoriasis, etc. (14). A few have also turned up in nodes of patients with non-malignant disease (13), in blood of patients with sarcoidosis (15), in cultures of normal human skin (16), and in PHA-stimulated lymphocyte cultures from healthy persons (17). Because the abnormal cell continued to be found in largest numbers in mycosis fungoides and the Sezary syndrome (13) many observers have expressed confidence in its importance to the diagnosis, although other features must also be used.

Membrane markers and immunologic function of Sezary and mycosis cells

Crossen first showed in 1971 that the atypical cells of Sezary syndrome behaved like lymphocytes rather than histiocytes or monocytes (18). That is, the cells usually responded to plant mitogens, failed to adhere to nylon columns, and contained beta-glucuronidase and PAS-positive material, but not peroxidase or esterases characteristic of monocytes (10,18,19,20).

SURFACE MARKERS FOR MONONUCLEAR CELLS

	SIg	E	C_3	F_c	Ag
B	+	-	+	+	±
K	-	-	-	╫	-
MONOCYTE -HISTIOCYTE	-	-	±	╫	-
T	-	+	- (+)	- (+)	+

Other features provided strong evidence that the cells represented abnormal but partially functional T-lymphocytes. Specifically, they lacked surface membrane-bound immunoglobulin, or F_c receptors for aggregated IgG, or receptors for complement components (19). They also possessed receptors for sheep erythrocytes, but when rosetting appeared weak and inconstant, they could be identified by anti-T-cell antiserum (19).

PERCENT OF BLOOD MONONUCLEARS WITH SURFACE MARKERS

PATIENT	N	T-CELL MARKERS	B-CELL MARKERS	MONOCYTE MARKERS
ATYPICAL LEUKEMIA	1	80%	70%	-
SEZARY SYNDROME (SMALL CELL)	5	70-90%	1-5%	-
SEZARY SYNDROME (LARGE CELL)	5	70-90%	3-20%	-
CLL	5	5%	80%	-
NORMAL	12	65%	15%	15%

MODIFIED FROM EDELSON

The same T-cell surface markers have been detected on cells eluted from finely minced frozen sections of skin and lymph node from patients with mycosis fungoides (21,22). Such cells also displayed E-rosettes with untreated sheep red cells, but only when previously released from tissue sections and studied in suspension. Sheep red cells did not adhere to such cells in tissue, when the investigator layered them over intact sections.

THE T-CELL CHARACTER OF THE MYCOSIS CELL IN MYCOSIS FUNGOIDES

Forms E-rosettes with sheep RBC

Is killed by rabbit anti-HTL antigen plus C'

Lacks markers for B-cells or macrophages

Not surprisingly, each patient with Sezary syndrome or mycosis fungoides provided cells that behaved differently when tested by these techniques. Some patients' cells failed to respond to plant mitogens, and others reacted with anti-T-cell antisera but formed no E-rosettes whatever with sheep red cells (19-23). One patient's cells failed to stimulate two sets of normal lymphocytes in mixed lymphocyte culture despite demonstrated differences in serologically detected HLA-loci (21).

HOW WELL DO SEZARY CELLS FUNCTION AS T-CELLS?

Weak or Inconstant Response	To plant mitogen
	To preformed blastogenic factor
	To MLC stimuli
	As killers in cytotoxicity assays
	Suppressor function with B-cells
Strong, constant Activity	Produce migration inhibitory factor
	Helper function with B-cells

modified from Broder, et al.

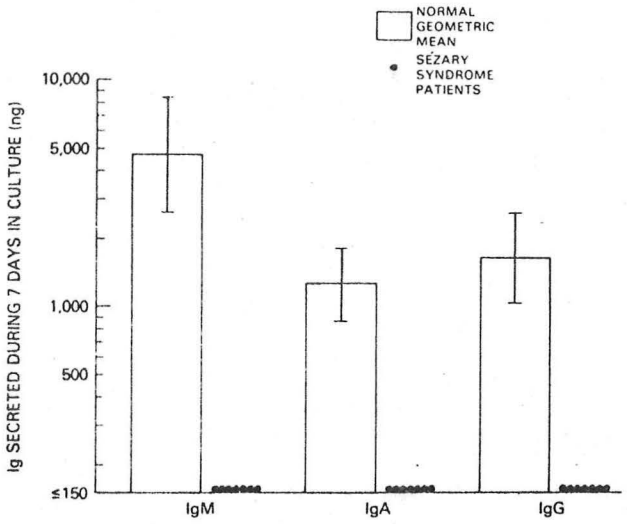
SUMMARY: FUNCTIONAL CAPACITY OF SEZARY T-CELLS

1. Each patient's cells have been functionally abnormal

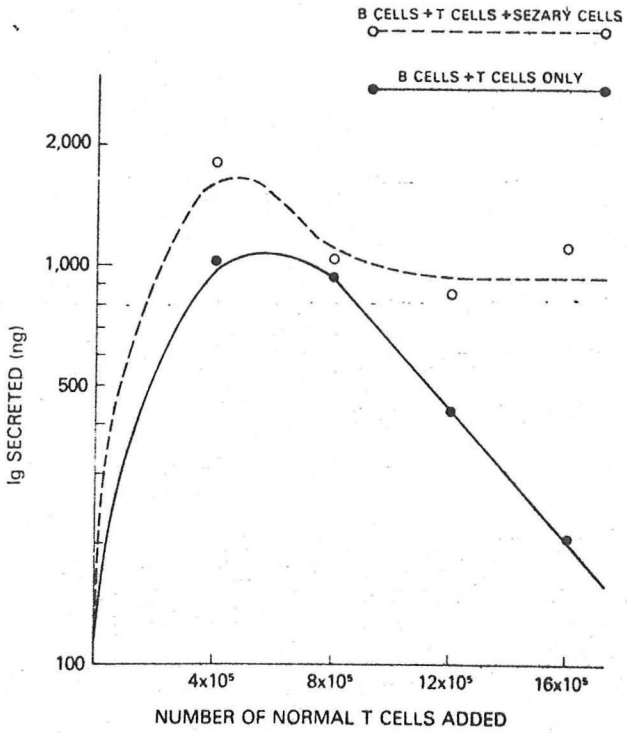
2. Cells from each patient react differently from cells of every other patient

3. Cells from a given patient may change characteristics

Very recently the NIH group found that the abnormal T-cells of each of seven Sezary patients behaved like a particular subtype of T-lymphocytes (24) called helper T-cells. Each of the patient's collected



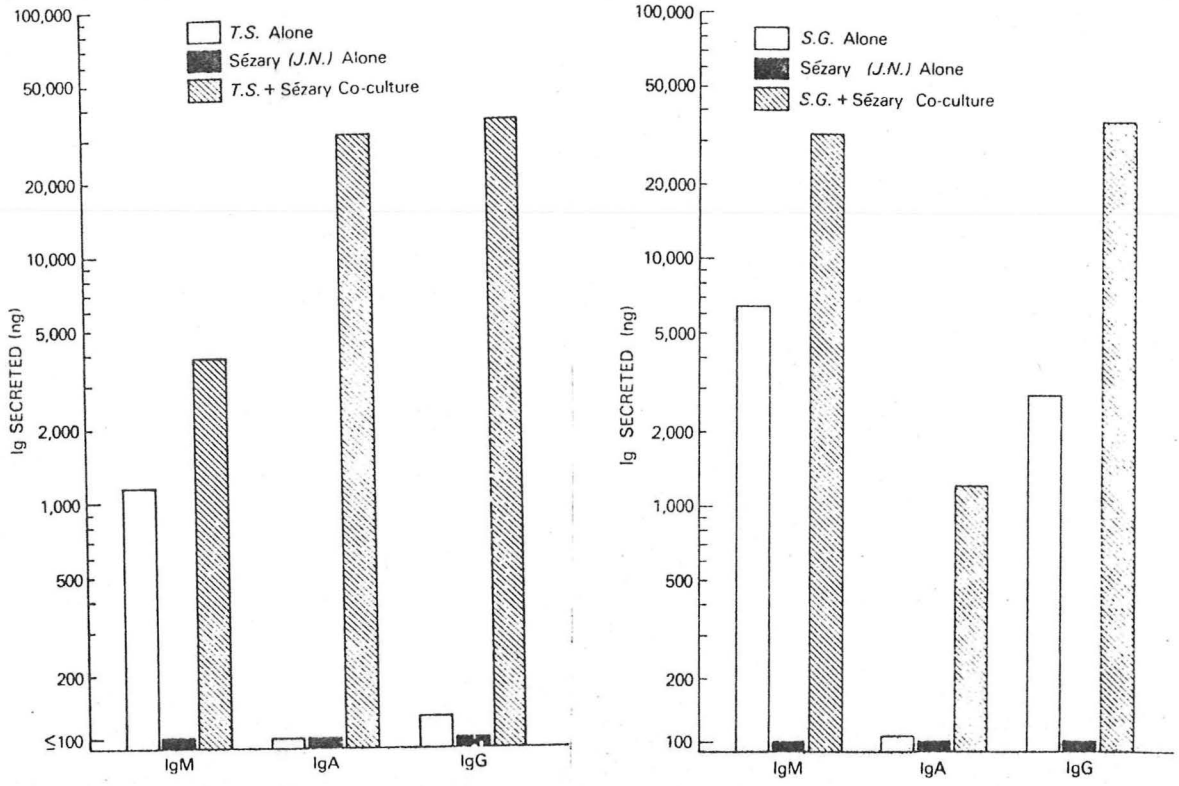
Immunoglobulin production by peripheral blood lymphocytes after stimulation by pokeweed mitogen. The geometric means±SD of 22 normal persons and the individual values of 7 patients with the Sézary syndrome are shown.



Restoration of immunoglobulin production at high normal T- and B-cell ratios by the addition of Sézary cells. In these experiments, varying numbers of normal T cells were added to 2×10^5 normal B cells. In addition, certain B cell—T cell mixtures received a constant number (1.0×10^6) of Sézary cells derived from patient E. H. Immunoglobulin values illustrated represent IgA.

from Broder, et al.

lymphocyte pools helped enhance the synthesis of immunoglobulin by B-cells from two congenitally hypoglobulinemic patients, one with Nezelof's syndrome, the other with ataxia telangiectasia and selective IgA deficiency. Similarly the Sezary T-cells showed no tendency to suppress immunoglobulin synthesis by normal B-cells even when added in enormous excess, a result that contrasts with the suppressor activity usually found at high T:B ratios in normal lymphoid populations.



Helper interaction of Sezary cells with lymphocytes from patients with thymic deficiency states: T. S. was a child with Nezelof's syndrome. S. G. is a child with ataxia telangiectasia. The Sezary cells used in these experiments were from patient J. N.

from Broder, et al.

Consistent with this identification with helper T-cells, several studies have recorded consistently raised levels of IgA and IgE in some patients with mycosis fungoides (25,26) and Sezary syndrome (24) as well as consistent elevation of migration inhibitory factor in the plasma of patients with the Sezary syndrome (27) but not in non-erythrodermic mycosis fungoides (28). But since others have found that lymphocytes collected from patients with benign forms of erythroderma (29) as well as from other lymphomas (30) can demonstrate elevated release of lymphokines, this finding may have little diagnostic value. The presence of raised levels of MIF in the serum appears to reduce the pool of circulating monocytes as well as reducing their chemotactic activity (22) in Sezary patients, and may impair host resistance.

IMMUNOLOGIC DERANGEMENTS IN SEZARY'S SYNDROME

Decreased delayed hypersensitivity
Dilution of normal T-cells by leukemic
High circulating levels of MIF

Enhanced antibody synthesis by B-cells
High levels of IgA, IgE, other Ig

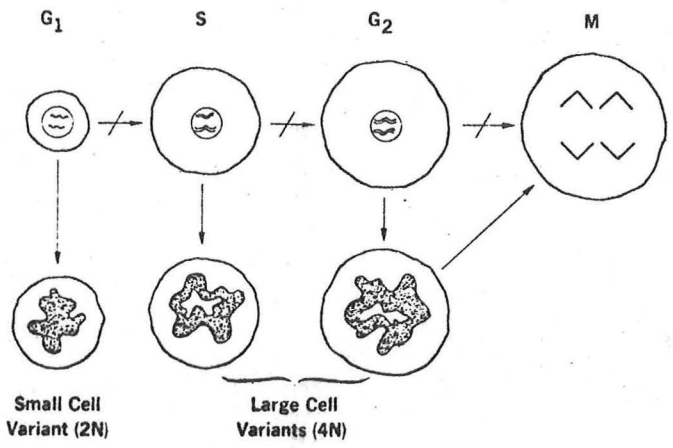
Reduced chemotactic activity

modified from Lutzner, et al.

