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Invited Lecture

Conceptual Basis of the Classification of Malignant Lymphomas

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One of the basic principles of tumor pathology is that tumors are defined according to the tissue or cells from which they originate. In many types of tumor this is easy to do, but in others it is difficult or impossible. With tumors of the lymphoid tissue, the malignant lymphomas, it is particularly difficult, because our current knowledge of experimental immunology indicates that there are countless variants, corresponding to the function of the various lymphoid cells. In fact, there are even malignant lymphomas that are derived from

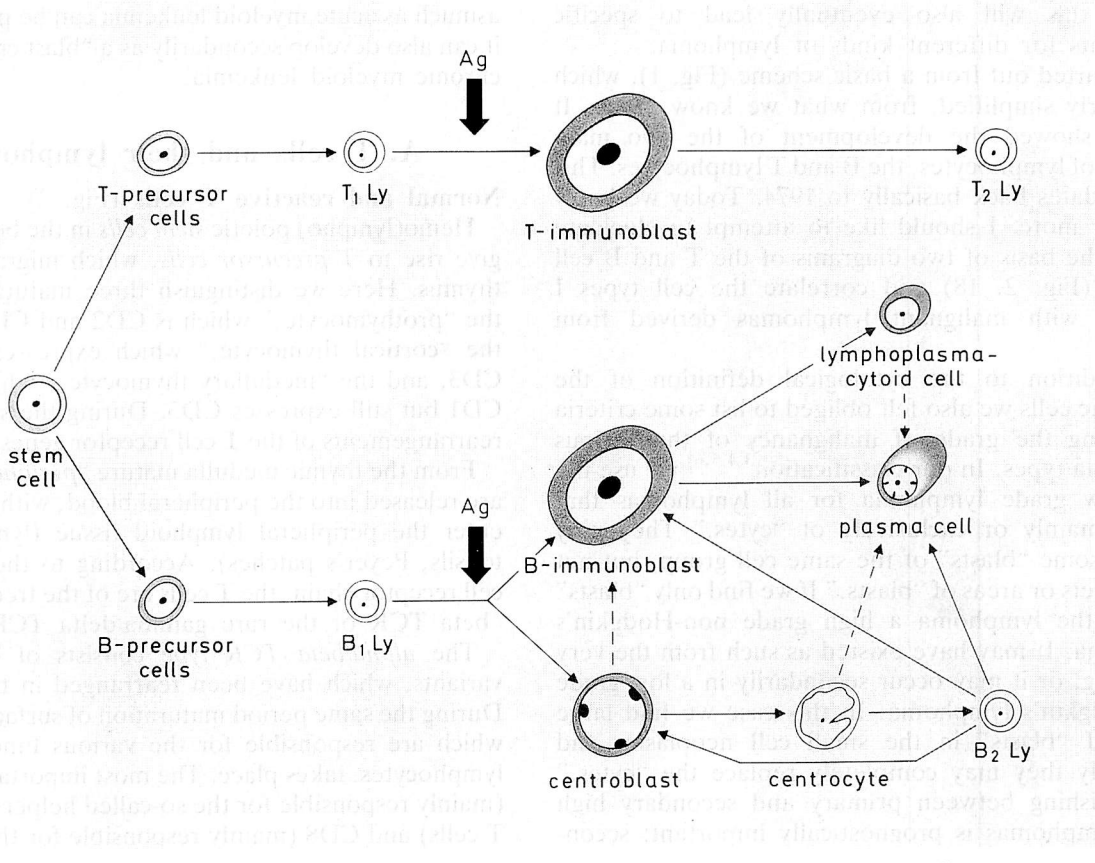

Fig. 1. Original, greatly simplified scheme of the B and T lymphocyte systems (1975[2)] and later).

cells that are not present in normal lymphoid tissue and only occur in inflamed or reactive lymphoid tissue (e. g., monocytoid B cells). No wonder that the number of types of lymphoma is greater than people used to think in the good old days.

