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Comprehensive Cancer Center
A National Cancer Institute-Designated Comprehensive Cancer Center

Overview of Cutaneous Lymphomas: Diagnosis and Staging

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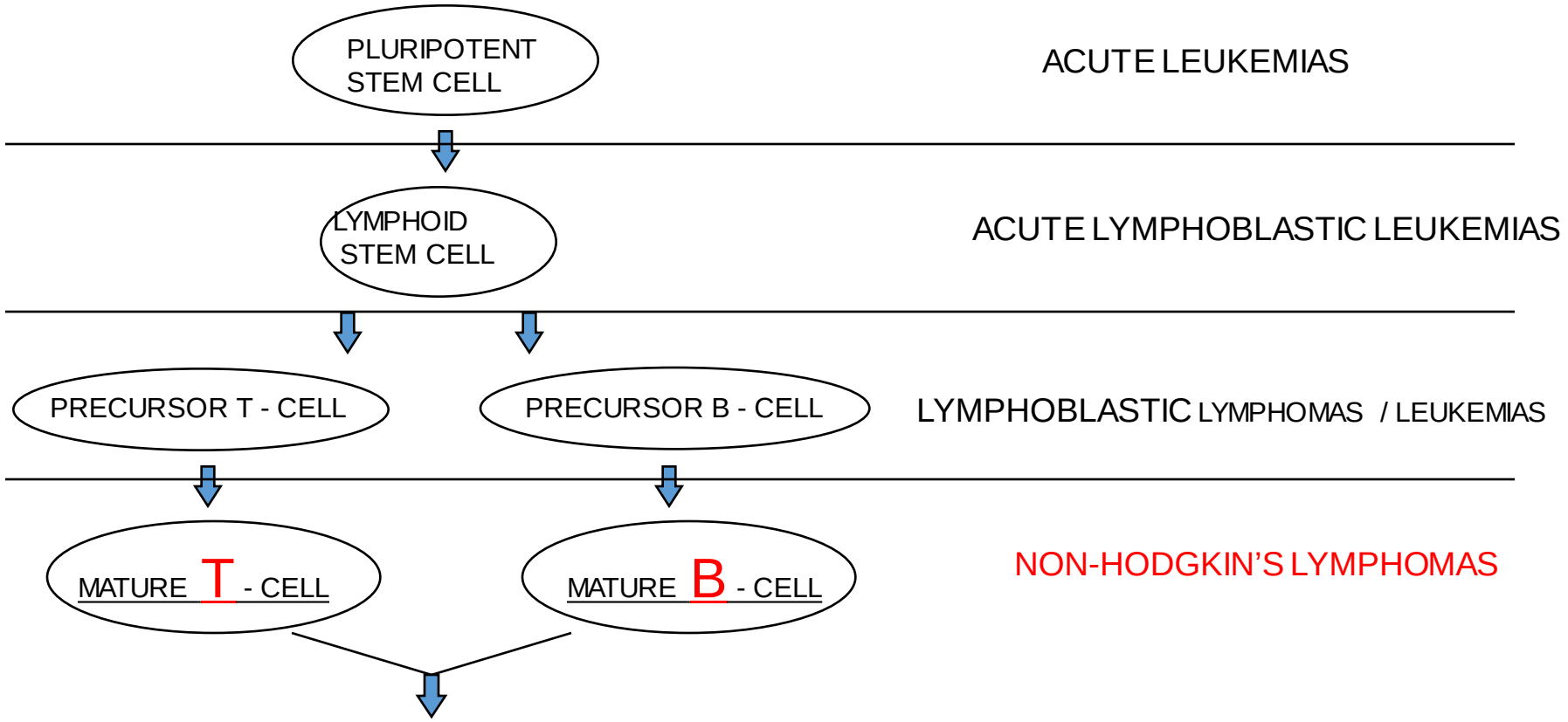
Definition of Lymphoma

- A cancer or malignancy that comes from a clonal expansion of one lymphocyte (B, T, or natural killer) in a lymph node, blood or other tissue such as skin.

- Lymphocytes are a part of our immune system.

- The skin is the second most common extranodal (outside of lymph nodes) site of involvement for lymphomas.

Cellular Origins of Lymphomas / Leukemias



S. J. Schuster, 2003

Cutaneous Lymphomas: Why are they different?

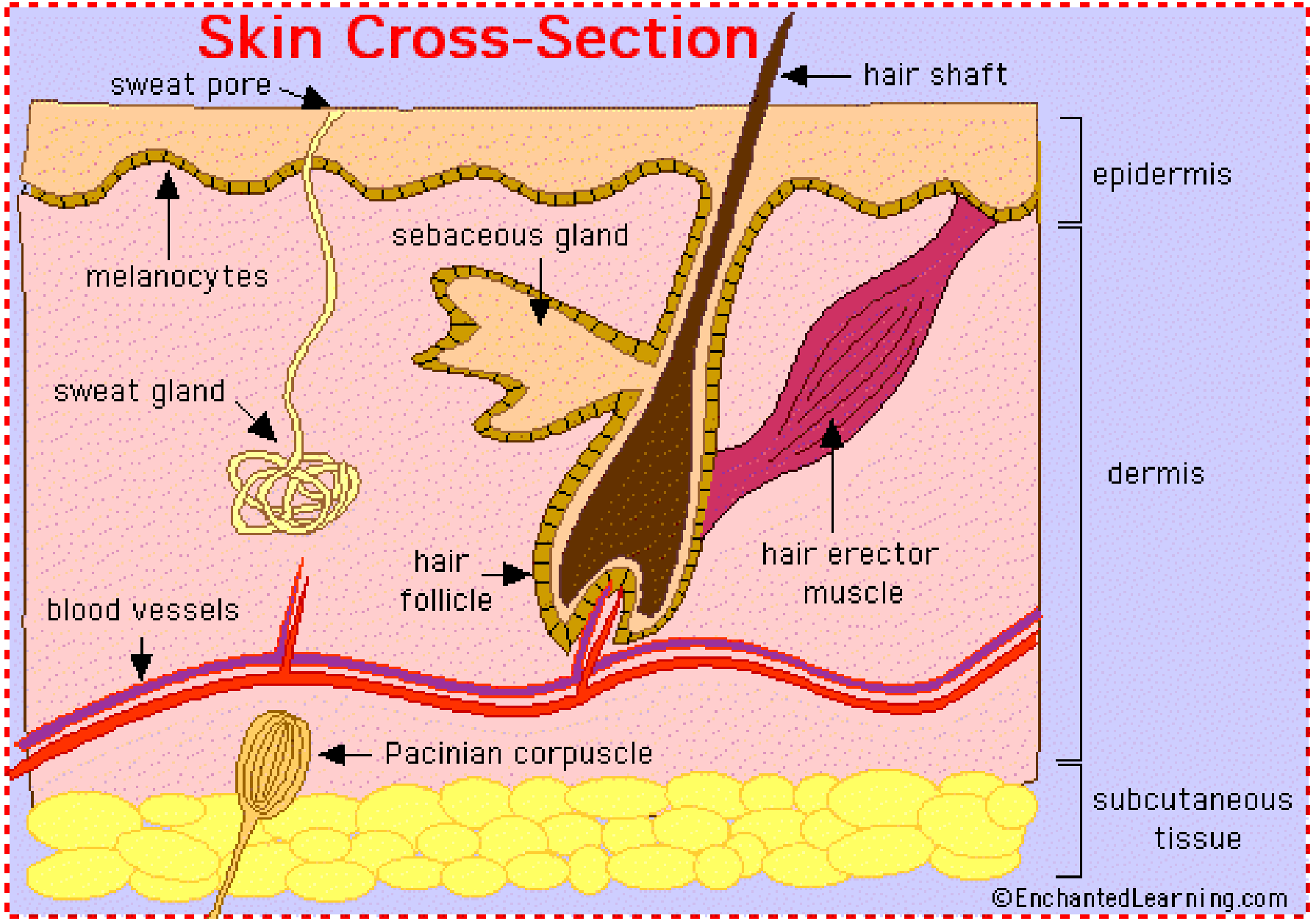
- T-cell lymphoma accounts for 60-80% of all primary (limited to the skin) cutaneous lymphomas*; the reverse of lymphomas in general.*