In contrast to Hodgkin's disease and the Sezary syndrome most patients with mycosis fungoides demonstrate intact cellular and humoral immunity until late in the disease course (25,31,32). Recently, however, one group has shown that the function of monocytes in the peripheral blood was abnormal in 15 of 15 patients studied, none of whom had received systemic therapy (33). The defect was found in chemotaxis only, not in phagocytosis or killing. There was no reduction in numbers of circulating monocytes. The significance of this finding is unknown, though deficiency in chemotaxis could also contribute to late-stage infectious illness.

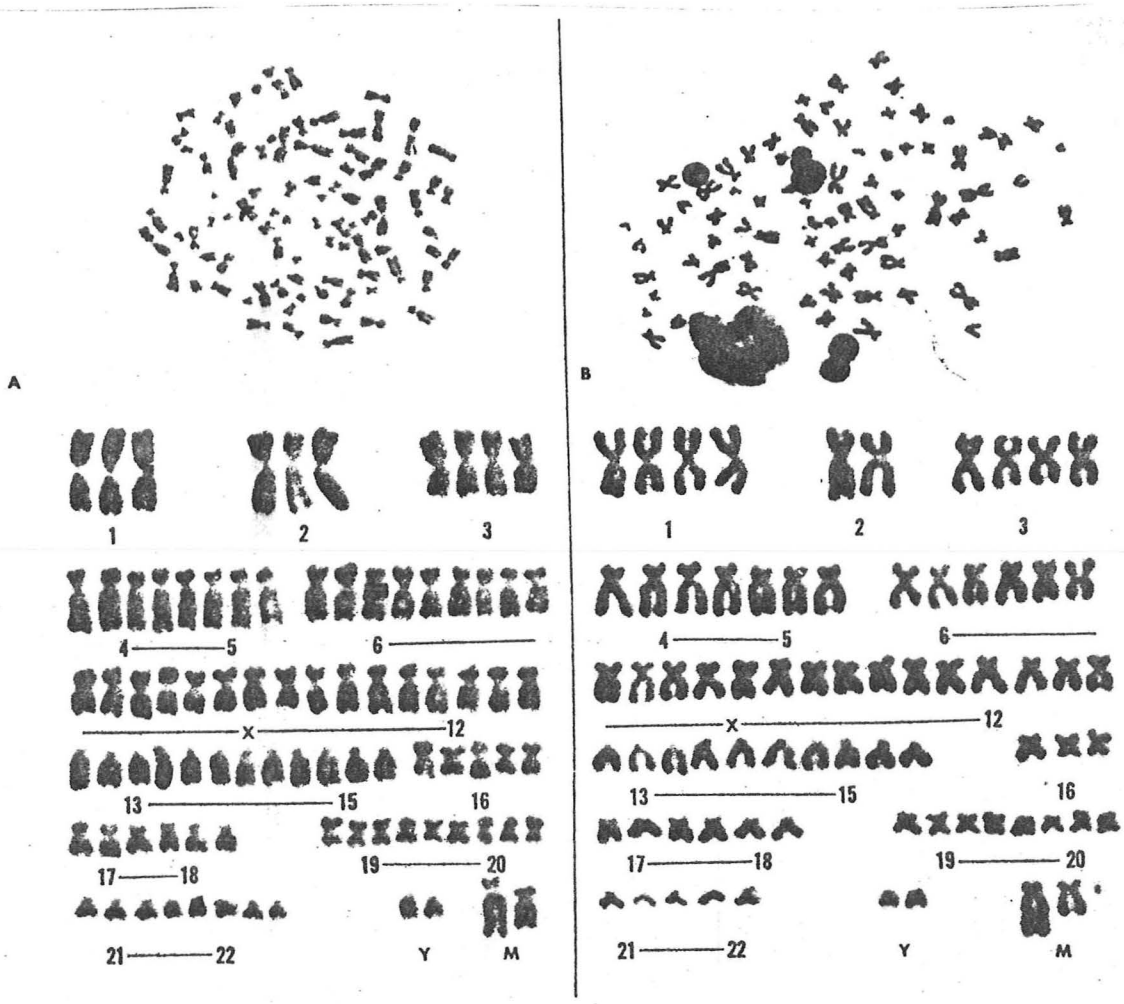
Chromosomal abnormalities

Chromosomal and cytophotometric studies show that cells of the Sezary syndrome (10,18,34) as well as those of mycosis fungoides (35,36) consistently displayed aneuploidy. The large 15 to 25μ cell usually contained a near-tetraploid number of chromosomes, while the smaller, 7 to 12μ cell contained pseudo-diploid or hyperdiploid numbers. The two major size distributions may occur because of asymmetry between nuclear DNA synthesis and the process of mitosis (22). Marker chromosomes were often seen in both types of cell. Two or even three populations of similar-appearing cells coexisted over a long period in the



Proposed cell cycle blocks in Sezary cells. G_1 and G_2 are growth phases one and two, respectively. S is DNA synthesis phase, and M is mitotic phase. 2N is diploid or near-diploid state, and 4N is tetraploid or near-tetraploid state.

from Lutzner



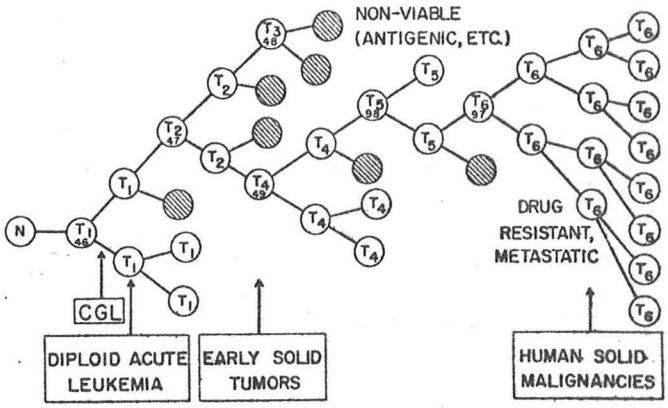
Two metaphases and karyotypes from patient ED.
(A) This cell contains 87 chromosomes, including two marker chromosomes.
(B) This cell contains 75 chromosomes, including three marker chromosomes.

from Whang-Peng, et al.

circulation of one Sezary patient (18). In other cases no modal number or apparent clone formation could be found; instead the presence of heteroploidy and multiple marker chromosomes was thought to reflect a continuously disordered replication mechanism (34).

The group at NIH found some evidence from a small group of patients that an abundant, spontaneously dividing population of cells along with a high percentage of heteroploid forms signalled malignant intensification (34), a situation resembling the blastic crisis of myelocytic leukemia. Rapid takeover by a specific clone of cells also signified a rapid course. These observations agree with the generally accepted thesis, recently summarized by Nowell (37), that progression from less aggressive tumor toward more aggressive growth results from sequential selection of more rapidly proliferating sublines of tumor cells.

Model of clonal evolution in neoplasia. Carcinogen-induced change in progenitor normal cell (N) produces a diploid tumor cell (T_1, 46 chromosomes) with growth advantage permitting clonal expansion to begin. Genetic instability of T_1 cells leads to production of variants (illustrated by changes in chromosome number, T_2 to T_6). Most variants die, due to metabolic or immunologic disadvantage (hatched circles); occasionally one has an additional selective advantage (for example, T_2, 47 chromosomes), and its progeny become the predominant subpopulation until an even more favorable variant appears (for example, T_4). The stepwise sequence in each tumor differs (being partially determined by environmental pressures on selection), and results in a different, aneuploid karyotype in each fully developed malignancy (T_6). Biological characteristics of tumor progression (for example, morphological and metabolic loss of differentiation, invasion and metastasis, resistance to therapy) parallel the stages of genetic evolution. Human tumors with minimal chromosome change (diploid acute leukemia, chronic granulocytic leukemia) are considered to be early in clonal evolution; human solid cancers, typically highly aneuploid, are viewed as late in the developmental process.



from Nowell

Mycosis fungoides: Historical aspects

Jean Louis Alibert (1766-1837) one of the first French physicians to devote his attention to skin diseases, introduced his published atlas with a vivid, personal reflection on the trials of a pioneer.

> "I have entered upon a career which few men have pursued before me, where no previous work has been done to guide me, where everything is new to the eye, where everything is a problem to the mind. I have myself cleared the path which I follow. You may judge the numerous obstacles that I have had to overcome." (quoted in ref. 1)

One of his patients was a man named Lucas, aged 56, who provided the very first description of mycosis fungoides. Lucas's disorder began with a brawny, desquamative rash. Soon he developed small tumors over various parts of the body. These were smooth and flesh-colored at first, then became brownish. They appeared on the face, forehead, brows, lids, nose, lips, chin, armpits, knee creases and elsewhere. They grew so that their appearance soon resembled mushrooms half submerged in the skin. They opened and drained, then crusted. Many eventually shrank and disappeared spontaneously. Lucas developed pustules due to secondary infection on the ravaged skin. He lost weight, appetite, eventually developed diarrhea, then fever. He died after five years of illness.

Alibert knew from his contact with North Africa the tumors characteristic of frambesia or yaws and thought of Lucas's condition as a form of yaws. But he emphasized that Lucas had never lived in an endemic region and therefore might have something different. In a later publication he formalized this suggestion by calling the condition mycosis fungoides. Modern physicians sometimes mistakenly assume he wished to incriminate fungal infection; the first human disease due to fungi was not to be recognized for another 50 years. Instead this term described the mushroom-like tumors that Lucas had so strikingly exhibited.

Clinical picture

As more cases were observed during the 19th and early 20th century it became clear that the disease could present in several ways. Whatever the mode of onset, the process only gradually disabled the patient, its course often stretching over decades. Its manifestations varied confusingly. At first the eruption might seen benign and variable but later it became stable and much more serious. A short terminal stage supervened when tumors, ulcers, or signs of lymphoid and visceral spread developed.

Frequency

The problem of underdiagnosis makes exact figures difficult to come by. Based on better reporting for the population of Scandinavian countries, most authorities estimate the incidence at one case per year per 500,000 population (38) and the death rate at a lower figure.

Sex ratio

Results of several large studies agree that mycosis fungoides is somewhat more common among males (reviewed in ref. 1).

SEX DISTRIBUTION IN MYCOSIS FUNGOIDES

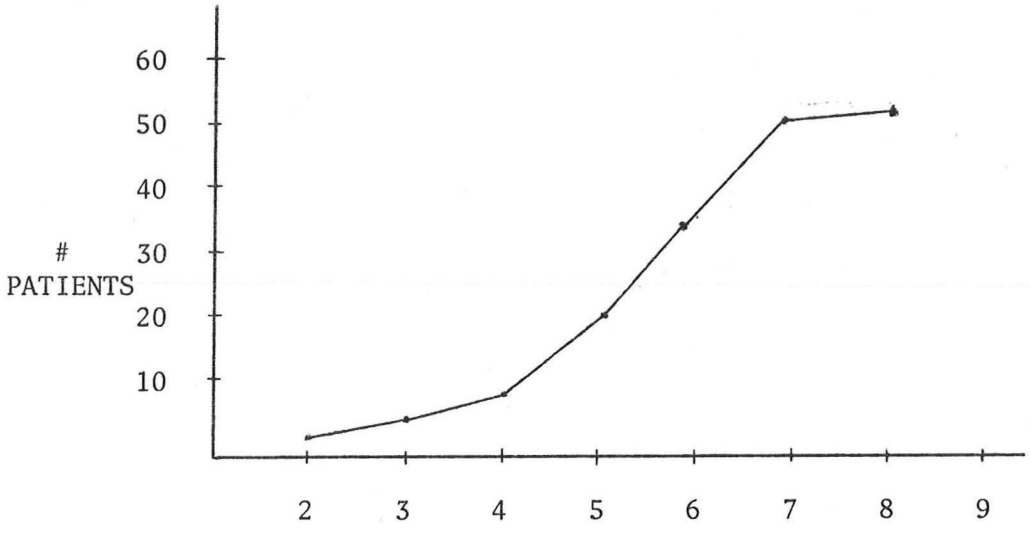
REPORT	N	% MEN	% WOMEN
HEITE AND SOCHA 1951	588	57	43
BLUEFARB 1959	308	58	42
DEGOS, ET AL. 1965	91	52	48
CYR, ET AL. 1966	165	64	36
EPSTEIN, ET AL. 1972	144	58	42
FUKS, ET AL. 1973	132	68	32
SWEDISH CANCER REGISTRY 1958-1971	204	59	41

MODIFIED FROM BREHMER-ANDERSSON

Age

Unlike some tumors of lymphoid tissues the disease is never or very rarely seen in childhood. Instead most of the patients develop skin lesions between 40 and 60 and receive a diagnosis between 45 and 70 years of age.

AGE DISTRIBUTION IN MYCOSIS FUNGOIDES



MODIFIED FROM BREHMER-ANDERSSON

Familial incidence

It is extremely rare to hear of more than one case in the same family. A single instance of the disease in a mother and daughter was reported (39) while one other concordance occurred in a brother and sister (40).

