



# Minimal Standards and Standardization in Histological Diagnosis

*Prof. Dr. Şevket Ruacan  
Institute of Oncology  
Hacettepe University  
Ankara, Turkey*



# Diagnosis of Lymphoma

- Clinical methods
- Histopathology
- Cytology
- Immunohistochemistry
- Flow cytometry
- Molecular techniques

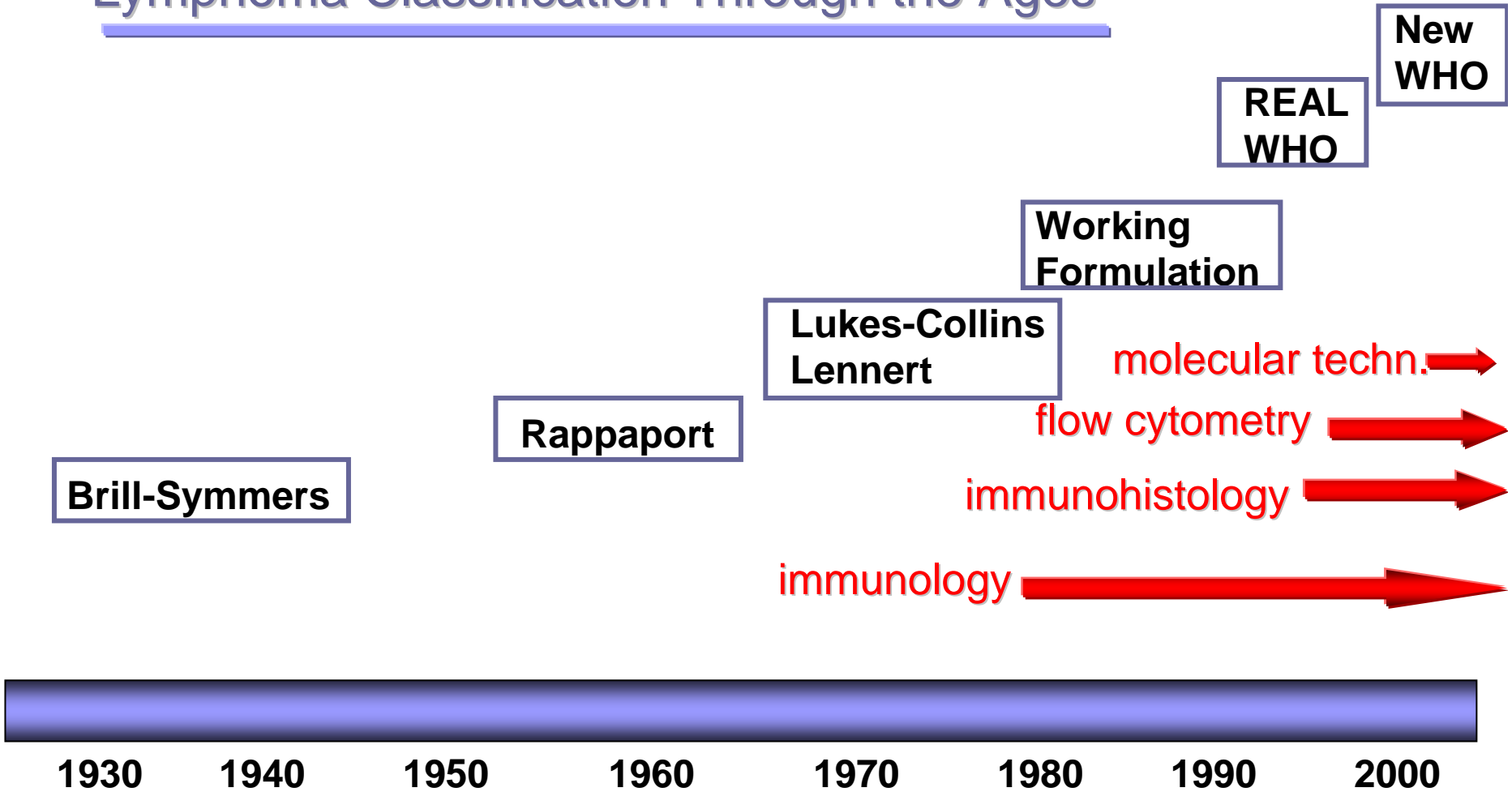


# Lymphoma Diagnosis and Classification

---

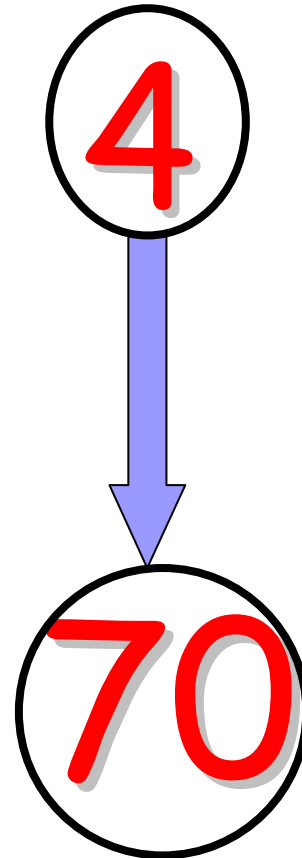
- Hodgkin(1832)
- Virchow(1845)
- Brill-Symmers(1925)
- Gall-Mallory(1942)
- Jackson-Parker(1933)
- Lennert(1967)
- Rappaport(1966)
- Lukes-Collins(1974)
- BNLI(1974)
- WHO(1976)
- Working Formulation
- REAL(1996)
- WHO(1999)
- nWHO(2008)

# Lymphoma Classification Through the Ages





# Categories in Changing Classifications



# nWHO 2008

Medscape® www.medscape.com

**Precursor B-Cell Neoplasm**  
Precursor B-lymphoblastic leukemia/lymphoma

**Mature B-Cell Neoplasms**  
Chronic lymphocytic leukemia/small lymphocytic lymphoma  
Variant: with plasmacytoid differentiation or monoclonal gammopathy  
B-cell prolymphocytic leukemia  
Lymphoplasmacytic lymphoma  
Splenic marginal zone B-cell lymphoma (with or without villous lymphocytes)  
Hairy cell leukemia  
Variant: hairy cell variant  