- The behavior and treatment for a skin lymphoma will often be radically different from a similar looking or named lymphoma that begins in the lymph node, *so cutaneous lymphomas have their own classification and staging systems to help decide on treatment*

Cutaneous Lymphomas: Why are they different?

- Unlike the general group of lymphomas or other malignancies, the pathologists' diagnosis in a case of cutaneous lymphoma may not be the final diagnosis, but rather, may suggest a group of conditions such that clinico-pathologic correlation (cooperation between the pathologist and clinician) will determine the final diagnosis.

- Patients with skin lymphomas may use a ***team*** of doctors for their care (pathologists, dermatologists, oncologists, radiologists and radiation therapists).


Skin Cross-Section
sweat pore
hair shaft
epidermis
melanocytes
sebaceous gland
sweat gland
dermis
hair
follicle
hair erector
muscle
blood vessels
Pacinian corpuscle
subcutaneous
tissue
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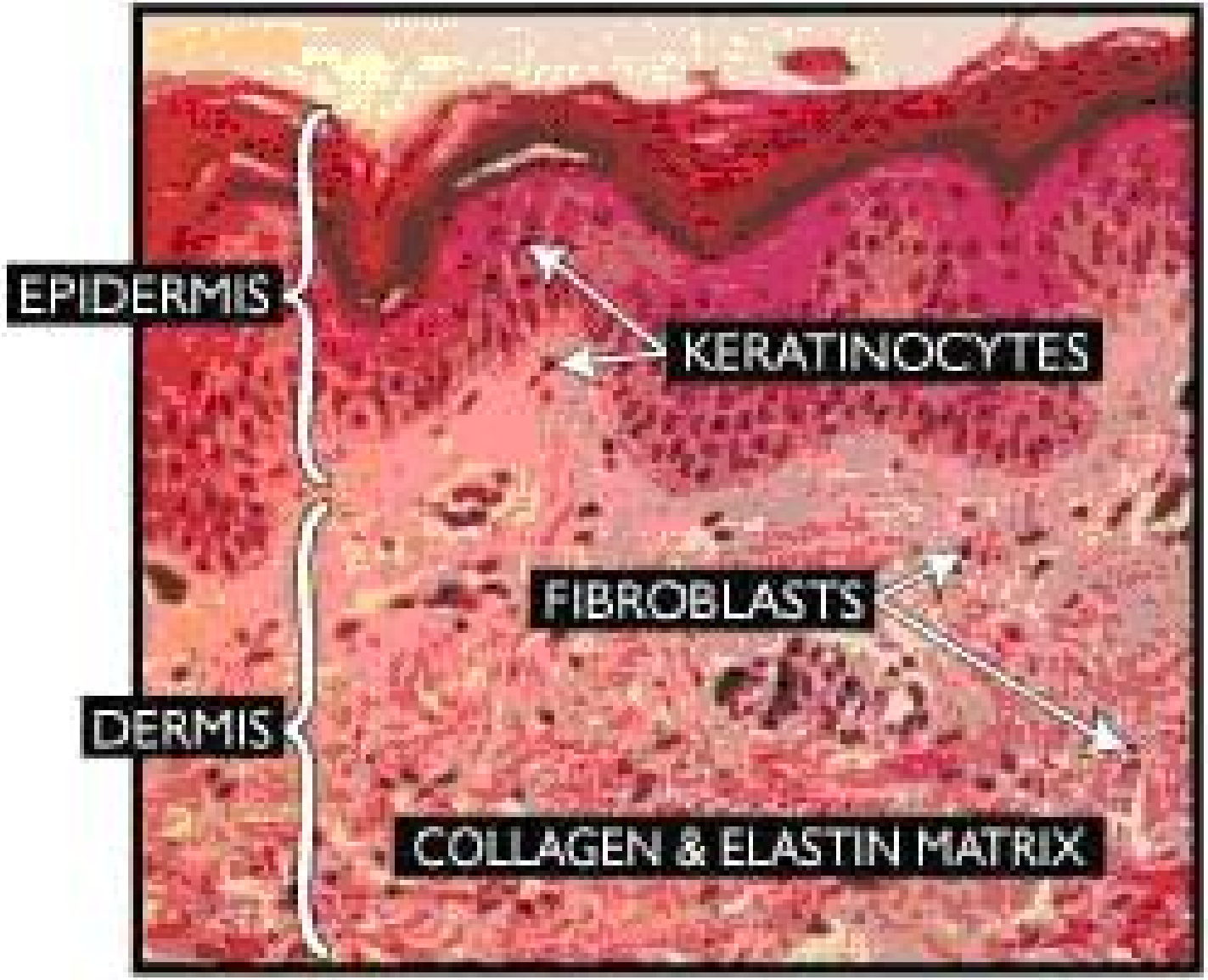