Presentation

MYCOSIS FUNGOIDES: MODES OF PRESENTATION

Alibert-Bazin form

Three stages: (1) Erythema or eczema

(2) Plaques

(3) Tumors

Erythroderma (Sezary syndrome)

Tumor d'emblee form

In the typical case the patient's illness falls clearly into three clinical stages: 1) the erythematous or premycotic stage, 2) the plaque or infiltrative stage, and finally 3) the tumor stage. This division can be misleading because some patients may never progress beyond the first or second stage, while others may develop signs of all these stages simultaneously. Rarely the patient may develop tumors de novo. A great deal of controversy has arisen over this small group, who have often been labelled lymphosarcoma or primary cutaneous Hodgkin's disease. Another small group of patients presents with erythroderma. The Sezary syndrome has erythroderma as one of its features, but also requires that abnormal cells be found in the blood. More often erythroderma develops in the early stages of mycosis fungoides as a nonspecific reactive state when the peripheral smear is normal. Both such groups may later develop plaques and tumors.

The premycotic stage

This stage can present a wide variety of nonspecific-appearing reactive conditions, including eczema, psoriasis-like patches with or without characteristic finger-like extensions, or a peculiar change comprising hyper-and hypopigmentation, atrophy and telangiectasia. This last condition closely resembles the residue of a mild x-ray burn to the skin and is called poikiloderma atrophicans vasculare. Itching usually accompanies the premycotic stage, and may be quite severe.

Samman in a series of articles (41,42) has emphasized that many patients with mycosis fungoides recall many relapses and remissions in their cutaneous symptoms. In order to portray the slowly and irregularly progressive course of the disease Wilson-Jones has published a striking graph (43) illustrating the subtle and minimal rate of progress seen in some patients, compared with the rapid deterioration of a handful of them.

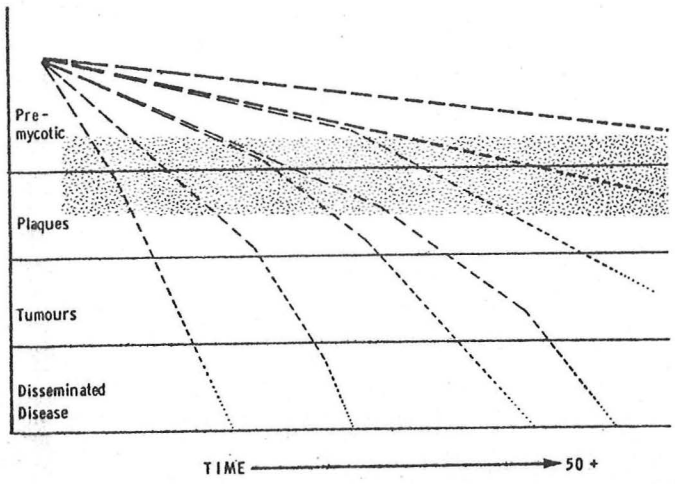


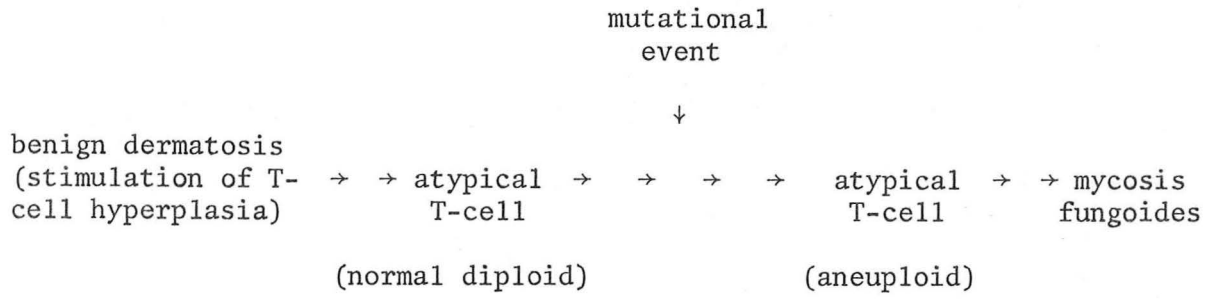
DIAGRAM TO SHOW PROGRESS OF MYCOSIS FUNGOIDES

from Wilson-Jones

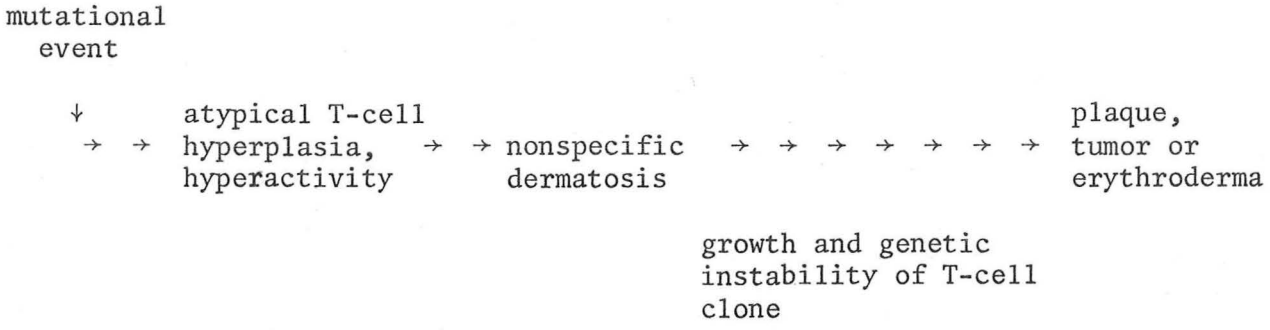
What accounts for the variety and banal nature of the premycotic stage, a stage when by definition the pathologist cannot detect tumor cells

or other changes sufficient to diagnose mycosis fungoides? Two theories have

PATHOGENESIS OF MYCOSIS FUNGOIDES (I)



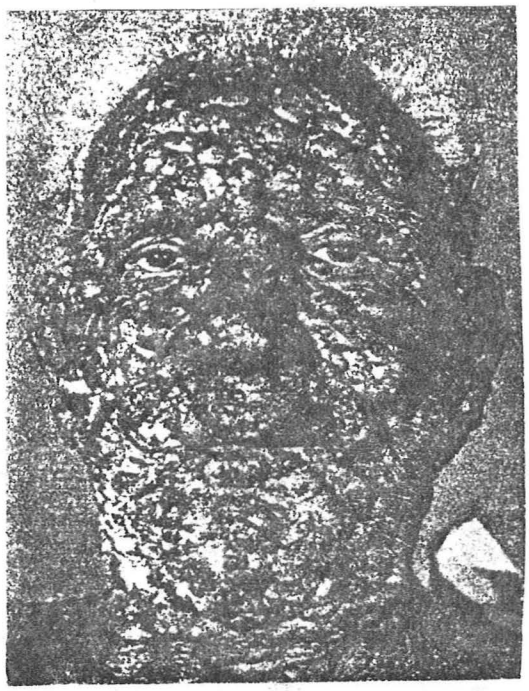
PATHOGENESIS OF MYCOSIS FUNGOIDES (II)



drawn support: 1) the disease begins in a site or sites of chronic inflammatory or infectious stimulation to cutaneous T-cells. With such stimulus as the promoting influence some other mutagenic event triggers emergence of an autonomous clone, one which proceeds at an unpredictable pace to kill the patient, 2) alternatively the disease reflects from beginning to end the constant accumulation of a malignant clone of cells, but at first a very slow-growing and minimally-deviated one. The abnormal T-cells actively produce lymphokines and pursue their other functions such as enhancing synthesis of antibody. Lymphokines draw in other inflammatory cells. The presence of the reactive cells then makes it impossible to identify the few cells of the mutated clone and also leads to a wide variety of clinical presentations at the skin surface.

Plaque or infiltrative stage

Plaques appear as oval or round thickened areas with a brick red- to purple, shiny surface. Central clearing can cause a donut-like or annular appearance. Typically these lesions feel soft and cushiony to the touch, though more rarely they may become scaly or hyperkeratotic. A diffuse component may cause leonine facies, and any plaques that develop in hair-bearing areas usually cause local alopecia.



Leonine facies in mycosis fungoides

from Clendenning, et al.

Tumor stage

Tumors may occur anywhere on the body but seem to favor the face and flexural folds. They attain sizes up to several centimeters, although smaller ones are the rule. They may coalesce into unsightly masses, may ulcerate, and most remarkably may disappear spontaneously in a short period of time (days or weeks) (44, 45). Such capricious behavior has inspired some to speculate that either mutational instability or the destructive effect of the normal, reactive cell infiltrate has extinguished the local clone of abnormal T-cells within that particular lesion.

But not many tumors fade spontaneously. Instead most break down, become infected, and as the patient's tumor load increases these open ulcers contribute to a losing battle with sepsis. As noted below, the cellular infiltrates of mycosis fungoides tend to spare normal structures, sparing them from destruction far longer than other lymphomatous malignancies do. Perhaps for this reason tumors usually remain painless unless infected, and itching that may have been agonizing earlier during the erythematous and plaque stages may disappear.

Erythroderma

Universal redness with desquamation may complicate many skin diseases, and is not specific for the Sezary syndrome (which requires the presence of characteristic cells in the blood). Erythroderma can therefore constitute the premycotic stage of mycosis fungoides (8,46,47) and precede the development of tumors by many years (48) or can develop during the plaque or tumor stage.

Typically these patients suffer from severe itching, adenopathy that may become massive, more or less complete alopecia, and alternating spells of improvement and worsening that cannot be related to treatment.

Tumors d'emblee

This form of the disease is the most controversial, since some observers contend that all such patients have lymphosarcoma or Hodgkins disease (39). A few bona fide cases appear to have been reported, however (1,46,47).

Clinical course

Despite widespread plaques and even tumors many patients enjoy good health, remaining employed and vigorous for long periods. Alibert was surprised that Lucas could continue to work for five years after the lesions appeared. Cases with a history extending over 58 years have been recorded (49), and a protracted course has long been considered a characteristic feature of the illness (39).

As with other disorders one's ideas of prognosis depend upon the source of the published series: those from large referral centers like NIH, where the most florid and troublesome cases seek admission, tend to portray the outlook in the blackest tones (46). For a contrasting view one must turn to a setting involving an outpatient registry, where bias due to selection of the worst cases can be excluded. Samman has published reports on such a register maintained at the St. John's Hospital for Diseases of the Skin in London since 1959 (41,42) and has accumulated data on more than 600 cases involving cutaneous reticulosis. Material from this source shows that only about 8% of all cases suffer death from the disease during the ten years following diagnosis. Taking into account the tendency of most persons to become

MYCOSIS FUNGOIDES: PROGNOSIS

SAMMAN - OUTPATIENT REGISTRY	
DIED (10Y)	21%
ALIVE (>10Y)	49%
LUTZNER - REFERRAL CENTER	
DIED (3½ Y)	50%

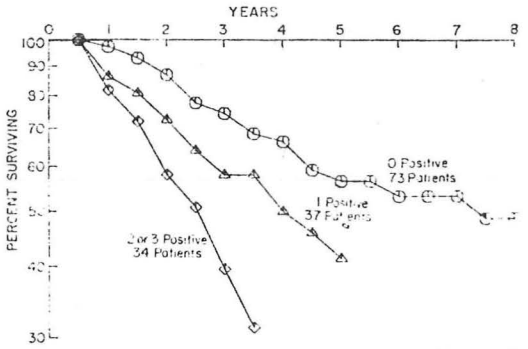
MYCOSIS FUNGOIDES: PROGRESS OF THE DISEASE

STATUS	MEN N=160	WOMEN N=85
Lost from observation	24	9
Died of disease	25	20
Died of intercurrent disease	13	4
Cleared	7	1
Alive after 0-5Y	3	3
6-10Y	21	11
11-15Y	23	8
16-20Y	21	11
21-25Y	11	5
26-30Y	6	5
>30	6	8

affected late in life he found that very few of the remainder have their lives appreciably shortened by the process. The physician should recall that an unselected sample portrays mycosis fungoides as a relative benign

disorder before he commits a patient with early, minimal disease to heroic therapy.

On the other hand he should attempt to sift from the favored majority those few patients destined to progress rapidly, so that they can receive active treatment. Epstein's series and later reports from NIH (46,50) have provided decisive evidence that age over 60 years, presence of palpable nodes, cutaneous tumors or cutaneous ulcers all shorten prognosis, while lymphopenia and evidence of visceral lymphoma on lymphangiogram or liver-spleen scan also reduces the patient's expected survival (51-53).



Survival of patients after biopsy diagnosis according to the number of parameters (cutaneous tumors, cutaneous ulcers, and palpably enlarged lymph nodes) developed previous to diagnosis. Curves stop at ten patients remaining in each group.

from Epstein, et al.