Why should we get upset about this? No one complains about the more than 100 types of tumors of the soft tissue. And no hematologist is bothered by the

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fact that the French-American-British group distinguishes eleven variants of acute myeloid leukemia. This distinction has very important practical consequences. A subtype was found that is clearly different from the others morphologically, cytogenetically and clinically: promyelocytic leukemia. Most important for the clinician is that Chinese colleagues[1] discovered 6 years ago that it is possible to treat this subtype more successfully than before with a derivative of vitamin A (all-*trans* retinoic acid), which does not help in the other 10 types of AML. Thus the morphological subtyping of acute myeloid leukemia in the FAB classification was not just a game being played by some morphological enthusiasts, but instead the beginning of specific treatments for the various kinds of acute myeloid leukemia.

We tried to develop a classification of malignant lymphomas that is as precise as possible on the basis of the subtle morphological and immunocytochemical techniques that are available to us today[2]. Our dream is that this will also eventually lead to specific treatments for different kinds of lymphoma.

We started out from a basic scheme (Fig. 1), which was overly simplified, from what we know today. It already showed the development of the two main lineages of lymphocytes, the B and T lymphocytes. This scheme dates back basically to 1974. Today we know infinitely more. I should like to attempt to elucidate this on the basis of two diagrams of the T and B cell systems (Fig. 2, 18) and correlate the cell types I describe with malignant lymphomas derived from them.

In addition to the cytological definition of the neoplastic cells we also felt obliged to list some criteria concerning the grade of malignancy of the various lymphoma types. In our classification[3,4,5,6] we use the term low grade lymphoma for all lymphomas that consist mainly or exclusively of "cytes." They may contain some "blasts" of the same cell group, but not large sheets or areas of "blasts." If we find only "blasts" we call the lymphoma a high grade non-Hodgkin's lymphoma. It may have existed as such from the very beginning, or it may occur secondarily in a low grade non-Hodgkin's lymphoma. In this case we find large sheets of "blasts" in the small cell neoplasm, and eventually they may completely replace the "cytes." Distinguishing between primary and secondary high grade lymphomas is prognostically important: secondary high grade lymphomas usually show a much poorer response to chemotherapy than primary high grade lymphomas do.

We must point out, however, that the definition of low/high grade was not based on the clinical course, but only on the cytological picture. Nevertheless we were pleased to see that our low grade lymphomas usually corresponded to cases with a slow spontaneous course, whereas high grade lymphomas spontaneously show a rapid course. In general, B cell lymphomas progress more slowly than T cell lymphomas, but there are exceptions. Some high grade lymphomas (e.g. large cell anaplastic lymphoma) have a better prognosis than such low grade lymphomas as mantle cell lymphoma, which is usually incurable. The most important exception to the rule of the spontaneous course is induced by therapy: high grade lymphomas can be cured in more than 50% of the patients. Low grade lymphomas often cannot be cured by chemotherapy so far.

Our definition of low grade (-cytic) and high grade (-blastic) tumors is analogous to the customary clinical distinction between chronic (-cytic) and acute (-blastic) myeloid leukemia. These two basic types of myeloid leukemia share with the lymphomas the feature that chronic myeloid leukemia can, in exceptional cases, take a rapid course, whereas "acute" myeloid leukemia spontaneously can show a relatively favorable course. In the myeloid leukemias we also find a parallel to primary and secondary high grade lymphomas, inasmuch as acute myeloid leukemia can be primary, but it can also develop secondarily as a "blast crisis" from a chronic myeloid leukemia.

A. T cells and their lymphomas

Normal and reactive T cells (Fig. 2)

Hemo(lympho) poietic *stem cells* in the bone marrow give rise to *T precursor cells*, which migrate into the thymus. Here we distinguish three maturation steps: the "prothymocyte," which is CD2 and CD7 positive, the "cortical thymocyte," which expresses CD1 and CD3, and the "medullary thymocyte," which has lost CD1 but still expresses CD3. During the same period rearrangements of the T cell receptor genes take place.