Plasma cell myeloma/plasmacytoma  
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type  
Nodal marginal zone B-cell lymphoma (with or without monocytoid B cells)  
Follicular lymphoma  
Grading  
1: 0-5 centroblasts per HPF  
2: 6-15 centroblasts per HPF  
3: >15 centroblasts per HPF  
3a: >15 centroblasts, but centrocytes are still present  
3b: Centroblasts form solid sheets with no residual centrocytes  
Variants  
Cutaneous follicle center lymphoma  
Diffuse follicle center lymphoma  
Grade 1: 0-5 centroblasts per HPF  
Grade 2: 6-15 centroblasts per HPF  
Mantle cell lymphoma  
Variant: blastoid  
Diffuse large B-cell lymphoma  
Subtypes  
Mediastinal large B-cell lymphoma  
Intravascular large B-cell lymphoma  
Primary effusion lymphoma  
Morphologic variants  
Centroblastic  
Immunoblastic  
Anaplastic large B-cell  
T-cell/histiocyte-rich  
Plasmablastic  
Lymphomatoid granulomatosis type  
Burkitt lymphoma/Burkitt cell leukemia  
Morphologic variants  
Classic  
Burkitt-like  
With plasmacytoid differentiation (AIDS-associated)  
Subtypes (clinical and genetic)  
Endemic  
Sporadic  
Immunodeficiency-associated

HPF, high-power field.

Source: Am J Clin Pathol © 2003 American Society of Clinical Pathologists, Inc.