AVERAGE DURATION OF MYCOSIS FUNGOIDES

SERIES	N	AVERAGE DURATION (FROM FIRST SYMPTOM)
Cyr (1966)	106 Died	8.1 Y
	59 Living	12.5 Y
Larsen (1968)	34 Died	9.0 Y
Epstein (1972)	144 Died	9.1 Y

modified from Brehmer-Andersson

Prognostic Factors in Mycosis Fungoides

Factor	Median survival (Months)	Reference
At Time of Biopsy Diagnosis		
1. Age:		
Over 60 years	30	Epstein et al
Under 50 years	72	Epstein et al
2. Clinical Stage of Disease		
No skin tumors, ulceration or palpable lymphadenopathy	>72	Epstein et al Fuks et al
Presence of skin tumors, ulceration or palpable lymphadenopathy	<30	Epstein et al Fuks et al
During Course of Disease		
1. Clinical Findings		
Skin tumors, ulceration or palpable adenopathy	~24	Epstein et al Muller
All three of above	12	Epstein et al
Visceral lymphoma	~7	Epstein et al Block et al Cyr et al Fuks et al
2. Laboratory Findings		
Blood lymphocytes <1000/mm³	~18	Fuks et al
3. Histology of Lymph Nodes		
Dermatopathic changes	34	Epstein et al Block et al
Mycosis fungoides	<18	Epstein et al Block et al

from Levi and Wiernik

Causes of death

In those cases that die as a direct consequence of mycosis fungoides, the end has usually come from one of three complications: infection, toxicity of treatment, or from advanced and disseminated disease with cachexia (46,53).

Histopathology

The histopathologist has been forced to update his classification of monocytic malignancies affecting skin by using cell-surface markers (51).

MONOCYTIC MALIGNANCIES OF SKIN

B-Cell		T-Cell
Lymphocytic:	well differentiated poorly differentiated mixed lymph-histiocytic	Mycosis fungoides (Sezary syndrome) Hodgkin's disease
Myeloma		

Stem Cell

Burkitt lymphoma
Stem or pleomorphic stem-histiocytic cell

modified from Lever

HISTOPATHOLOGIC CRITERIA FOR DIAGNOSIS OF MYCOSIS FUNGOIDES

Erythematous stage:	Nonspecific
Plaque stage:	1) Many cell types 2) Immature, atypical cells (mycosis cells), mitotic figures 3) Band-like infiltrate 4) Intraepidermal microabscesses (Pautrier's)
Tumor stage:	1) Accentuation of infiltrate, fewer cell types and increase in atypical cells 2) Occasional appearance of giant cells

modified from Lever

Premycotic stage: In this setting the pathologist cannot, by definition, provide a definite diagnosis. Some authorities suggest (54) that the astute interpreter can suspect the presence of mycosis fungoides by noting the prevalence of histiocytes, particularly those with denser, more irregular nuclei in the upper dermal infiltrate.

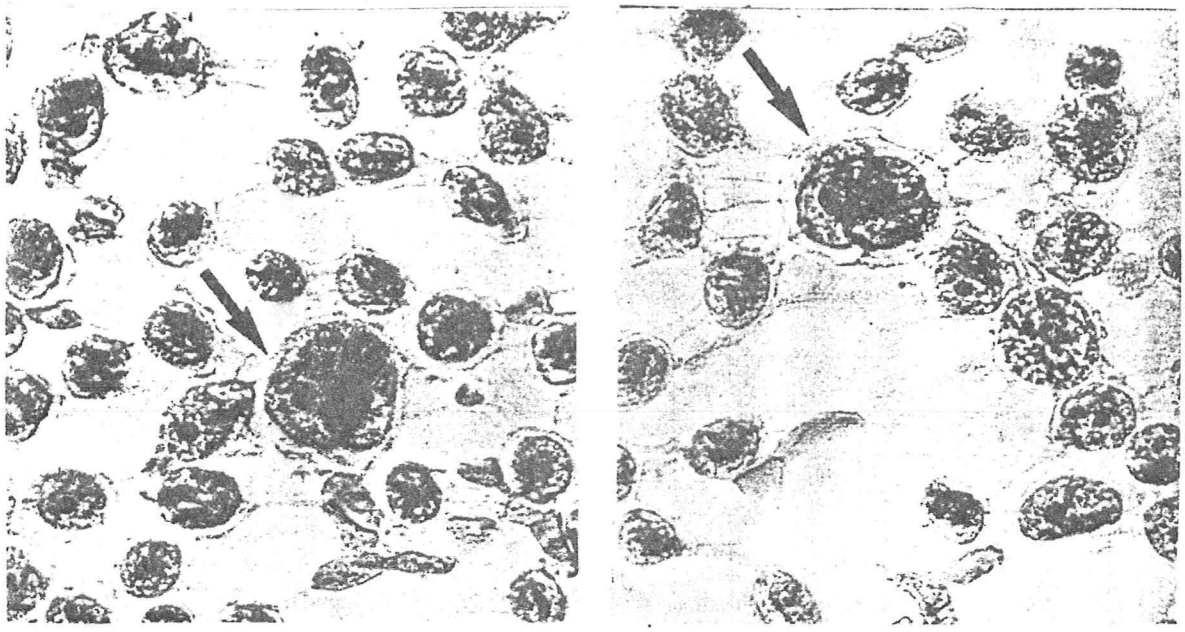
Plaque stage: Four criteria have been proposed (54): 1) A bandlike infiltrate in the upper dermis, becoming patchy lower down with the patches centering on blood vessels. The larger and more sharply demarcated the patches the more secure the diagnosis. 2) A mixture of cell types in the infiltrate: lymphoid cells, eosinophils, plasma cells, histiocytes, even mast cells may be increased. 3) The presence of mycosis cells as already discussed. Edelson has positively identified these neoplastic cells from the skin infiltrates of mycosis fungoides as having surface properties of T-lymphocytes (11,21). In light microscopic sections they appear as mononuclear cells with hyperchromatic, irregularly shaped nuclei. 4) Signs of epidermotropism of the mycosis cells. These cells appear to possess special affinity for the epidermis. This final criterion represents the most securely pathognomonic sign of the disease (55), and includes the tendency for mycosis cells to collect in small clusters, called Pautrier microabscesses with or without a few inflammatory cells, or in diffuse infiltrations (43,55), or even singly. Although some have observed Pautrier's microabscesses in reticulum cell sarcoma or histiocytic lymphomas of skin (56,57), the problem of differentiating between these stem cell forms and mycosis fungoides rarely arises in practice (55).

All three of the latter forms of exocytosis may affect hair follicles as well as surface epidermis. Even without overt cellular invasion large tracts of hair follicles in mycosis fungoides may lose their hair and begin synthesizing mucinous material rather than keratin, a change called alopecia mucinosa (58).

Tumor Stage: By this time the infiltrate has increased in depth to involve the fat, and has become more uniform, now being composed of neoplastic immature mycosis cells that often show mitotic figures. In some cases these immature cells assume the appearance of, or are interpreted as multinuclear Reed-Sternberg cells (13,49,55,59). Nevertheless they appear to differ from the characteristic cell of Hodgkin's disease by greater hyperchromasia and relatively more condensed, shrunken appearance of their nuclei, which usually lack prominent nucleoli (54,60). But the infiltrate may also assume such an immature and monotonous picture that reticulum or stem cell lymphoma represents another pitfall for the pathologist who receives only a single biopsy specimen, especially if this comes from a late-stage tumor while the earlier clinical history is unavailable. Both in the skin and in other organs (55) the infiltrating cells appear to spare the local structures or parenchymal cells. That is, mycosis fungoides destroys local tissue far more slowly than do other malignant lymphomas, perhaps accounting for the unexpected longevity of the average patient.

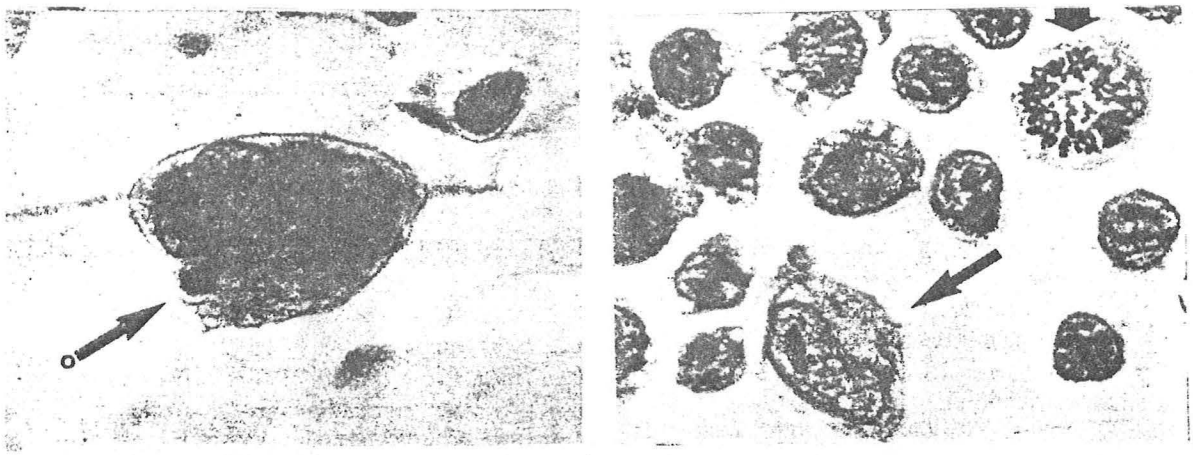
The concept of primary cutaneous Hodgkin's disease

Since experienced pathologists may differ over distinctions between multinucleate mycosis cells and Reed-Sternberg cells (53,54,55), considerable controversy has arisen over the concept of primary cutaneous Hodgkin's disease (summarized in ref. 1, pp. 124-125). In those few



Two giant cells have mirror-image nuclei and large nucleoli (←).

from Brehmer-Andersson



There are cells with a rich cytoplasm, a large, light nucleus with prominent nuclear membrane and a very large, eosinophilic, round or oval nucleolus (←). In the upper right field there is a mitotic figure (↞). In the lower left field there is a multi-nucleated giant cell with a phagocytized nuclear fragment (←o). Hematoxylin-eosin, x 1000.

from Brehmer-Andersson

cases reported as Hodgkin's disease in which cutaneous lesions remained the sole manifestation (61), it must be asked whether the case represented an example of inadequate systemic evaluation (62), or whether it implied a state of balance between the tumor and the host's immune response, or whether the patient in fact had the tumor d'emblee form of mycosis fungoides, or one of its precursors (53,54). Some have suggested that a common ancestor cell-type might explain part of the confusion between mycosis fungoides and primary cutaneous Hodgkin's disease. Evidence that Hodgkin's disease issues from proliferating, altered, T-lymphocytes has come from a number of sources (54,63). Although space does not permit an extended discussion of a very controversial subject, the similarities between the two disorders are reflected in the mixed cellularity of the infiltrate, the early localization of changes in T-dependent regions in nodes and spleen, and the occasional overlap of cutaneous appearance.

Systemic pathology

Some pathologists at one time considered it uncommon to find at autopsy that mycosis fungoides had spread beyond the skin (64). Another group interpreted any signs of spread as examples of transformation of the disease to a histiocytic or stem cell lymphoma, or to Hodgkin's disease (53, 54, 65). But a much larger sampling of opinion, going back to Bennek in 1938 (quoted in ref. 1) and given strong support more recently (8,46,55,66) has emphasized that secondary involvement by tumor that retains diagnostic features of mycosis fungoides can occur in practically any organ of the body. Peripheral and visceral lymph nodes most commonly displayed the disease, although similarities in such nodes between benign, reactive dermatopathic lymphadenitis and partial replacement by mycosis fungoides made morphologic diagnosis difficult without electron microscopic study (13,55). Rappaport and Thomas nevertheless felt they could detect cytologic changes specific for mycosis fungoides in such lymph nodes, since reactive histiocytes appeared larger, more vacuolated with fat or melanin, and had less dense nuclei than did mycosis cells (55).

LYMPH NODE AND VISCERAL INVOLVEMENT
IN MYCOSIS FUNGOIDES

Site	%*
Lymph node	75
Lung, spleen, liver	55-65
Kidney, thyroid, pancreas	40-45
Adrenal, ovary, meninges	15-20

* of those having extracutaneous spread

modified from Rappaport and Thomas

The latter writers found that 32 of 45 patients (71%) had extracutaneous involvement at autopsy, a very high proportion until one realizes that they selected their cases from the 140 studied at NIH by Epstein, et al. (46). Of these 140, 120 had died and 86 had come to autopsy. The highly selected nature of this group may account for the impression that extracutaneous spread occured so frequently. One of their most important findings concerned a correlation between involvement of lymph nodes and spread to viscera: when nodes displayed definite signs of invasion, then visceral spread was almost invariably present. Only when all nodes appeared clear of disease could one predict that deeper structures had also remained clear (55).