From the thymic medulla mature "*peripheral T cells*" are released into the peripheral blood, with which they enter the peripheral lymphoid tissue (lymph nodes, tonsils, Peyer's patches). According to the type of T cell receptor chain, the T cells are of the frequent alpha / beta TCR or the rare gamma/delta TCR type.

The *alpha/beta TCR type* consists of millions of variants, which have been rearranged in the thymus. During the same period maturation of surface antigens, which are responsible for the various functions of T lymphocytes, takes place. The most important are CD4 (mainly responsible for the so-called helper function of T cells) and CD8 (mainly responsible for the cytotoxic function of T cells). CD4 or CD8 positive T lymphocytes can be recognized only by their immunological markers, not by their morphology.

Today the most important monoclonal antibodies for characterizing peripheral T lymphocytes are CD3 (TCR+ T cells), CD4 (T helper cells), and CD8 (cytotoxic T cells). The antibody βF1 selectively stains the beta chains of the TCR. An additional monoclonal antibody that is used was first called Ki-1 (Ki stands for Kiel, because it was produced in Kiel), and has since

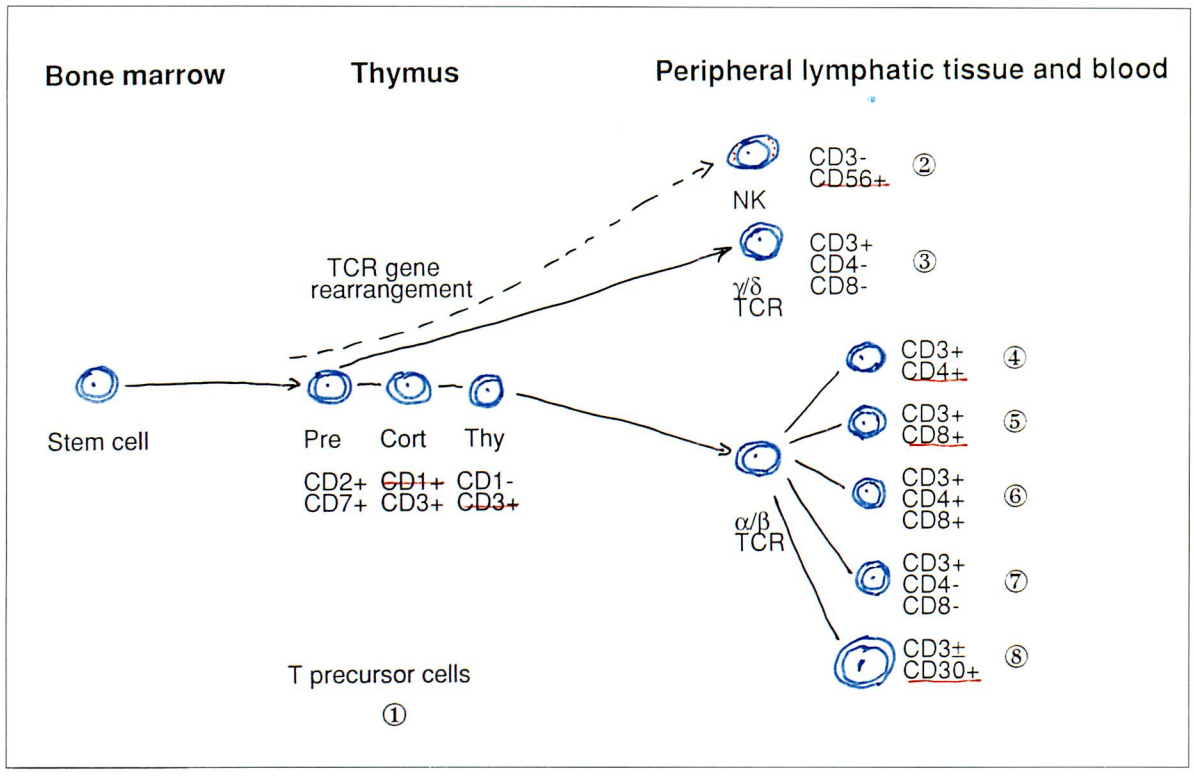


Fig. 2. T cell system (including NK cells) depicted according to morphology and especially to immunophenotypes.

been characterized as CD30. This antibody recognize lymphocyte activation antigens.