Medscape® www.medscape.com

**Precursor T-Cell Neoplasm**  
Precursor T-lymphoblastic lymphoma/leukemia

**Mature (Peripheral) T-Cell Neoplasms**  
T-cell prolymphocytic leukemia  
Morphologic variants  
Small cell  
Cerebriform cell  
T-cell granular lymphocytic leukemia  
Aggressive NK-cell leukemia  
Adult T-cell leukemia/lymphoma (HTLV-1+)  
Clinical variants  
Acute  
Lymphomatous  
Chronic  
Smoldering  
Hodgkin-like  
Extranodal NK/T-cell lymphoma, nasal type  
Enteropathy-type T-cell lymphoma  
Hepatosplenic T-cell lymphoma  
Subcutaneous panniculitis-like T-cell lymphoma  
Mycosis fungoides/Sézary syndrome  
Variants  
Pagetoid reticulosis  
Mycosis fungoides-associated follicular mucinosis  
Granulomatous slack skin disease  
Primary cutaneous CD30+ T-cell lymphoproliferative disorder  
Variants  
Lymphomatoid papulosis (type A and B)\*  
Primary cutaneous anaplastic large cell lymphoma  
Borderline lesions  
Peripheral T-cell lymphoma, not otherwise characterized  
Morphologic variants  
Lymphoepithelioid (Lennert)  
T-zone  
Angioimmunoblastic T-cell lymphoma  
Anaplastic large cell lymphoma, primary systemic type (anaplastic lymphoma kinase positive or negative)  
Morphologic variants  
Lymphohistiocytic  
Small cell

NK, natural killer.

\* For clinical purposes, not considered a neoplasm.

Source: Am J Clin Pathol © 2003 American Society of Clinical Pathologists, Inc.

Medscape® www.medscape.com

Nodular lymphocyte predominant Hodgkin lymphoma  
Classic Hodgkin lymphoma  
Nodular sclerosis Hodgkin lymphoma (grades 1 and 2)  
Lymphocyte-rich classic Hodgkin lymphoma  
Mixed cellularity Hodgkin lymphoma  
Lymphocyte depleted Hodgkin lymphoma

Source: Am J Clin Pathol © 2003 American Society of Clinical Pathologists, Inc.

Medscape® www.medscape.com

Early lesions\*  
Reactive plasmacytic hyperplasia  
Infectious mononucleosis-like  
Polymorphic PTLD  
Polyclonal (rare)  
Monoclonal  
Monomorphic PTLD (classify according to World Health Organization classification)  
B-cell lymphomas  
Diffuse large B-cell lymphoma  
Burkitt lymphoma/atypical Burkitt lymphoma variant  
Plasma cell myeloma  
T-cell lymphomas  
Peripheral T-cell lymphoma, not otherwise categorized  
Other types (hepatosplenic, gamma/delta, NK/T-cell)  
Other types (rare)  
Hodgkin lymphoma-like lesions (associated with methotrexate and other immunosuppressive therapy)  
Hodgkin lymphoma  
Plasmacytoma-like lesions

NK, natural killer.  
\* Not considered neoplasms.

Source: Am J Clin Pathol © 2003 American Society of Clinical Pathologists, Inc.



# REAL Classification

- Real disease entities + clinical relevance
- All characteristics accounted for: morphology, immuno, genetics, clinical
- No gold standard

# Classification is easy when there is no effective treatment

## THE FAR SIDE



Like most veterinary students, Doreen breezes through Chapter 9.

## Equine Medicine

- Broken leg: shoot
- Infected eye: shoot
- Splayed hoof: shoot
- Runny nose: shoot
- Fever: shoot....



# Requirements for Accurate Classification

---

- Good tissue technique
- Experienced hematopathologist
- Immunohistochemistry
  - \*Varying numbers of antibodies, flow...
- Molecular techniques
  - \*PCR, FISH, microarray...



# Experience in Hematopathology

- Rare entities
- Few cases in routine pathology practice
- 3 – 4 cases of Hodgkin's
- 10- 20 case of lymphomas / year

***Methods and pathways for consultation must be provided for pathologists during training***



# Criteria for Diagnosis

- **Morphology:**  
principal method of diagnosis
- **Immuno + genetics:**  
not necessary in every case  
objective, accessory techniques
- **Clinical studies:**  
necessary for proper classification



# **Minimal Standards**

---

## ■ **Adequate biopsy + histotechnique**

\* biopsy, fixation, histology, staining, clinical information...

## ■ **Consultation**

\* tissue, section, telepathology...

## ■ **Centralized facilities**

\* immunohistochemistry, molecular...

## ■ **Training**

\* courses, workshops, publications, rotations...



## Things you can count on:

- Death
- Taxes
- A new lymphoma classification!

*N. Harris (2009)*