CORRELATION BETWEEN LYMPH NODE AND VISCERAL INVOLVEMENT IN MYCOSIS FUNGOIDES AT AUTOPSY

		Visceral Involvement		
		PRESENT	EQUIVOCAL	ABSENT
Lymph Node Involvement	PRESENT	24	0	0
	EQUIVOCAL	4	1	1
	ABSENT	4	0	12

Laboratory examinations

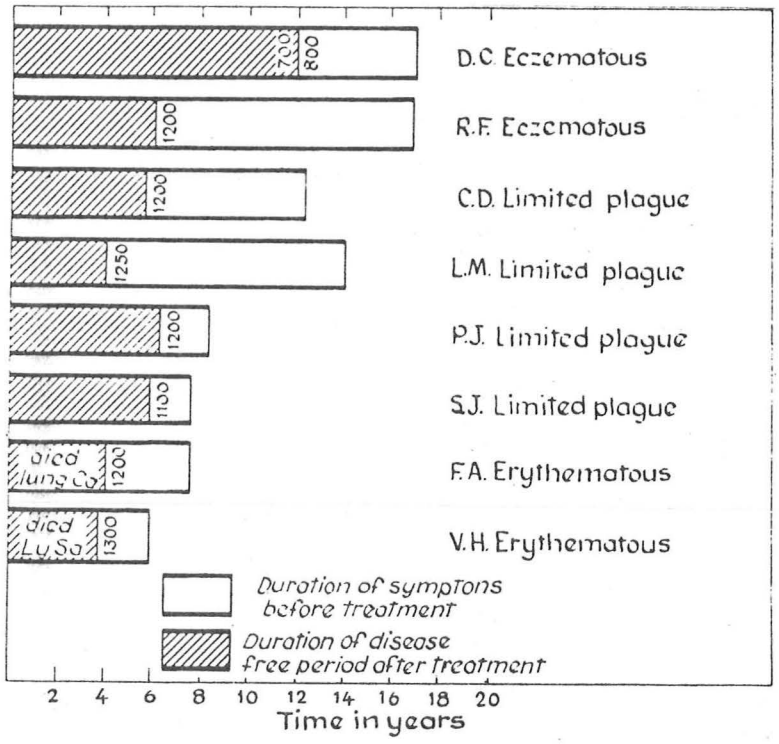
Eosinophilia has acquired a reputation as the only regular alteration in standard laboratory tests of patients with mycosis fungoides (45,53,67). Immunoelectrophoresis of serum, however, showed frequent in elevation levels of IgA (25) in the Sezary syndrome and in a small subset of patients with mycosis fungoides (26), perhaps reflecting the helper function of the affected T-cell clone (24). One report has shown reduced numbers of T-cells in peripheral blood of patients with mycosis fungoides (26) but all patients had received some treatment, and differences were small.

Many reports have appeared of patients with mycosis fungoides who suffered terminal leukemoid reactions (8,39,53,67,68,69). In retrospect these were almost surely abnormal lymphocytes similar to those seen in the Sezary syndrome.

Bone marrow biopsy usually showed no abnormality aside from eosinophilia (53) or increased numbers of plasma cells (52, 53). Rappaport and Thomas found involvement of bone marrow by tumor in 12 of 31 autopsied cases (39%).

Staging: Rational or irrational?

Because some have considered mycosis fungoides curable by vigorous use of electron beam as long as it remained limited to the skin (51,70) a



Patients without evidence of disease three years or more after their first treatment with electrons. The numbers indicate the dose (rads) delivered to the skin.

from Fuks and Bagshaw

wave of enthusiasm for staging procedures has swept the clinical literature (71,72). Some of this enthusiasm seems misplaced. One has only to compare the claimed rate of radiotherapeutic cures -- eight of 56, or 15%, of those patients with early, limited disease after a three to eleven year followup -- with the small proportion of patients who if left untreated or treated conservatively actually have their lives shortened by the disease to see that differences are questionable. The controversial report of cures resulting from radical treatment of early disease (70) failed to provide histologic data. One third of the responders had early and therefore possibly non-diagnostic lesions. More than a third of the patients required two courses of radiation with associated morbidity. Samman's outpatient register (42) showed that, excluding those lost to followup and those dying of intercurrent disease, 112 of 195 or 57% lived longer than 11 years, while 4% had cleared spontaneously. In another study, pathologic examination of affected skin following electron beam showed some reduction in the polycellular infiltrate but no change in the number of distribution of mycosis cells (73), although earlier studies had claimed a reduction in these cells also (74).

But going beyond comparisons of survival, the dogma that mycosis fungoides arises in the skin should be questioned more seriously now that the responsible cell is known to derive from the T-lymphocyte. The migratory T-cells surely display epidermotropism for skin but are not confined to it. These cells appear to shuttle between skin and T-dependent paracortical areas

of peripheral lymph nodes from the first (75,76). Such a recirculating pool of cells will evade any practical degree of penetration by electron beam. At most one could expect treatment to reduce the numbers of such cells, a reduction that may, of course, prolong life in some instances.

Staging: Practical aspects

The physician ordinarily carries out the first and most important staging maneuver as he examines the patient. If he finds enlarged peripheral lymph nodes, the patient's prognosis has already fallen statistically (50) whether a later biopsy shows mycosis fungoides or only an apparently reactive state (dermatopathic change). How much investigating should one do if all peripheral nodes feel normal in size? Several groups agree that viscera or retroperitoneal nodes may show invasion even with normal peripheral nodes, though at much lower frequency (55,71,77,78). For this reason a consensus recommends that even patients with no palpable adenopathy should undergo biopsy of a node from a zone draining affected skin (71) as well as lymphangiography to visualize retroperitoneal nodes (77,78). As an additional screening test the group at the University of Chicago has recommended liver-spleen scan with splenectomy and liver biopsy if the scan was abnormal. Bone scans and bone marrow exams yielded little added information while radiography of kidneys or gi tract offered nothing (71).

MYCOSIS FUNGOIDES,
CLINICAL STAGING PROCEDURES

Complete physical examination:	Note type of skin lesions
Laboratory studies:	Routine, including liver and renal function tests
Bone marrow:	Aspiration and core biopsy
Lymph node biopsy:	From area draining skin lesions
Radiological studies:	Chest Inferior venacavagram Bipedal lymphangiogram
Scintigraphic studies:	^{67}Ga (whole body scan) ^{99m}Tc sulphur colloid (liver, spleen and bone marrow) ^{99m}Tc EHDP* (bone scan)

from Griem, et al.

Treatment

Whether or not mycosis fungoides ever remains truly limited to skin, those patients with apparently limited disease are likely to harbor a clone or clones of cells that display fewer features of malignancy than those of patients with deeper spread. For this reason limited disease should probably not receive radical or heroic therapy, particularly since the prognosis often appears good. But patients with disease in nodes, viscera or severe ulcerating lesions of skin -- those whose prognosis has been shown to be short (46,50) -- need systemic therapy.

TREATMENT OF MYCOSIS FUNGOIDES

Local:	Mustargen (other alkylators)
	Corticosteroids
	DNCB
	Radiotherapy
	Photochemotherapy
Systemic:	Chemotherapy

Local treatment

During the erythematous or premycotic stage when the diagnosis can only be suspected, therapy should be conservative but followup observation compulsive because of the unpredictable course of the disease. Topically applied steroids, emollients, and ultraviolet light ameliorate the symptoms at this stage.

The difficult choices begin after biopsy establishes a diagnosis. Despite the eloquent example in the literature on Hodgkin's disease, most physicians have been inhibited from committing the patient with early, minimal disease to radical radiotherapy or chemotherapy (42,50,79,80). Effective topical therapy for plaque-stage or erythrodermatous disease includes:

1) Nitrogen mustard (81-83): Twenty to fifty mg per 100 ml water has been applied to the skin daily or more often either with or without a preliminary 'tolerizing' series of intravenous injections (83). Response rates averaged 57% (50) and took up to six or eight weeks before reaching a plateau. Clearing persisted longer when maintenance was given. At times a remission lasted three or more years, while systemic toxicity was unheard of. The main threat to success was development of delayed contact sensitivity to mustargen, against which 'desensitizing' injections have had variable success (83,84). Mustargen has cleared patients who were relapsing following electron beam (85) and its use did not preclude a return to beam. Other topically applied alkylating agents have been used successfully (86) although systemic toxicity has been seen with topically applied lomustine (87).

2) Corticosteroids (88,89): These agents palliate and reduce inflammatory symptoms during early-stage disease.

3) Induction of delayed hypersensitivity: Several investigators noted that lesions of mycosis fungoides improved more rapidly in patients who suffered delayed hypersensitivity to nitrogen mustard than they did in those who escaped this complication (81-83,85). Ratner (90) and others (91) then showed that sensitizing chemicals, such as DNCB, could induce short-lived regression of plaques, while primary irritants of equivalent biologic effect such as sodium dodecyl sulfate could not.

4) Radiotherapy: Various forms of x-irradiation have been used in mycosis fungoides (summary in ref. 50). Application of kilovoltage (100-140 k_V) rays should be limited to small fields composed of infiltrated plaques and tumors, where it plays a useful role (92). For those affected over wide areas of the body only high-energy electrons offer sufficiently controlled and limited penetration with uniform delivery of dose, convenience of whole-body coverage, and acceptably low exposure of the bone marrow and gut (51,70,93-95). Beam energies of 2.5 to 3.0 mev yielded the ideal penetration, an 80% depth dose at 4.5 to 7 millimeters. Patients have received between 800 and 2000 rads in two to six weeks -- Fuks alone has published data on doses up to 3000 rads in 40 days (51,70) -- with 60 to 90% regression rate for plaques, lower for tumors. Longer remissions tended to correlate with higher doses, but atrophy, telangiectasia, and ultimately ulceration tended to replace one disability by another if high or repeated doses were used.

5) Systemic chemotherapy: A wide variety of therapeutic agents have been used, but the rarity of the disease and the recent refusal of NCI to fund a cooperative multicenter trial has reduced the opportunity for controlled studies. Generally chemotherapy has been used for patients with advanced disease after other modes of treatment have been exhausted. Among the most promising appear to be the alkylater cyclophosphamide (46,96), methotrexate (79,97), and bleomycin (98,99), although steroids can be briefly successful alone (46,79,97). The literature on combined chemotherapy for mycosis fungoides remains in its infancy with only brief mentions of a four-drug regimen in a few patients (46). Unfortunately, despite the undoubted success of mustargen and electron beam in producing long-term remission no proof exists that any treatment has prolonged survival in mycosis fungoides (46,79).

6) Photochemotherapy: In the presence of the relatively deeply penetrating UVA portion of the sun's spectrum (λ=320-380 nm) an orally-administered photosensitizing furocommarin compound with an action spectrum of 340-360 nm produces photo-adducts with mammalian DNA, stopping proliferation of cells. Such therapy has proved quite successful in psoriasis (100). The Harvard group has recently shown that mycosis fungoides also responds (101). Four of nine patients cleared while the others improved dramatically. Whether this mode of treatment will provide more than palliation remains uncertain, however.

Case presentation

The patient is a 66 year old white male who developed pain in the small joints of his hands and feet during the early 1960's. Within a few years time he developed a scaly erythematous eruption on the back and lower legs. Since his father had had psoriasis he was prepared for the diagnosis,

and was pleased when his arthralgia remitted spontaneously.

In 1964 he received methotrexate for his by now severe psoriasis. He and his physician were disappointed by his lack of response, an unusual happening in psoriasis. Steroids helped a little, but produced emotional depression. Other antipsoriatic measures used during the early 1970's demonstrated no worthwhile activity.

His eruption had by the early 1970's covered 90% of his body, causing painful cracking of his feet and hands, with marked hair loss. Still he felt well and continued to work. In February 1974 his first abnormal white blood cell count was obtained on a routine examination. In a short time the diagnosis of chronic lymphocytic leukemia was made on peripheral smear. No specific treatment was prescribed.

DATE	TOTAL WBC /cu mm x1000	% LYMPHS
12/73	9.2	55
12/74	11.6	47
1/75	17.3	68
5/76	36.5	73
10/76	50.8	86
11/76	89.0	86

In October 1976 the diffuse erythroderma, indurated edema of the skin, loss of hair, nails, and severe palmoplantar scaling suggested a diagnosis of Sezary syndrome. Skin biopsies were interpreted as either mycosis fungoides or the Sezary syndrome.

Testing for surface markers was carried out by Dr. Toben of the Department of Cell Biology, University of Texas Southwestern Medical School. Anti-T-cell antisera identified virtually 100% of the peripheral lymphocytes, although only 40% of them formed rosettes spontaneously with sheep erythrocytes. However, less than 3% had F_c receptors characteristic of monocytes or B-cells.

When tested late in 1976 he did not show a skin test response to recall-antigens like mumps, Sk-Sd or trichophytin. His lymphocytes did not respond to PHA. His serum IgE level was elevated while the IgA was normal. Although he had marked peripheral adenopathy, his bone marrow and liver-spleen scan were normal.

In February 1977 an A-V shunt was inserted and the patient began on systematic leukapheresis. His white count has dropped from 89,000 to 16,000 with moderate clinical improvement after eight sessions on the pump.