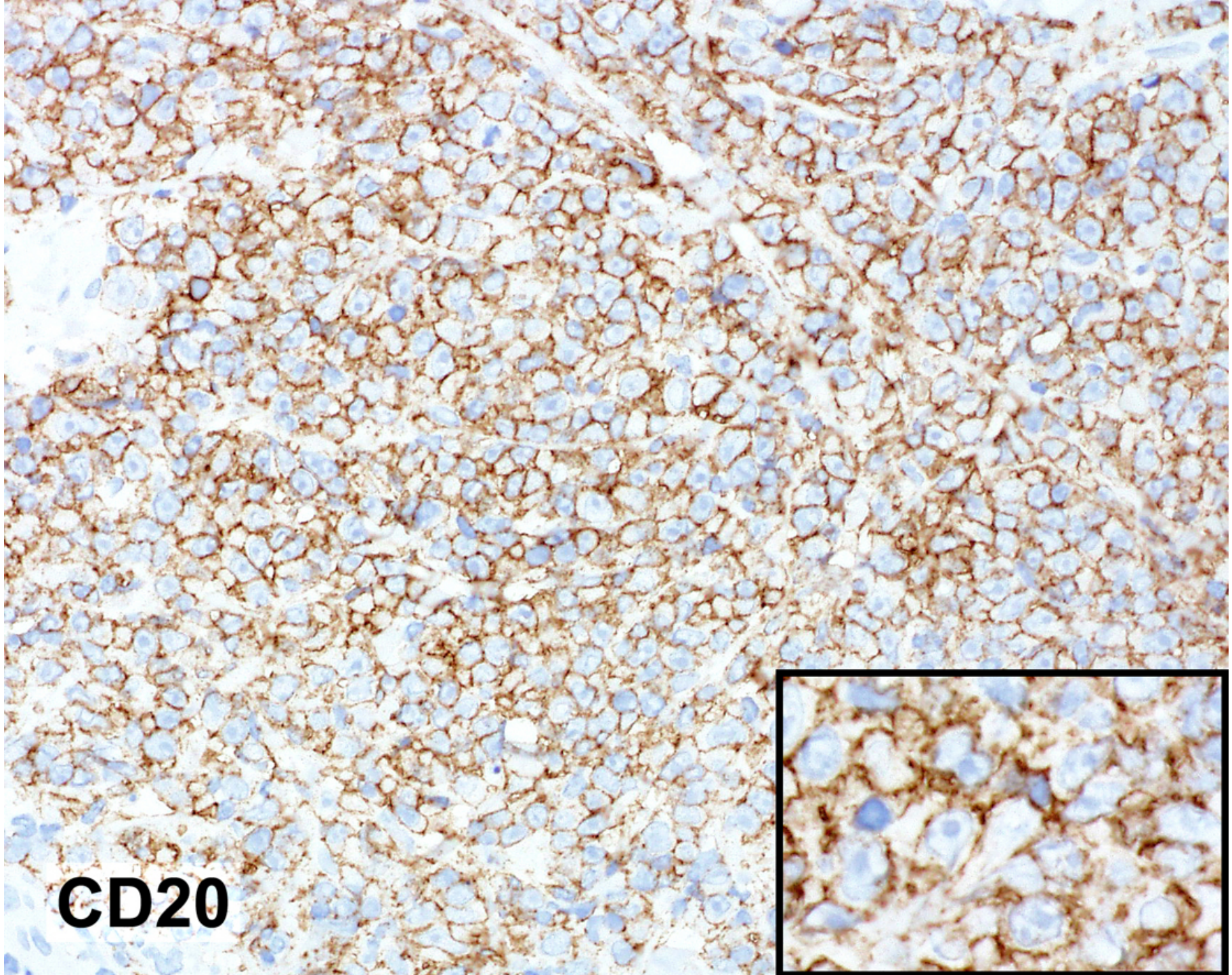
FIGURE 3. Skin Anatomy.

Monoclonal Antibodies

- Proteins that our bodies or a laboratory can make that bind (attach) to specific protein markers (called *antigens*) on lymphoma or other cells.

- They can be used to help make a diagnosis on slides or from blood

- They can be used as a treatment of specific cancers


CD20

Types of Cutaneous B-cell Lymphomas (CBCLs)

Indolent (slow) CBCL

- **Primary cutaneous follicle center lymphoma (11%)**
- **Primary cutaneous marginal zone lymphoma (7%)**

Aggressive (faster) CBCL

- **Primary cutaneous diffuse large B-cell lymphoma, leg type (4%)**
- **Primary cutaneous diffuse large B-cell lymphoma, other, intravascular large B-cell (<1%)**

Indolent (slow) CBCLs

- Red nodules rarely ulcerating
- Primary cutaneous marginal zone lymphomas can present acutely or more slowly over months; primary cutaneous follicular center lymphomas over months to years
- Over 50% return in skin but patients continue to have an excellent outcome; less than 10% become extracutaneous (outside the skin) (especially marginal zone lymphomas)

Cutaneous T-Cell Lymphoma (CTCL)

- CTCL defines a heterogenous group of malignant lymphomas with primary manifestations in skin. The term was “coined” in **1979**.
-
- Mycosis fungoides (MF) is the most common CTCL.
- Sezary’s Syndrome (SS) represents 5% of all cases of MF.

Types of Cutaneous T-Cell Lymphomas (CTCLs)

Indolent CTCLs

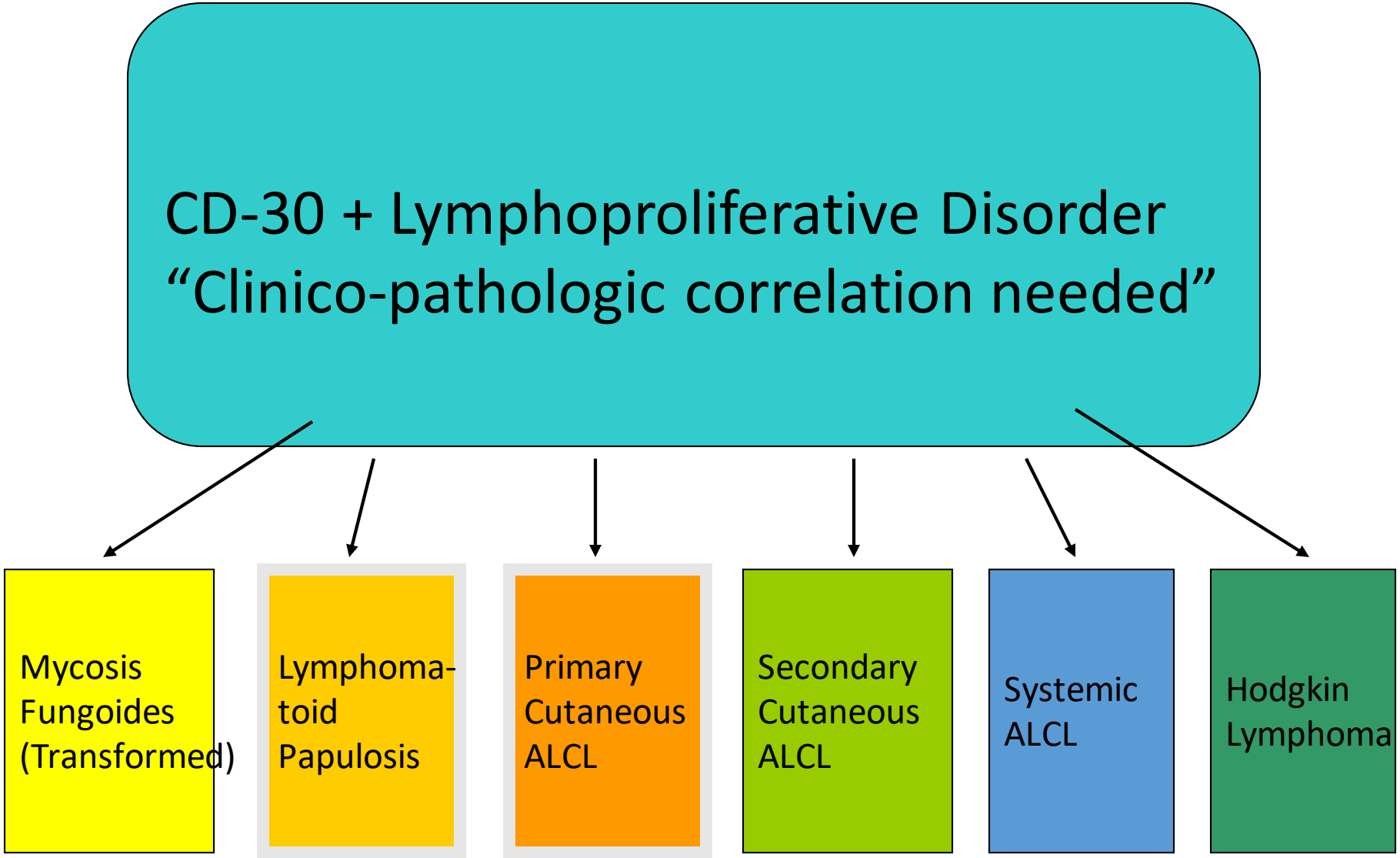
- **Mycosis fungoides (MF) (44%)**
- **MF variants and subtypes**
  - Folliculotropic MF (4%)
  - Pagetoid reticulosis (<1%)
- Granulomatous slack skin (<1%)