Corresponding to the various surface antigens we may distinguish roughly 5 immunohistochemical subtypes of alpha/beta T lymphocytes (Fig. 2), which are all positive for CD3 and βF1: CD4+, CD8+, CD4+/8+, CD4−/8−, CD30+. The last antibody does not describe one cell type because some different cell types especially of the T cell system may become CD30+ by being activated.

The second main type of T lymphocyte shows rearranged *gamma/delta TCR genes*. This rearrangement takes place in the very early stage of cell maturation in the thymus and results in only relatively low percentages of gamma/delta cells. They make up ~ 1-5% of the T cells in the peripheral blood. Their privileged homing site is the red pulp of the spleen.

Finally, there is a special cell in the peripheral blood which has long been known by hematologists. It is the lymphocyte with large azurophil granules ("large granular lymphocyte"), now recognized as the so-called *NK cell*. Its origin is not clear - probably near the prethymocyte. Morphologically normal NK cells can only be recognized in smears or imprints or with the aid of an electron microscope. Immunocytochemically they are normally CD3− (but CD3+ cells with azurophil granules are also found!) and always show the characteristic marker antigen: *CD56*. In addition other monoclonal antibodies (for instance CD16) may be positive.

Bearing all of these T cell types and NK cells in mind, we can correlate them with T cell lymphomas; but unfortunately morphology and immunophenotype are usually not congruent, i. e., you may have different morphological subtypes with identical immunophenotype.

The malignant lymphomas of the T cell system

We shall describe the most important examples of T cell lymphomas that we try to correlate with their normal counterparts. They are characterized in Figure 2 as 1 to 8.

1. Lymphomas of the various T *precursor* cells are called **lymphoblastic**. They may or may not have convoluted nuclei[7]. The cells are medium sized, the chromatin is fine, the nucleoli are small to medium sized, the cytoplasm is moderately basophilic (in slides stained with Giemsa). There is usually high mitotic activity. Lymphoblastic lymphoma of T cell type cannot be distinguished from lymphoblastic lymphoma of B cell type on the basis of morphology alone. They also show essentially the same morphology as acute lymphoblastic leukemia of T cell type.

2. Neoplastic NK cells are found in chronic lymphocytic leukemia with large granular lymphocytes (CD3+ or −), in nasal T/NK cell lymphoma ("midline reticulosis," Fig. 3, 4) and in rare aggressive extranodal

Fig. 3. Nasal T cell lymphoma, CD8+, Giemsa, ×1024.

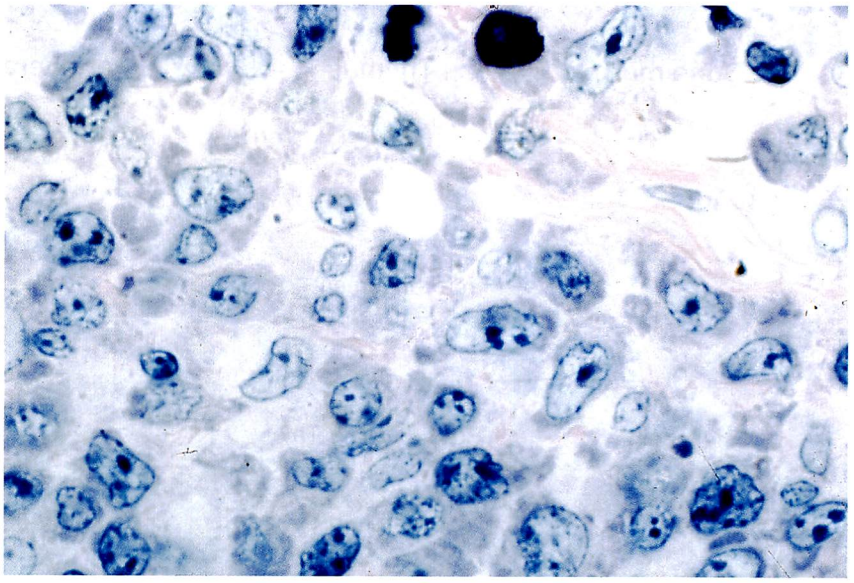


Fig. 4. Imprint of the same case as Fig. 3. Note the azurophil granules! Pappenheim, ×1536.