This case illustrates many of the features of T-cell malignancy -- a long course during which it mimics a banal dermatosis, preservation of physical vigor, and misdiagnosis of chronic lymphocytic leukemia. When did the disease begin -- the early 60's, 1964, or at the time of the first

elevated white cell count in 1974? A lack of response to methotrexate favored mycosis fungoides over psoriasis in 1964, but the peripheral blood was normal (data not shown) making a diagnosis of Sezary's difficult to apply.

The Sezary syndrome: Clinical presentation

The criteria for a diagnosis of this disorder have been summarized by Winkelmann (102). Sezary's original cases were all females from 58 to 69 years of age (103). They gradually developed erythroderma with edema,

CLINICAL FEATURES OF 28 PATIENTS WITH SEZARY SYNDROME

	No.	%
Erythroderma	28	100
Edema	28	100
Pruritus	28	100
Adenopathy	16	57
Hepatomegaly	10	36
Alopecia	9	32
Onychodystrophy	9	32
Keratoderma	8	29
Hyperpigmentation	3	11
Excoriation	2	7

from Winkelmann (ref. 103)

leonine facies, marked pigmentation, severe itching, hyperkeratosis and fissuring of palms and soles, lymphadenopathy, atypical 'monster' lymphohistiocytes in blood, skin, and nodes, but sparing of internal organs and marrow.

The sequence began with itching. After a few months the patients developed erythematous, scaly plaques that were often mistaken for psoriasis or eczema. Later these thickened and pigmented. Lymphadenopathy occurred late, always secondary to extensive skin lesions.

The diagnosis requires not only a generalized erythroderma, but abnormal circulating cells, 'cellules monstreuses' in Sezary's term. But it has become clear that the leukemic T-cells need not appear unusually large in size. The small-cell variant closely resembles a mature small lymphocyte (10) to the unwary observer, and many cases labelled as chronic lymphatic leukemia with erythroderma have, upon reexamination, been found to suffer from the Sezary syndrome (11). The only sure means of diagnosis involves identification of immunologic surface markers (21,22) although use of the electron microscopic to examine the buffy coat should help when available. Most authors insist upon finding at least 10% atypical cells whatever the total peripheral white count. As the tables summarizing the three largest series (10,104,106) show, the total white blood count need not be greatly elevated.

SUMMARY OF THREE LARGE SERIES OF SEZARY SYNDROME

	MEN	WOMEN	AGE	ADENOPATHY	BLOOD	MARROW
TASWELL AND WINKELMANN 1961	6	1	34-75	6/7 - NONSPECIFIC	10.4-32.1 $10^3/mm^3$ 13%-58% ATYPICAL	7/7 NORMAL
WINKELMANN, ET AL. 1973-74	17	11	AVG 63 (MEN) AVG 55 (WOMEN)	16/28 - DERMATO-PATHIC	$<20,000/mm^3$ >13% ATYPICAL	28/28 NORMAL
EDELSON, ET AL. 1974	8	5	AVG 42 (MEN) AVG 54 (WOMEN)	13/13 - PERMEATED BY ABNORMAL CELLS	3 CASES 75,000-240,000 10 CASES 8,500-46,000	10/13 NORMAL (3 MODERATE INCREASE LYMPHS)

SUMMARY OF THREE LARGE SERIES OF SEZARY SYNDROME (CONTINUED)

	SKIN	COURSE
TASWELL AND WINKELMANN 1961	4/7 MYCOSIS FUNGOIDES 2/7 RETICULUM CELL SARCOMA 1/7 NONSPECIFIED	5 DIED 4-6Y 2 LIVING
WINKELMANN, ET AL. 1973-74	17/28 LYMPHOCYTIC 7/28 ATYPICAL RETIC CELL 4/28 LYMPHOMA	13/28 ALIVE 10/28 LYMPHOMA 2/28 UNRELATED DEATHS
EDELSON, ET ALL 1974	13/13 MYCOSIS FUNGOIDES	6/13 DIED

MODIFIED FROM BREHMER-ANDERSSON

Skin Biopsy

Not only do pathologists find it impossible to distinguish between the Sezary cell and the mycosis cell, they also have difficulty in differentiating between skin biopsies taken from the two conditions. The Sezary syndrome displays the same mixed cellularity, epidermotropism, and pattern in the dermis as does mycosis fungoides. The lymph nodes also appeared similar (8,10,21,54,103,107).

Hematologic findings

A moderate leukocytosis was found in most cases (10,000-30,000) although much higher numbers could accumulate at times (21,104). Besides the specific cells with their hyperchromatic and cerebriform nuclei taking up 80% of the cell volume, the differential count usually showed an absolute lymphocytosis. The bone marrow was normal.

Course

The available literature has failed to provide specific prognostic signs for the Sezary syndrome, although those criteria that were useful in predicting the course of mycosis fungoides may help here as well.

Interpretation and classification

CLASSIFICATION OF THE SEZARY SYNDROME

1. A distinct disease unrelated to mycosis fungoides
   (Winkelmann, Montgomery)

2. A variant of mycosis fungoides
   (Clendenning, Edelson)

3. A syndrome which can appear in different types of malignant lymphoma
   (Fleschmajer and Eisenberg)

from Brehmer-Andersson

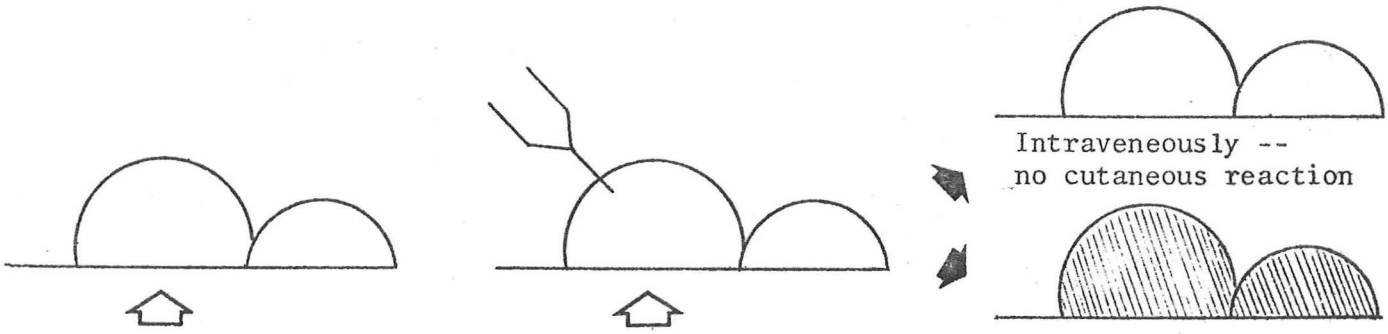
Winkelmann's views (102,104-106) stand almost alone in the literature in considering the Sezary syndrome a benign and reversible disease which occurs in otherwise healthy older individuals. He felt that the condition arose in relation to drugs, atopic or contact dermatitis, or graft-versus-host reactions, and rarely transformed itself into a malignant lymphoma. In fact, others have noted that just as with mycosis fungoides, an occasional patient does clear completely. Even more commonly the abnormal peripheral lymphocytes rise and fall in number over time without apparent cause.

But this view ignores the cytogenetic findings of consistent aneuploidy, the resemblance to mycosis fungoides and the likelihood that

early Sezary's syndrome does in some cases represent a relatively minimal-deviation neoplasm, a slowly growing, non-agressive clone that may cause little trouble aside from erythroderma.

Genesis of the erythroderma

As was mentioned above, the abnormal population of Sezary cells often performs certain functions of T-lymphocytes quite well while it handles others poorly. Most patients show signs of vigorous production of macrophage inhibition factor and may be presumed to have high levels of other lymphokines as well (27). As a clinical correlate the universal redness, scaling, and edema suffered by Sezary patients contrasts markedly with the locally affected patient with mycosis fungoides who develops only local plaques and whose serum lacks MIF (28). Why does the human skin react in this way?

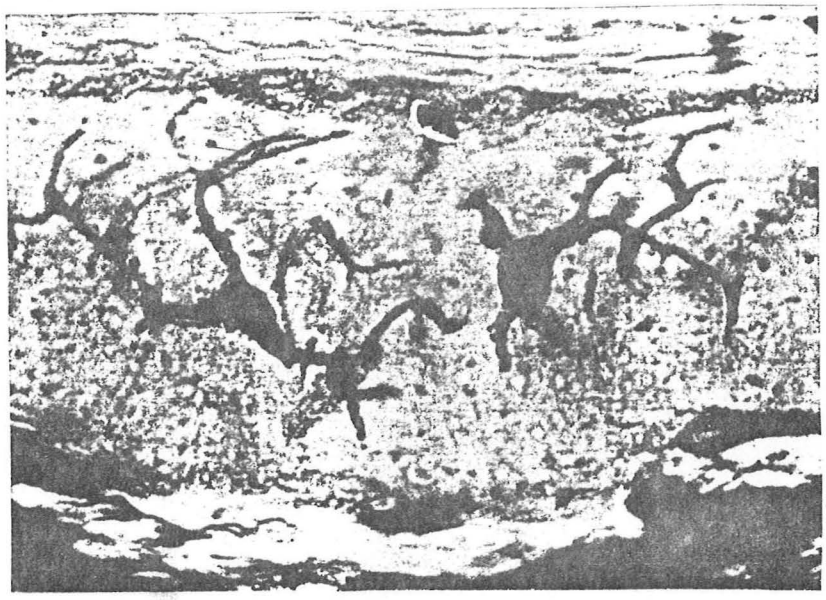


A more subtle understanding of the pathogenesis of the cutaneous changes in these two diseases, but particularly in the Sezary syndrome comes from comparing the clinical illnesses with experimental graft-versus-host (gvh) disease in hamsters, a model that has been elegantly explored by Wayne Streilein (108-110). Dr. Streilein found that in contrast to earlier views, the presence of transplantation antigens at the surface of all cells in the body did not render all cell types equally susceptible to destruction by homologous disease. In fact by careful procurement of appropriate chimeras, Dr. Streilein could dissect the gvh reaction into two segments: 1) an interaction between grafted lymphoid cells and host target cells, and 2) the consequences of such an interaction observable in the tissues of the host. His experiments were designed so that skin and other affected host tissues certifiably bore transplantation antigen identical to those of the attacking grafted lymphocytes, that is, they could not act as targets themselves, but only innocent bystanders.

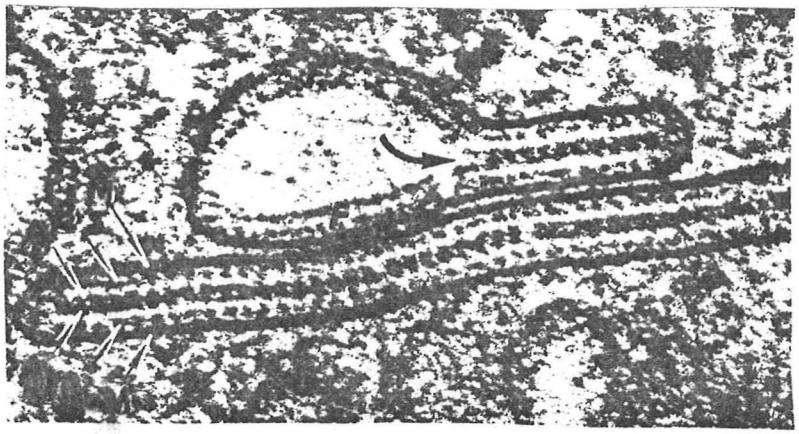
By thus partitioning gvh disease into a two step reaction he could establish that, in the first or attack stage, the target of attack was not the constitutive cells of most organs or tissues, but instead focused on the lymphoid elements within those organs, the so-called passenger cells. Such cells had previously been identified as contributors of antigen in local gvh reactions in skin and kidney, presumably because their surfaces expressed far larger amounts of antigen than did constitutive cells through which they travelled. He found further that the severity of the skin manifestations, many of which resembled symptoms of Sezary's syndrome, correlated directly with the number of attacking collisions that occurred in the skin. That is, if attacking cells were injected intracutaneously, then maximal, body-wide lesions developed. If they were injected intraveneously, then skin showed little change. All of his results suggested then that antigen-activated lymphocytes released substances (lymphokines) which preferentially damaged the skin, perhaps by virtue of confrontations with in-situ passenger lymphocytes.

But other indications also point to a special relationship between the skin and a population of T-cells. The epidermotropism expressed clinically by erythroderma and histologically by Pautrier's microabscesses may represent an enormous neoplastic amplification of normal skin-T-cell interaction. This interaction may include the homing in the skin of a population of T-lymphocytes or even terminal differentiation of T-cells in that site, a process which may normally subserve specific immunologic functions. In this respect four recent experimental findings in animals appear more than coincidentally important.

1) One of the earliest cellular events seen in contact-sensitized humans and guinea pigs is a clustering of lymphoid cells, probably T-cells, in contact with a specific cell type within the epidermis. This specific cell is the dendritic but non-pigmented Langerhans cell (111), a histiomonocytic cell which may exert specific attraction for T-cell during the initiation of cell-mediated sensitivity.