- **CD30+ lymphoproliferative disorders**
  - Anaplastic large cell lymphoma (8%)
  - Lymphomatoid papulosis (12%)
- Subcutaneous panniculitis-like T-cell lymphoma (1%)
- *CD4+ small/medium pleomorphic T-cell lymphoproliferative disorder(2%)*

Aggressive CTCLs

- **Sézary syndrome (SS) (3%)**

- *Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (<1%)*
- Primary cutaneous γ/δ T-cell lymphoma (<1%)
- Primary cutaneous acral CD8+ T-cell lymphoma (provisional)


CD-30 + Lymphoproliferative Disorder
"Clinico-pathologic correlation needed"
Mycosis Fungoides (Transformed)
Lymphoma-toid Papulosis
Primary Cutaneous ALCL
Secondary Cutaneous ALCL
Systemic ALCL
Hodgkin Lymphoma

CD 30+ Lymphoproliferative disorders are a spectrum of conditions

- Primary cutaneous Anaplastic Large Cell Lymphoma (PC-ALCL)
- Lymphomatoid Papulosis (LyP)

- *LyP and PC-ALCL can overlap clinically and histologically, so clinico-pathologic correlation is essential for correct diagnosis*

- Transformed MF and MF are also in differential diagnosis of CD30+ skin lesions
- Different skin lesions can appear on the same person

Lymphomatoid Papulosis (LyP)

- “Clinically benign; histologically malignant”
- Recurrent crops of papules (like insect bites) <2 cm (smaller than an inch) which heal by themselves in 3-6 weeks sometimes leaving a dark area or a scar
- Lesions are red-brown, with central red or black appearing on the trunk or extremities
- As lesions evolve, they can have a blister or pus in the center
- Variable frequency and/or severity or outbreaks with different patients and in same patient over time
- Younger median age than primary cutaneous ALCL (45 vs. 60 yo)
- Increased chance of MF, ALCL and Hodgkin lymphoma

Primary Cutaneous ALCL (PC-ALCL)

- 25% of CTCL
- Presents as solitary or localized skin lesions (>2cm) that may be ulcerated tumors, nodules, or papules in patients without any other diagnosis of LyP, lymphoma or extracutaneous involvement
- 20% have more than one area of skin disease
- Characterized by partial or complete spontaneous regression (40%), but frequent skin relapses
- 10-25% develop extracutaneous dissemination, mainly to regional nodes, mostly those with many skin lesions at once

Mycosis Fungoides (MF)

- The term “MF” was first used in 1806 by Alibert, a French dermatologist because he though the lesions looked like a fungus (it’s not!)

- “MF” is the most common type of cutaneous lymphoma, and CTCL (40% of cases)

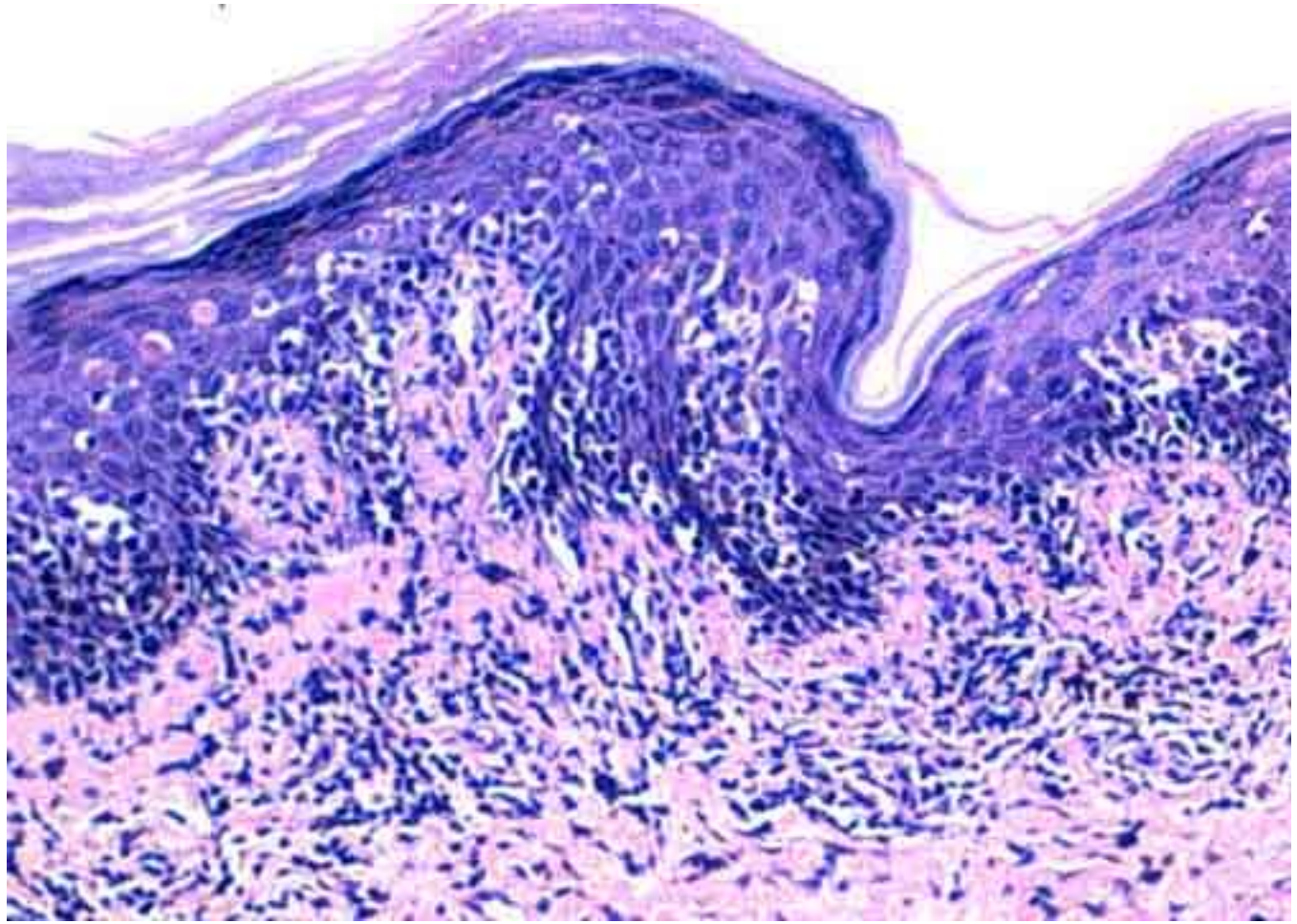
- Pathologically, MF affects the most superficial layer of the skin, the epidermis, and “epidermotropism” (with/without Pautrier’s microabscesses) distinguishes MF from other skin lymphomas.

