The concepts of Lymphomas have undergone fundamental changes over the past half century owing to major Immunology discoveries made in the beginning of this period. Until the late fifties, lymphomas were subdivided into three types: Lymphosarcoma, Reticulosarcoma and Hodgkin disease (1-2). As stated by Robert Lukes, the malignant lymphomas went through a dark age of medical understanding for decades because of the lack of basic knowledge of immunology and lymphopoiesis.

In 1966, in the first series of the AFIP Tumor Pathology fascicles, Henry Rappaport published his classification of lymphomas which was largely adopted by the clinicians and remained predominant for over two decades (Table 1) (3). The Rappaport classification correctly identified the follicular lymphomas and was clinically significant because it indicated that nodular lymphomas have a better prognosis than diffuse lymphomas and small cell lymphomas better than large cell lymphomas. However it was incorrect in stating that all lymphomas may assume a nodular or a diffuse form since the nodular or follicular lymphomas are a distinct entity of their own. Also incorrect was the assumption that the large cell lymphomas are of histiocytic origin as it was later proven that they are in fact derived from transformed lymphocytes (Table 2).

Two major discoveries in Immunology, both in the early 60-ties brought about basic changes in our concepts of lymphoma. (Table 3).
The small circulating lymphocytes although morphologically identical to each other are in fact heterogeneous, belonging to the major classes of B-cells and T-cells. The B-cells express immunoglobulins on their membranes, the T-cells have cell markers which induce the formation of rosettes with sheep erythrocytes (Fig.1) (4).

The development of monoclonal antibodies led in the following decades to the production of hundreds of antibody reagents to some of the great number of cell markers both on fresh cells in flow cytometry and on formalin-fixed paraffin-embedded tissues which revolutionized our concepts of lymphomas as well as their diagnosis.

The second discovery which greatly advanced our understanding of lymphomas and also occurred in the early 60-ties was the observation made by Peter Nowell, a pathologist at the University of Pennsylvania that lymphocytes in vitro in contact with Phytohemagglutinin, an extract of kidney beans, undergo a major transformation involving both morphology and function (Fig.2) (5). Small lymphocytes enlarge 4-6 times, acquire abundant cytoplasm, endoplasmic reticulum and ribosomes, nuclei with open pattern chromatin, nucleoli and mitoses. (Fig.3). These transformed cells are able to synthesize DNA, produce proteins and initiate new cell cycles (6). More importantly these astounding changes may occur in contact with an infinite variety of antigens to which lymphocytes are able to react. Previously thought to
represent reticulum cells or histiocytes, the transformed lymphocytes, centroblasts in the germinal centers and immunoblasts in the interfollicular areas, are in fact the precursors of the large cell lymphomas.

Leading the introduction of immunologic discoveries in the understanding of lymphomas were Robert Lukes in America and Karl Lennert in Germany with their remarkable associates. The classification of Hodgkin lymphomas by Lukes and Butler, still in use today (7), and the Lukes-Collins of non-Hodgkin Lymphomas which served as the basis for most subsequent classifications prevailed in the US (8), while the Lennert classification based on his concepts of lymphopoiesis was adopted in most European countries but remained mainly unknown in America (9).

In the early 60-ties, cytogenetics recorded the first consistent chromosomal translocations in human malignant neoplasia, the Philadelphia chromosome in chronic myeloid leukemia, t(9;22) (10), and the \textit{myc} oncogene in Burkitt lymphoma t(8;14) (11). At the same time significant discoveries were made in experimental research with the identification of a host of leukemogenic viruses in rodents starting with the Gross leukemia virus (12), the first agent producing a malignant tumor in a mammal that could then be cultured in vitro (13) and transmitted in vivo.

The decades of the 60-ties and 70-ties saw the attempts to produce a generally acceptable classification of lymphomas (14), however the rapidly proliferation of proposals failed to reach a consensus. (Table 4). Clinicians expressed frustration
with the apparently conflicting opinions and confusing nomenclatures which lasted for a long time while new efforts were made to establish an effective classification (15,16)...

In 1982, the National Cancer Institute under the leadership of Costan Berard introduced the so-called Working Formulation for Clinical Usage which according to its authors attempted to provide the means of “translation” between the various classifications (17). It was easily adopted by the clinicians in this country because it graded the various types of lymphoma which had valid prognostic implications. Yet it did not include the B-cell / T-cell division of lymphocytes or any other immunologic or molecular criteria and although widely used in the US over the next two decades was not taken up in Europe.