Langerhans cells in human epidermis
as revealed by the ATPase technique.

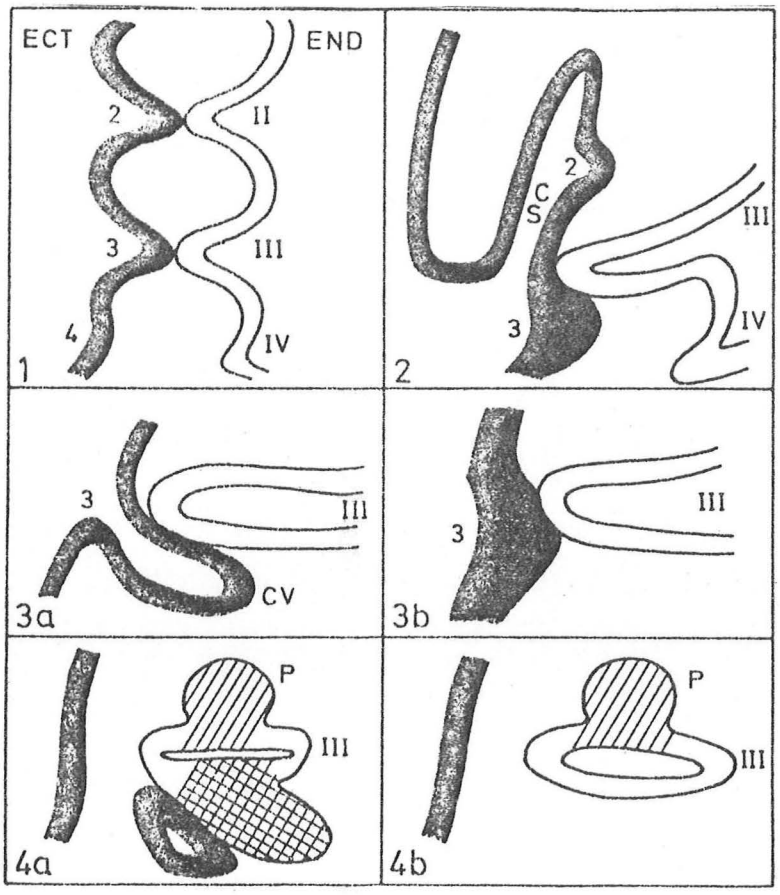


High power electron micrograph of Langerhans cell granules. The curved arrows indicate the zipper-like fusion of the fuzzy coats (F) of the vesicular portions of the granule. The delimiting membrane (M) envelopes two sheets of particles (B) attached to it and a central lamella composed of two linear arrays of particles (A).

from Wolff, K. Current Prob. Derm. 5:84, 1972.

2) Murine T-lymphocytes and epidermal cells share certain specific antigenic determinants (112).

3) Hassall's corpuscles in the thymus appear morphologically to contain cornifying squamous epithelium identical to skin (113).



Schematic representation of embryogenesis of the thymus in normal and homozygous nude mice.

Black = ectodermal components (ECT)

White = endodermal components (END)

II, III, IV = branchial pouches
2, 3, 4 = branchial clefts
CS = cervical sinus
CV = cervical vesicle
P = parathyroid

1. Day 9 (both normal and nude)
2. Day 10 (both normal and nude)
3. Day 11 (a-normal, b-nude)
4. Day 12 (a-normal, b-nude)

from Cordier and Heremans

4) Inbred athymic 'nude' mice, whose name derives from their defective growth of a skin appendage, hair, fail to develop a thymus or functioning T-cells because a portion of ectoderm from the third branchial pouch fails to pinch off and enter the thymic anlage during embryonic life (114).

Therapy

The Sezary syndrome has been treated, with partial success, in the same ways as mentioned for mycosis fungoides. Edelson, et al. (115) exploited in an exciting way some of the unique features of the Sezary syndrome when he succeeded in depleting skin, enlarged nodes, and peripheral blood of abnormal cells by leukapheresis using a cell separator. Over a 35 day period some 35 x 10" leukocytes were removed, bringing the patient's peripheral count from 216,000 per cu mm to 21,000. Whether this mode of therapy will succeed in patients with the more modest leukocytosis of 10-30,000 remains to be seen.

THERAPEUTICALLY EXPLOITABLE FEATURES OF T-CELL LYMPHOMAS

Migratory pattern (skin-nodes, skin-peripheral blood)

Sparing of the bone marrow

Slow spontaneous rate of replication

T-cells antigens on the surface

Presence of a leukemic phase

from Lutzner, et al.

Summary

The following conclusions could easily be matched by contradictory opinions from the long and contentious literature on these confusing diseases.

1) Mycosis fungoides and the Sezary syndrome are malignant lymphomas of T-lymphocytes that occur in adults through evolution of clones that for the most part behave as 'minimal-deviation' tumors.

2) The multiplicity of cell types in the lesions, the hyperglobulinemia and the preservation of integrity of bone marrow all stem from expression of unchecked T-lymphocyte functions such as production of MIF, helper function with B-cells and preferential recirculation between T-dependent areas of lymph nodes and the target organ skin.

3) Like chronic myelogenous and other leukemias mycosis fungoides and Sezary's syndrome may pursue a benign course during which conservative therapy is palliative, followed unpredictably by a sudden or gradual increase in severity during which conventional therapy fails to control the process. Attempts to show that radical therapy can cure if given early have so far failed.

REFERENCES

Reviews

1. Brehmer-Andersson, E. Mycosis Fungoides and its relation to Sezary's Syndrome, lymphomatoid papulosis, and primary cutaneous Hodgkin's disease. Acta. Derm. Venereol. 56:Suppl. 75, 1976.

2. Constantine, V.S. Current concepts in Mycosis Fungoides: its nosology, diagnosis and treatment. Internat. J. Derm. 15:723, 1976.

3. Edelson, R.L. Cutaneous T-cell lymphomas: clues of a skin-thymus interaction. J. Invest. Derm. 67:419, 1976.

Electron microscopic discoveries: Sezary and Mycosis Cells

4. Orfanos, C. and Stüttgen, G. Elektron mikroskepische beobachtungen bei der Mycosis Fungoides. Nachweis von cytoplasmatischen "Zelleinschlüssen". Arch. Klin. Exper. Derm. 215:438, 1963.

5. Lutzner, M.A. and Jordan, H.W. The ultrastructure of an abnormal cell in Sezary's Syndrome. Blood 31:719, 1968.

6. Lutzner, M.A., Hobbs, J.W. and Horrath, P. Ultrastructure of abnormal cells in Sezary Syndrome, Mycosis Fungoides, and parapsoriasis en plaque. Arch. Derm. 103:375, 1971.

7. Orbaneja, J.G., Yus, E.S., Diaz-Flores, L., et al. Cytology of the Mycosis Fungoides and the Sezary Syndrome. Correlation between light and electron microscopy. Brit. J. Derm. 87:96, 1972.

8. Clendenning, W.E., Brecher, G. and Van Scott, E.J. Mycosis Fungoides. Arch. Derm. 89:785, 1964.

9. Sezary, A. and Bouvrain, Y. Erythrodermie avec presence de cellules monstrueuses dans le derme et le sang circulant. Bull. Soc. Franc Derm. Syph. 45:254, 1938.

10. Lutzner, M.A., Emerit, I., Durepaire, R., et al. Cytogenetic, cytophotometric, and ultrastructural study of large cerebriform cells in the Sezary Syndrome and a description of a small cell variant. J. Nat'l. Cancer Inst. 50:1145, 1973.

11. Edelson, R.L., Lutzner, M.A., Kirkpatrick, C.H., et al. Morphologic and functional properties of the atypical T-cells of the Sezary Syndrome. Mayo Clin. Proc. 49:558, 1974.

12. Flandrin, G. and Brouet, J.C. The Sezary cell: cytological, cytochemical and immunologic studies. Mayo Clin. Proc. 49:575, 1974.

13. Rosas-Uribe, A., Variakojis, D., Molnar, Z., et al. Mycosis Fungoides: an ultrastructural study. Cancer 34:634, 1974.

14. Flaxman, B.A., Zalazny, G. and Van Scott, E.J. Nonspecificity of characteristic cells in Mycosis Fungoides. Arch Derm. 104:141, 1971.

15. Biberfield, P. and Hedfors, E. Atypical blood lymphocytes in sarcoidosis: morphology, cytochemistry, and membrane properties. Scand. J. Immunol. 3:315, 1974.

16. Flaxman, B.A., Van Scott, E.J. and Goldman, L.I. Sezary-like cells in cultures of normal human skin. Arch. Derm. 109:577, 1974.

17. Yeckley, J.A., Weston, W.L., Thorne, E.G., et al. Production of Sezary-like cells from normal human lymphocytes. Arch. Derm. 111:29, 1975.

Membrane markers and immunologic function of Sezary and Mycosis cells

18. Crossen, P.E., Mellor, J.E.L., Finley, A.G., et al. The Sezary Syndrome: cytogenetic studies and identification of the Sezary cell as an abnormal lymphocyte. Am. J. Med. 50:24, 1971.

19. Brouet, J.C., Flandrin, G. and Seligmann, M. Indications of the thymus-derived nature of the proliferating cells in six patients with Sezary's Syndrome. New England J. Med. 289:341, 1973.

20. Zucker-Franklin, D., Melton, J.W. and Quagliata, F. Ultrastructural, immunologic and functional studies on Sezary cells: a neoplastic variant of thymus-derived (T) lymphocytes. PNAS 71:1877, 1974.

21. Edelson, R.L., Kirkpatrick, C.H., Shevach, E.H., et al. Preferential cutaneous infiltration by neoplastic thymus-derived lymphocytes. Ann. Intern. Med. 80:685, 1974.

22. Lutzner, M.A., Edelson, R.L., Schein, P., et al. Cutaneous T-cell lymphomas: the Sezary Syndrome, Mycosis Fungoides and related disorders. Ann. Intern. Med. 83:534, 1975.

23. Braylan, R., Variakojis, D. and Yachnin, S. The Sezary Syndrome lymphoid cell: Abnormal surface properties and mitogen responsiveness. Brit. J. Haem. 31:553, 1975.

24. Broder, S., Edelson, R.L., Lutzner, M.A., et al. The Sezary Syndrome. A malignant proliferation of helper T-cells. J. Clin. Invest. 58:1297, 1976.

25. Blaylock, W.K., Clendenning, W.E., Carbone, P.P., et al. Normal immunologic reactivity in patients with lymphoma mycosis fungoides. Cancer 19:233, 1966.

26. Zachariae, H., Ellegaard, J., Grunnet, E., et al. T- and B-cells and IgE in mycosis fungoides. Acta. Derm. Venereol. 55:466, 1975.

27. Yoshida, T., Edelson, R.L., Cohen, S., et al. Migration inhibiting activity in serum and cell supernaturants in patients with Sezary Syndrome. J. Immunol. 114:915, 1975.

28. Thurlin, H. Absence of leucocyte migration inhibitory factor in serum from patients with mycosis fungoides. Arch. Derm. Res. 257:157, 1976.

29. Weston, W.L. and Krueger, G.G. Eryth oderma: a model for overproduction of mediators of cellular immunity. Am. Res. 21:484, 1973.

30. Cohen, S., Fisher, B., Yoshida, T., et al. Serum migration-inhibitory activity in patients with lymphoproliferative disease. New Eng. J. Med. 290:882, 1974.

31. Schuppli, R. Is mycosis fungoides an 'immunoma'? Dermatologica 153:1, 1976.

32. Tan, R.S-H., Butterworth, C.M., McLaughlin, R.H., et al. Mycosis Fungoides, a disease of antigen persistence. Brit. J. Derm. 91:607, 1974.

33. Weston, W.L., Norris, D.L., Seitz, L.E., et al. Deficient monocyte chemotaxis in mycosis fungoides. Clin. Res. 23:497A, 1976.

Chromosomal abnormalities

34. Whang-Peng, J., Lutzner, M.A., Edelson, R.L., et al. Cytogenetic studies and clinical implications in patients with Sezary syndrome. Cancer 38:861, 1976.

35. Erkman-Balis, B. and Rappaport, H. Cytogenetic studies in mycosis fungoides. Cancer 34:626, 1974.

36. Van Vloten, W.A., Van Duijn, P. and Schaberg, A. Cytodiagnostic use of feulgen-DNA measurements in cell imprints from the skin of patients with mycosis fungoides. Brit. J. Derm. 91:365, 1974.

37. Nowell, P.C. The clonal evolution of tumor cell populations. Science 194:23, 1976.

Frequency

38. Clemmesen, J. Statistical studies in the aetiology of malignant neoplasms. IV Acta. Path. Microb. Scand. (A) Suppl. 247, 1974.