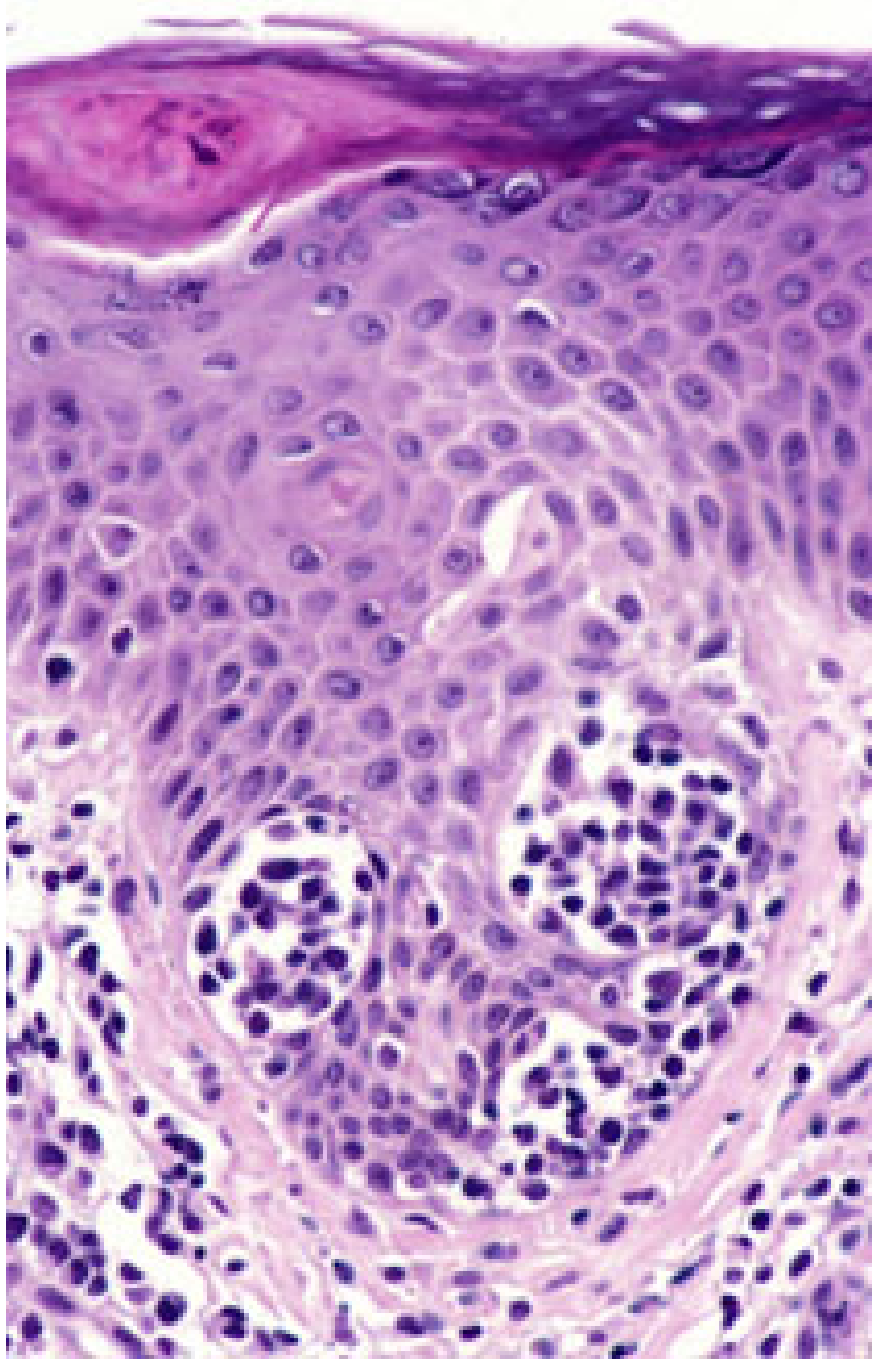
Sezary's syndrome (SS)