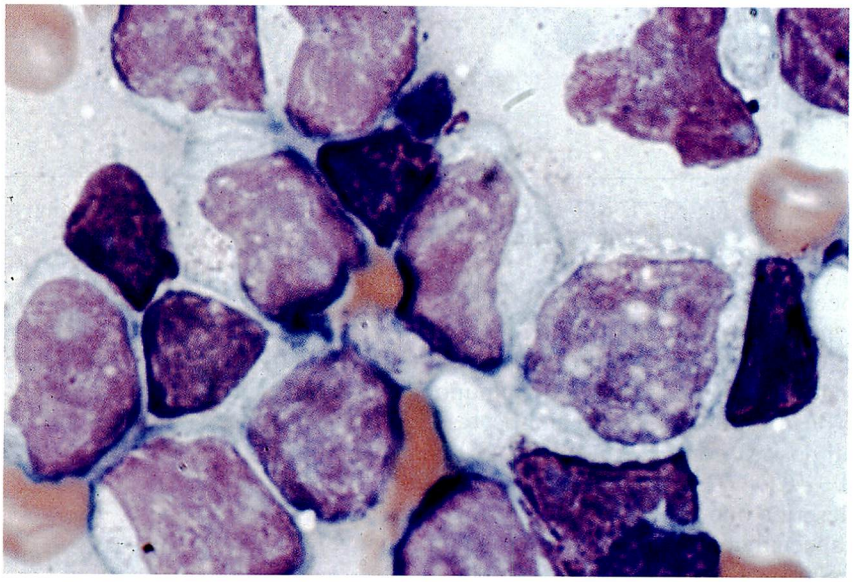
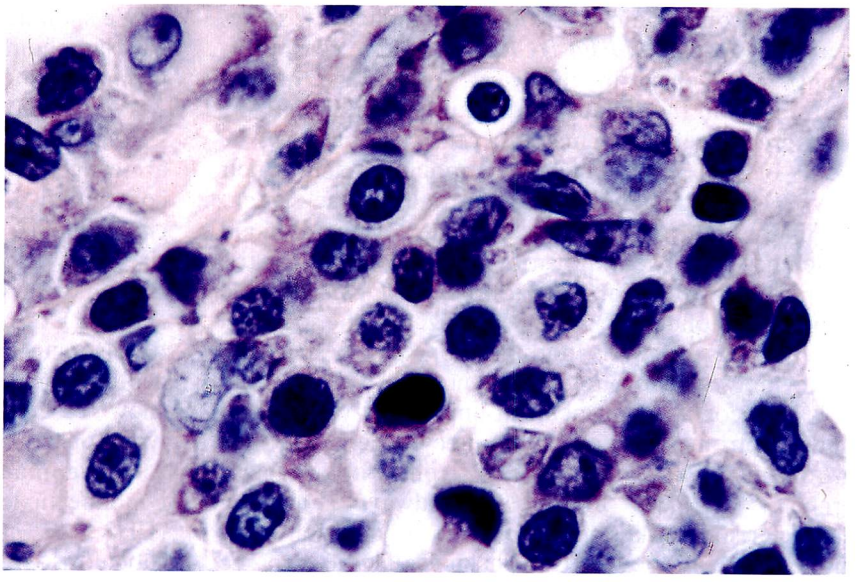


Fig. 5. NK cell lymphoma, skin. Three cells with small azurophil granules. Giemsa, ×1400.