Familial Incidence

39. Bluefarb, S.M. Cutaneous manifestations of the malignant lymphomas. (Thomas Springfield, 1959).

Clinical Presentation

40. Sandbank, M. and Katzenellenbogen, I. Mycosis fungoides of prolonged duration in siblings. Arch. Derm. 98:620, 1968.

41. Samman, P.D. Cutaneous reticuloses. Trans. St. John's Hosp. Derm. Soc. 61:11, 1975.

42. Samman, P.D. Mycosis fungoides and other cutaneous reticuloses. Clin. Exper. Derm. 1:197, 1976.

43. Wilson-Jones, E. Prospectives in Mycosis fungoides in relation to other lymphomas. Trans St. Johns Hosp. Derm. Soc. 61:16, 1975.

44. Ackerman, A.B. and Flaxman, B.A. Granulomatous mycosis fungoides. Brit. J. Derm. 82:397, 1970.

45. Cawley, E.P., Curtis, A.C. and Leach, J.E.K. Is mycosis fungoides a neoplastic entity? Arch. Derm. Symph. 64:255, 1951.

46. Epstein, E.H., Levin, D.L., Croft, J.D., et al. Mycosis fungoides: survival, prognostic features, response to therapy and autopsy findings. Medicine 51:61, 1972.

47. Lapiere, S. The realm and frontiers of mycosis fungoides. J. Invest. Derm. 42:101, 1964.

48. Reed, R.J. and Cummings, C.E. Malignant reticulosis and related conditions of the skin. Cancer 19:1231, 1966.

Clinical Course

49. Montgomery, H. Dermatopathology (Harper and Row, N.Y., 1967) p. 1210.

50. Levi, J.A. and Wiernik, P.H. Management of mycosis fungoides: current status and future prospects. Medicine 54:73, 1975.

51. Fuks, Z.Y., Bagshaw, M.A. and Farber, E.M. Prognostic signs and the management of mycosis fungoides. Cancer 32:1385, 1973.

52. Block, J.B., Edgcomb, J. and Eisen, S., et al. Mycosis fungoides: natural history and its relationship to other malignant lymphomas. Am. J. Med. 34:228, 1963.

53. Cyr, D.P., Geokas, M.C. and Worsley, G.H. Mycosis fungoides: hematologic findings and terminal course. Arch. Derm. 94:558, 1966.

Histopathology

54. Lever, W.F. and Schaumberg-Lever, G. Histopathology of the Skin. ed. 5 (Lippincott, Philadelphia, 1975) pp. 697-705.

55. Rappaport, H. and Thomas, L.B. Mycosis fungoides. The pathology of extracutaneous involvement. Cancer 34:1198, 1974.

56. Kim, R., Winkelmann, R.K. and Dockerty, M. Reticulum cell sarcoma of the skin. Cancer 16:646, 1963.

57. Petrozzi, J.W., Raque, C.J. and Goldschmidt, H. Malignant lymphoma, reticulum cell type. Ultrastructural and cytologic demonstration of Lutzner cells. Arch. Derm. 104:38, 1971.

58. Emmerson, R.W. Follicular mucinosis. Brit. J. Derm. 81:395, 1969.

59. Poulsen, A. On mycosis fungoides. Acta. Derm. Venereol. 21:365, 1940.

60. Helwig, E.B. Malignant lymphomas and reactive lymphoid hyperplasias in Dermat. Pathology ed. by J. H. Graham, W. C. Johnson and E. B.Helwig (Harper & Row, N.Y., 1972) p. 683.

Primary Cutaneous Hodgkin's Disease

61. Szur, L., Harrison, C.V., Levene, G.M. and Samman, P.D. Primary cutaneous Hodgkin's disease. Lancet 1:1016, 1970.

62. Ultman, J.E. and Moran, E.M. Clinical course and evaluation in Hodgkin's disease. Arch. Int. Med. 131:332, 1973.

63. DeVita, V.T., Jr. Lymphocyte reactivity in Hodgkin's disease: a lymphocyte civil war. New Eng. J. Med. 289:801, 1973.

Systemic Pathology

64. Allen, A.C. The Skin - A clinicopathologic treatise (Mosby, St. Louis, 1954) pp. 1010-1024.

65. Rauschkolb, R.R. Mycosis fungoides. Arch. Derm. 83:217, 1969.

66. Long, J.C. and Mihm, M.C. Mycosis fungoides with extracutaneous dissemination: a distinct clinicopathologic entity. Cancer 34:1745, 1974.

Laboratory Examination

67. Edgcomb, J., Block, J., Eisen, A., et al. Mycosis fungoides. NCI Monograph No. 10:275, 1963.

68. Fraser, J.F. Mycosis fungoides. Its relation to leukemia and lymphosarcoma. Arch. Derm. Syph. 12:814, 1925.

69. Aub, J.C., Wohlback, S.B., Kennedy, B.J., et al. Mycosis fungoides followed for fourteen years. Arch. Path. 60:535, 1955.

Staging

70. Fuks, Z. and Bagshaw, M.A. Total-skin electron beam treatment of mycosis fungoides. Radiology 100:145, 1971.

71. Griem, M.C., Moran, E.M., Ferguson, D.J., et al. Staging procedures in mycosis fungoides. Brit. J. Cancer 31 (Suppl. 2): 362, 1975.

72. Variakojis, D., Rosas-uribe, A. and Rappaport, H. Mycosis fungoides: pathologic findings in staging laparotomies. Cancer 33:1589, 1974.

73. Brownlee, T.R. and Murad, T.M. Ultrastructure of mycosis fungoides. Cancer 26:686, 1970.

74. Waldorf, D.S., Ratner, A.C. and Van Scott, E.J. Cells in lesions of mycosis fungoides following therapy: changes in number and type. Cancer 21:264, 1968.

75. Goudie, R.B., Macfarlane, P.S. and Lindsay, M.K. Homing of lymphocytes to non-lymphoid tissues. Lancet 1:292, 1974.

76. Fichtelius, K.E., Groth, O. and Liden, S. The skin, a first-level lymphoid organ? Int. Arch. Allergy 37:607, 1970.

77. Escovitz, E.S., Soulen, R.L., Van Scott, E.J., et al. Mycosis fungoides, a lymphographic assessment. Diagn. Radiology 112:23, 1974.

78. Fuks, Z.Y., Castellino, R.A., Carmel, J.A., et al. Lymphography in mycosis fungoides. Cancer 34:106, 1974.

Therapy

79. Haynes, H.A. and Van Scott, E.J. Therapy of mycosis fungoides. Prog. Dermatol. 3:1, 1968.

80. Klein, E., Burgess, G.H. and Helm, F. Neoplasms of the skin in Cancer Medicine ed. by Holland, J.F. and Frei, E. (Lea and Febiger, Philadelphia, 1973) pp. 1789-1822.

Nitrogen Mustard

81. Waldorf, D.S., Haynes, H.A. and Van Scott, E.J. Cutaneous hypersensitization and desensitization to mechlorethamine in patients with mycosis fungoides lymphoma. Ann. Intern. Med. 67:282, 1967.

82. Van Scott, E.J. and Winters, P.L. Responses of mycosis fungoides to intensive external treatment with nitrogen mustard. Arch. Derm. 102:507, 1970.

83. Van Scott, E.J. and Kalmanson, J.D. Complete remissions of mycosis fungoides lymphoma induced by topical nitrogen mustard (HN_2). Cancer 32:18, 1973.

84. Pariser, D.M., Childers, R.C., Kechijian, P., et al. Intravenous desensitization to mechlorethamine in patients with psoriasis. Arch. Derm. 112:1113, 1976.

85. Arundell, F.D. and Chan, W.H. Mycosis fungoides. Topical use of nitrogen mustard in recurrent cases. Calif. Med. 109:458, 1968.

86. Zackheim, H.S. Treatment of mycosis fungoides with topical introsourea compounds. Arch. Derm. 106:177, 1972.

87. Peck, G.L., Guss, S.B. and Key, D. Topical comustine in the treatment of psoriasis. Arch. Derm. 106:172, 1972.

Corticosteroids

88. Farber, E.M., Zackheim, H.S. and McClintock, et al. Treatment of mycosis fungoides with various strengths of fluocinolone cream. Arch. Derm. 97:165, 1968.

89. Farber, E.M., Cox, A.J. and Stemberg, J. Therapy of mycosis fungoides with topically applied fluocinolone cream under occlusive dressing. Cancer 19:237, 1966.

Delayed hypersensitivity

90. Ratner, A.C. Alterations of mycosis fungoides lymphoma by direct imposition of delayed hypersensitivity reactions. Cancer 21:83, 1968.

91. St. Jernsward, J. and Levin, A. Delayed-hypersensitivity-induced regression of human neoplasms. Cancer 28:628, 1971.

Radiotherapy

92. Szur, L. Radiotherapy in skin reticuloses. Brit. J. Derm. 76:10, 1964.

93. Bagshaw, M.A. and Eltringham, J.R. Observations on the electron beam therapy of mycosis fungoides. Frontiers in Rad. Ther. Oncol. 2:163, 1968.

94. D'Angio, G.J., Nisce, L.Z. and Kim, J.H. Weekly total skin electron beam therapy for mycosis fungoides and other cutaneous lymphomata: further experience. Brit. J. Cancer 31 (Suppl II): 379, 1975.

95. Szur, L. Treatment of mycosis fungoides and related conditions with particular emphasis on electron therapy. Brit. J. Cancer 31 (Suppl II):368, 1975.

Chemotherapy

96. Van Scott, E.J., Auerbach, R. and Clendenning, W.E. Treatment of mycosis fungoides with cyclophosphamide. Arch. Derm. 85:107, 1962.

97. Wright, J.C., Lyons, M.M., Walker, O.G., et al. Observations on the use of cancer chemotherapeutic agents in patients with mycosis fungoides. Cancer 17:1045, 1964.

98. deBast, C., Moriame, N., Wanet, J., et al. Bleomycin in mycosis fungoides and reticulum cell lymphoma. Arch. Derm. 104:508, 1971.

99. Spigel, S.C. and Coltman, C.A. Therapy of mycosis fungoides with bleomycin. Cancer 32:767, 1973.

Photochemotherapy

100. Parrish, J.A., Fitzpatrick, T.B., Tanenbaum, L., et al. Photochemotherapy for psoriasis. New Eng. J. Med. 291:1207, 1974.

101. Gilchrest, B.A., Parrish, J.A., Tanenbaum, L., et al. Oral methoxsalen photochemotherapy of mycosis fungoides. Cancer 38:683, 1976.

The Sezary syndrome

102. Winkelmann, R.K. Clinical studies of T-cell erythroderma in the Sezary syndrome. Mayo Clin. Proc. 49:519, 1974.

103. Sezary, A. Une nouvelle reticulose cutanee. La reticulose maligne leucemique a histio-monocytes monstrueux et a la forme d'erythrodermie oedemateuse et pigmentee. Ann. Derm. Syph. 9:5, 1949.

104. Taswell, H.F. and Winkelmann, R.K. Sezary syndrome - a malignant reticulemic erythroderma. JAMA 177:465, 1961.

105. Holdaway, D.R. and Winkelmann, R.K. Histopathology of the Sezary syndrome. Mayo Clin. Proc. 49:526, 1914.

106. Winkelmann, R.K. and Linman, J.W. Erythroderma with atypical lymphocytes (Sezary syndrome). Am. J. Med. 55:192, 1973.

107. Fleischmajer, R. and Eisenberg, S. Sezary's reticulosis. Arch. Derm. 89:9, 1964.

108. Streilein, J.W. and Billingham, R.E. An analysis of graft-versus-host disease in hamsters I. The epidermolytic syndrome - its description and procurement. J. Exper. Med. 132:163, 1970.

109. Streilein, J.W. and Billingham, R.E. An analysis of graft-versus-host disease in hamsters II. The epidermolytic syndrome: studies on its pathogenesis. J. Exper. Med. 132:181, 1970.

110. Streilein, J.W. A common pathogenesis for the lesions of graft versus host disease. Transplant Proc. 3:418, 1971.

111. Silberberg, I., Baer, R.L. and Rosenthal, S.A. The role of the Langerhans cells in allergic contact hypersensitivity. A review of findings in man and guinea pigs. J. Invest. Derm. 66:210, 1976.

112. Scheid, M., Boyse, E.A., Carswell, E.A. Serologically demonstratable alloantigens of mouse epidermal cells. J. Exper. Med. 135:938, 1972.

113. Mandel, T. The development and structure of Hassall's corpuscles in the guinea pig. A light and electron microscopic study. Z. Zellforsch. 89:180, 1968.

114. Cordier, A.C. and Heremans, J.F. Nude mouse embryo: Ectodermal nature of the primordial thymic defect. Scand. J. Immunol. 4:193, 1975.

115. Edelson, R.L., Facktor, M., Andrews, A., et al. Successful management of the Sezary syndrome. Mobilization and removal of extravascular neoplastic T-cells by leukapheresis. New Eng. J. Med. 291;293, 1974.