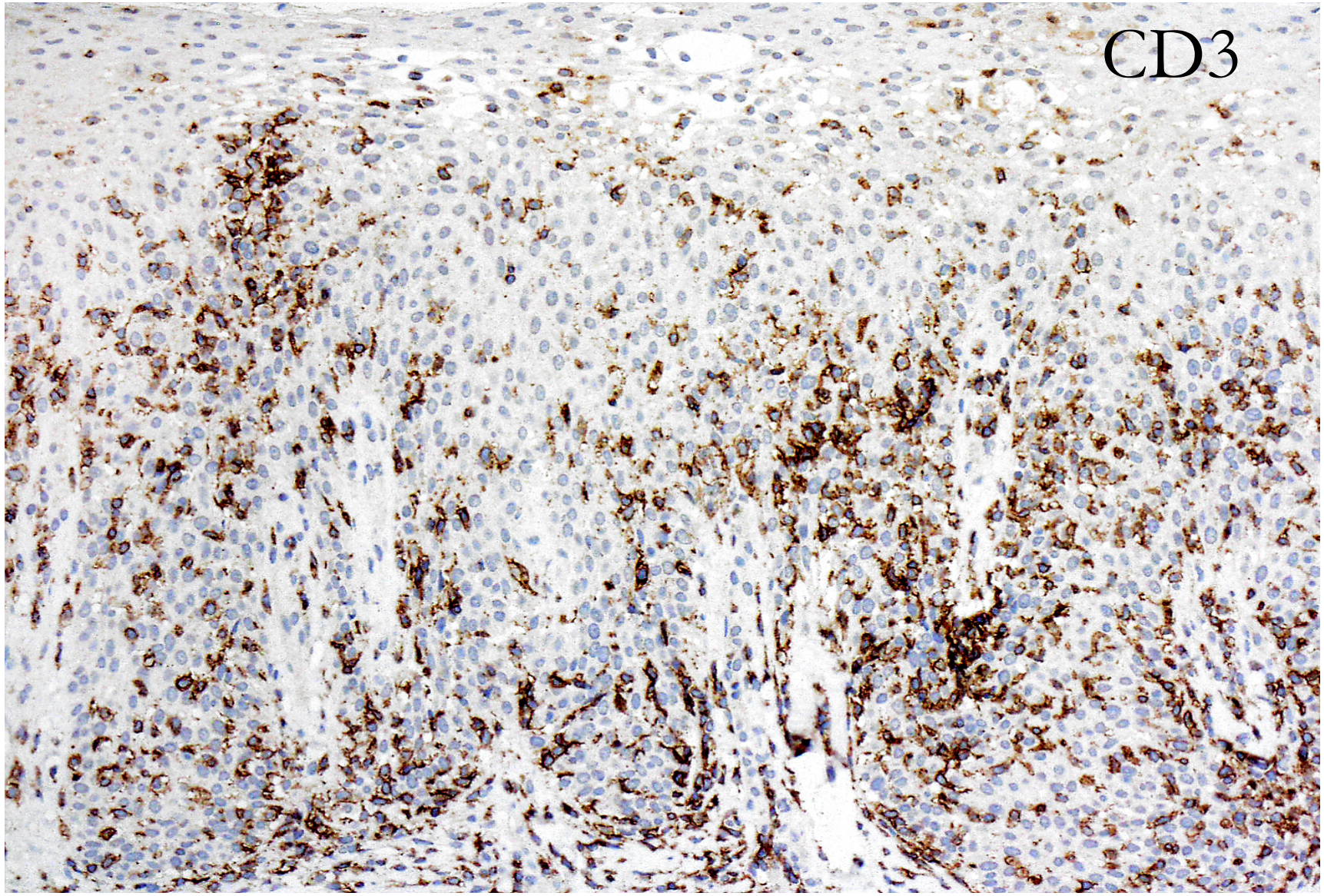
- Represents about 5% of all cases of MF
- Described by Sezary, another French dermatologist in 1938
- It is characterized by circulation of MF cells (or Sezary's cells) in the blood
- Patients **may** have generalized redness and scaling of the skin, enlarged lymph nodes, scaling and slits in the palms and soles, changes in their nails, swelling of their legs and/or changes in their eyelids and itching

Mycosis Fungoides:
Clinical and Histologic Variants/Subtypes

- Hypopigmented/vitiligenous MF
- Unilesional pagetoid reticulosis (Woringer-Kolopp type only)
- Follicular MF (+/- mucinosis)
- Granulomatous MF
  - Granulomatous slack skin
- Bullous MF
- PPE-like MF
- Interstitial MF
- Papular MF







Immunochemistry (proteins expressed by tumor cells): cells are typically CD3+, CD4+, CD8-, CD30-

Staging of Cutaneous Lymphomas

It’s different from other NHLs or HL!

Why do we have stages?

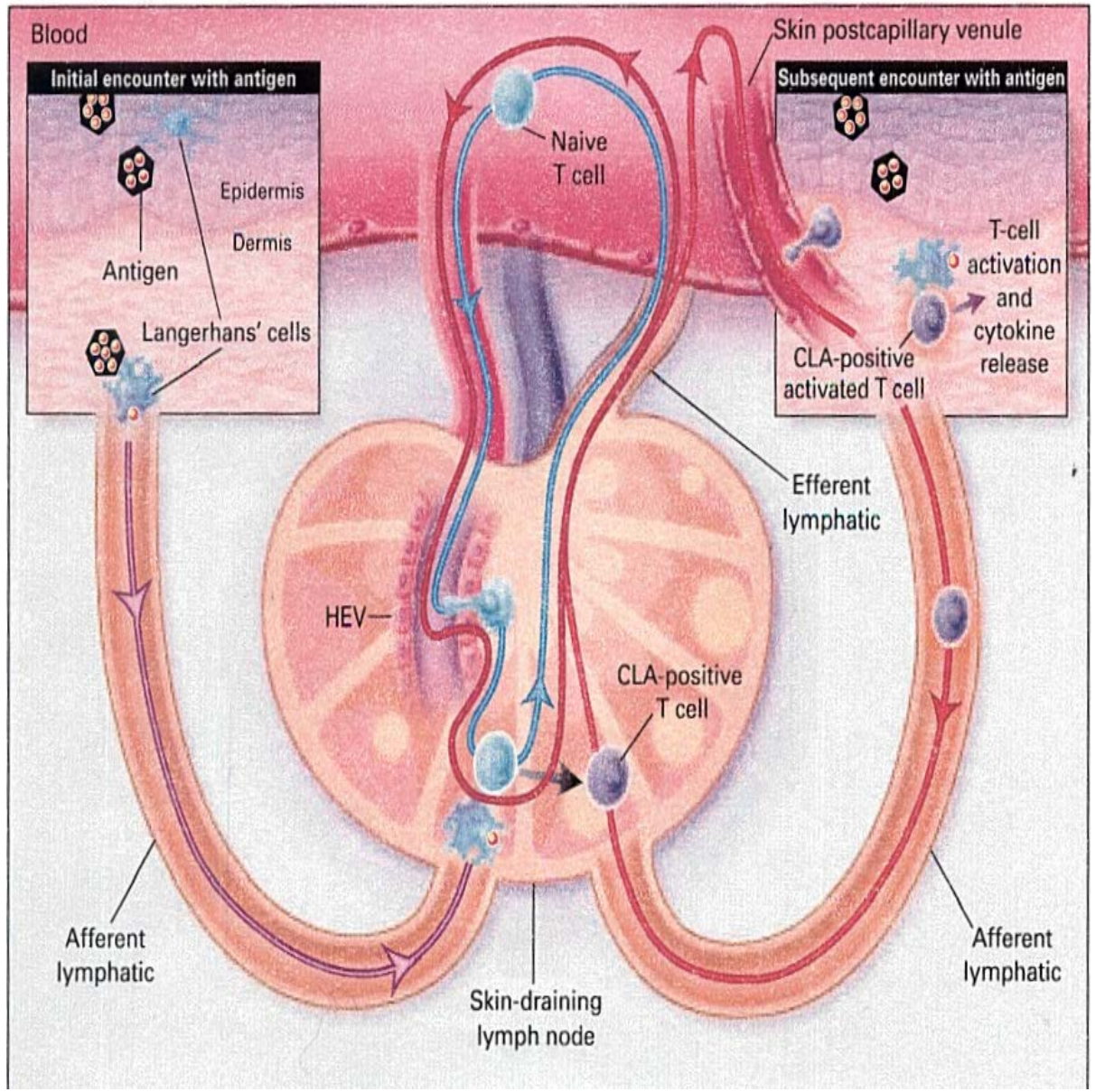
- To suggest an appropriate treatment
- To give an idea of what to expect
- To know what areas or test(s) to look at when we want to assess the effectiveness of a treatment in an individual
- To evaluate data from groups of participants in clinical trials and allow comparisons between trials

What don't stages tell us?