In 1994 an international group for the study of lymphomas, including hematopathologists of US and various European countries published a new classification known under the acronym of REAL which attempted to reach a general consensus which is necessary for comparable diagnosis and valid treatment trials (18). This new classification included the morphologic, immunologic, cytogenetic and molecular diagnostic techniques available but avoided the strict histogenetic or prognostic criteria as being still incompletely defined. Instead it simply listed the various kinds of lymphoma as clinico-pathologic entities characterized by their known specific features. The Lukes-Collins and the Kiel concepts and nomenclatures served as the bases for the new classification. The broad international participation of lymphoma experts insured its acceptance on both sides of the
Atlantic and in 2002 the REAL proposal with few modifications was adopted as the WHO classification of lymphomas (19) which was once more updated in the 2008 edition of the WHO classification of Hematopoietic Tumors (20). Currently used in most countries it divides lymphomas according to their clonal origins in B-cells and T / NK-cells with Hodgkin lymphoma as a separate group although also of B-cell derivation as demonstrated by the characterization of microdissected single Reed-Sternberg cells (21). Further morphologic, immunophenotypic and molecular studies revealed the existence of cases intermediate between Hodgkin and non-Hodgkin lymphomas with overlapping features and different treatment response which were referred to as Grey zone Lymphomas (22). Subsequently, similar borderline cases were identified between other types and subtypes of lymphomas which suggests the presence of a continuum spectrum between some apparently distinct types of lymphomas (23). Even more surprising to our earlier concepts were more recent reports of divergent clonal transformation during the progress of lymphomas resulting in changes of cell lineage such as from follicular lymphoma to histiocytic sarcoma (Fig. 4). (24). In experimental models in mice reprogramming of B-cells into T-cells or macrophages was obtained as a result of the ablation of Pax-5 transcription factor (25). These findings challenge our concepts of strictly committed lines of cellular unidirectional differentiation allowing for the possibility of reprogramming and transdifferentiation.
Understanding lymphomas for their better diagnosis and treatment has benefitted more than any other area of oncology from the great advances in Immunology and Molecular Biology of the past decades. Translation of newly acquired knowledge into the creation of treatments targeted on antigens or genes of specific lymphoma cells has been already successful beyond expectations such as with the highly efficient anti-CD20 molecule Rituximab antibody that has been saving thousands of lives.

References

15. Dehner L.P. – Here we go again: a new classification of malignant lymphomas. A viewpoint from the trenches
# Classification of Non-Hodgkin Lymphomas

<table>
<thead>
<tr>
<th>NODULAR</th>
<th>DIFFUSE</th>
</tr>
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<tbody>
<tr>
<td>Lymphocytic, well differentiated</td>
<td>Lymphocytic, poorly differentiated</td>
</tr>
<tr>
<td>Mixed cell, lymphocytic &amp; histiocytic</td>
<td>Histiocytic</td>
</tr>
<tr>
<td>Histiocytic</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

Henry Rappaport, AFIP, 1966

Table 1
The Rappaport Classification of Lymphomas

- Prevailed for over two decades because it was clinically significant
- Nodular Lymphomas - better prognosis than Diffuse
- Small cell types – better prognosis than Large cell

- Nodular pattern represents follicular origin and thus Follicular Lymphoma is a distinct entity
- “Histiocytic” or “Reticulum cell” Lymphomas are in fact lymphomas of transformed lymphocytes

Table 2
DISCOVERIES IN IMMUNOLOGY CHANGED CONCEPTS OF LYMPHOMAS

• Heterogeneity of Lymphocytes
  B- and T- cell systems

• Transformation of Lymphocytes
  Centroblasts, Immunoblasts

Table 3
Fig. 1 - Left: B-cell lymphocyte with membrane expression of IgM
Right: T-cell lymphocyte with sheep erythrocyte rosette
Fig. 2- Phytohemagglutinin-induced transformation in vitro from lymphocytes (right) to immunoblasts (left).
Fig.3- Normal lymphocyte (right) and activated lymphocyte (immunoblast) (left), four times larger with abundant cytoplasm, endoplasmic reticulum, ribosomes and reniform nucleus with open chromatin, nucleoli.
CLASSIFICATIONS OF LYMPHOMAS

- Rappaport 1966
- Lukes & Collins 1974
- Gerard-Marchant et al 1974
- Bennett et al. 1974
- Berard & Dorfman 1974
- Lennert, Mohri, Stein 1975
- Dorfman 1975
- Mathe et al 1976
- Working Formulation 1982
- Updated Kiel classification 1988
- Revised European-American classification (REAL) 1994

Table 4
Fig. 4 - Overlapping classical Hodgkin lymphoma (HL) with other variants of HL (left), T-cell lymphomas (top) and Large B–cell lymphomas (bottom). Modified after Stein et al. 2005