- A disease may not and does not have to *naturally* progress from one stage to another

- Assignment of a stage does not tell us how an *individual* will do with their disease or a particular treatment

Staging of MF/SS


Blood
Skin postcapillary venule
Initial encounter with antigen
Subsequent encounter with antigen
Naive
T cell
Epidermis
Dermis
Antigen
Langerhans' cells
T-cell
activation
and
cytokine
release
CLA-positive
activated T cell
Efferent
lymphatic
HEV
CLA-positive
T cell
Afferent
lymphatic
Skin-draining
lymph node
Afferent
lymphatic

Staging involves assessment of tissues trafficked by T-cells

- Skin
- Nodes
- Blood
- Liver, spleen, and lung

Staging Evaluation for MF/SS

Skin:

- Do photography and/or document extent, type and distribution of skin lesions; may require additional biopsies

Node:

- Record size, numbers and locations on exam
- Consider node biopsy if large nodes are felt on physical examination

Staging Evaluation of MF/SS

Blood:

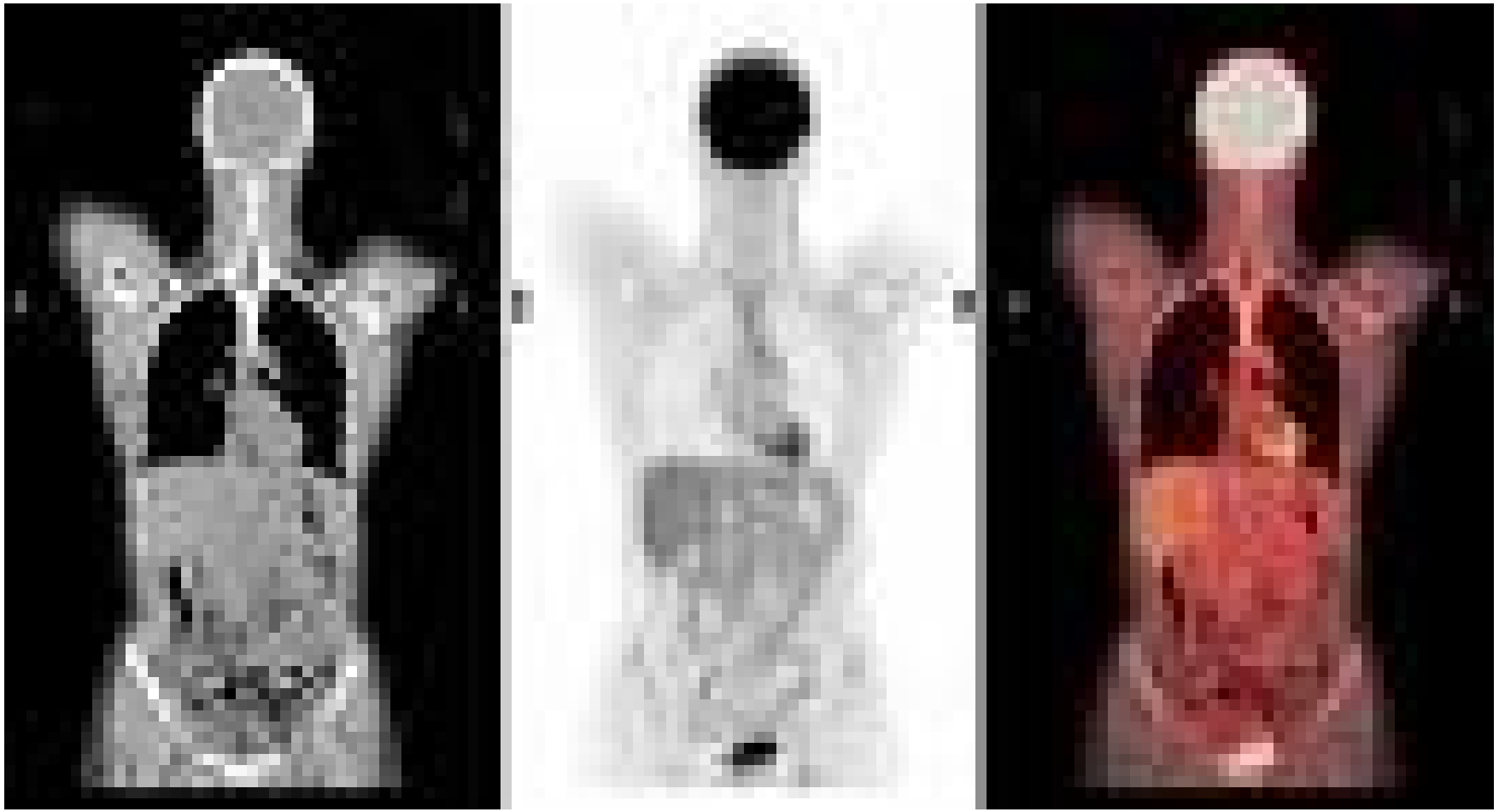
- **C**omplete **B**lood **C**ount/differential, liver function tests with LDH, sometimes HIV/HTLV I
- Flow cytometry, ± T-cell gene rearrangement

Viscera:

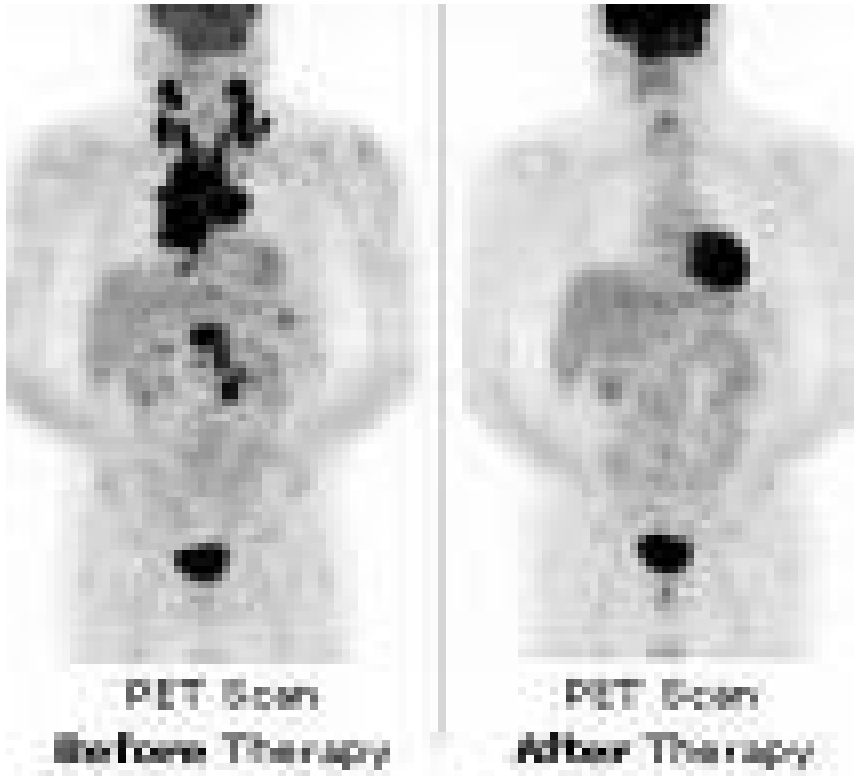
- Chest Xray and physical exam
- Sometimes PET/CT and/or marrow examinations depending on findings on physical examination and blood

Positron Emission Tomography (PET)/Computerized Tomography (CT)

PET/CT



PET/CT

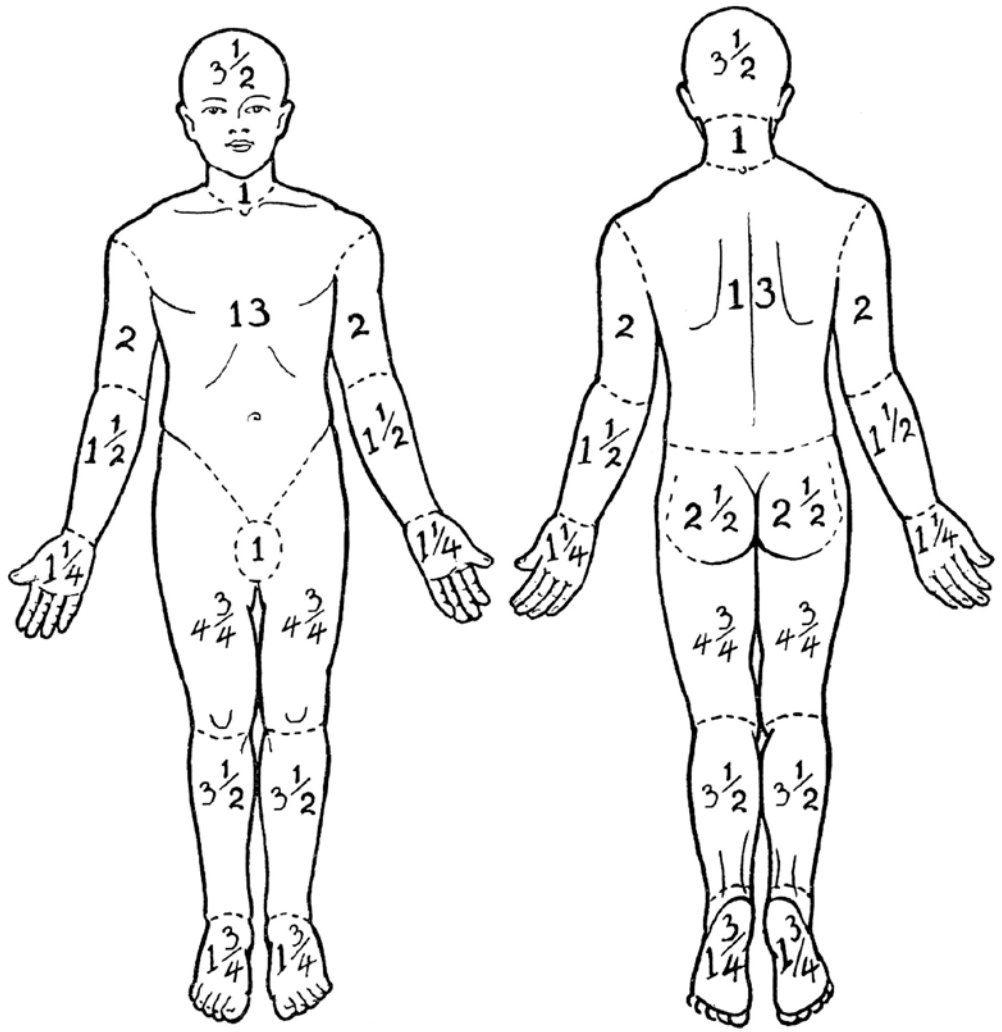


Revised MF/SS staging

TNMB[f]		TNMB Classification and Staging of Mycosis Fungoides and Sezary Syndrome[g]
Skin	T1	Limited patches,[h] papules and/or plaques[i] covering < 10 % of the skin surface
	T2	Patches,[h] papules and/or plaques[i] covering ≥ 10 % of the skin surface
	T3	One or more tumors[j] (≥ 1 cm in diameter)
	T4	Confluence of erythema ≥ 80 % body surface area
Node	N0	No clinically abnormal peripheral lymph nodes; biopsy not required[k]
	N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 1 or NCI LN 0-2
	N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 2 or NCI LN 3
	N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch Gr 3-4 or NCI LN 4
	NX	Clinically abnormal peripheral lymph nodes; no histologic confirmation
Visceral	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation[l] and organ involved should be specified)
Blood	B0	Absence of significant blood involvement: ≤ 5 % of peripheral blood lymphocytes are atypical (Sezary) cells[m]
	B1	Low blood tumor burden: > 5 % of peripheral blood lymphocytes are atypical (Sezary) cells but does not meet the criteria of B2
	B2	High blood tumor burden: ≥ 1000/mcL Sezary cells[l]

blood
JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Regional percent body surface area (BSA) in the adult.



Olsen E et al. Blood 2007;110:1713-1722

Revised MF/SS staging

	T	N	M	B
IA	1			
IB	2			
IIB	3			
III	4			
IIIA	4			0
IIIB	4			1
IVA1				2
IVA2		3		
IVB			1	

Staging of other cutaneous lymphomas

Clinical Staging for other Lymphomas

- History: attention to “B” symptoms (fever, night sweats, weight loss)
- Physical exam: attention to LN areas, liver, spleen
- Complete blood count with evaluation of blood smear and differential
- Serum chemistries, including LDH
- Flow cytometry as indicated
- CT scans of neck, chest, abdomen and pelvis
- Additional radiological studies as indicated (e.g., PET scan, chest Xray, and/or MRI scan)
- Bone marrow biopsies as indicated
- In some cases, cerebrospinal fluid exam, bone or gastrointestinal exam

Proposed ISCL/EORTC TNM Staging System for Cutaneous Lymphomas other than MF/SS

- Blood 2007; 110(2): 479-484
- Complicated system of questionable utility