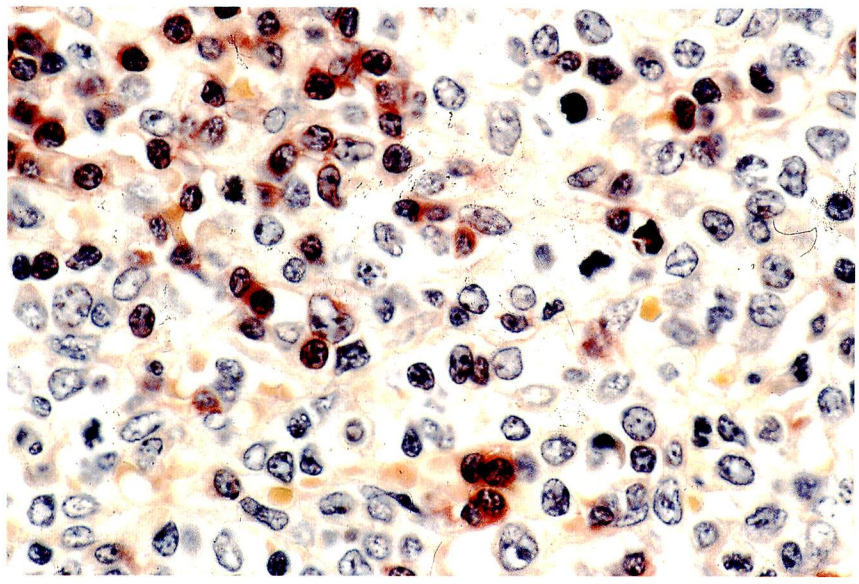


Fig. 6. Gamma/delta T cell lymphoma of the spleen. The tumor cells are βF1 negative - including the mitotic figures in two tumor cells. Remnants of normal T lymphocytes are βF1 positive. ×695.

lymphomas. In imprints or smears these aggressive lymphomas usually show the characteristic azurophil granules, which are only visible in exceptional cases in sections stained with Giemsa (Fig. 5). CD56 is always positive, various T cell markers may be found, but CD3 and the corresponding TCR rearrangement is found only rarely (Suchi, personal communication). In this case the T cell nature is absolutely clear.

3. Malignant lymphomas of the gamma/delta TCR type are found almost exclusively in the hepatosplenic form[8,9]. They consist of medium-sized, nonpleomorphic cells (Fig. 6) that grow mainly in the spleen and the liver sinusoids, much less prominently in the bone marrow and not in the lymph nodes. They react negatively with the beta receptor antibody βF1. Only one case has been reported in the nasal area[9].

Almost all peripheral T cell lymphomas are of the **alpha/beta TCR type**. They may show different immunophenotypes and are listed as nos. 4-7 in the following.

4. Malignant lymphomas of *CD4+ peripheral T cells*

These are the most frequent T cell lymphomas. Morphologically we may distinguish the subtypes shown in Table 1. Rare morphological subtypes are not listed, for them cf. [6]. We combine the first six as low grade types of lymphoma and the last three as high grade types. The last of these high grade types will be described in a separate paragraph (8).

The CD4+ T cell lymphomas differ according to their cell size and nuclear morphology and according to the demonstrability of lymphokine effects. Such *lymphokine effects* can be assumed to exist in lymphoepithelioid lymphoma (LeL) and in the AILD type of T cell lymphoma. In *lymphoepithelioid lymphoma* (Fig.7, 8) the neoplastic T cells produce migration inhibition factor, which attracts monocytes and - probably - induces them to transform into epithelioid cells. Epithelioid cells are not specific to this type of T cell lymphoma, however. They also occur in other T cell lymphomas and in Hodgkin's lymphomas[10].

Table 1. The most frequent peripheral T cell lymphomas

low grade	chronic (pro)lymphocytic leukemia	
	mycosis fungoides and Sezary's syndrome	
	lymphoepithelioid cell lymphoma (Lennert's lymphoma)	
	T cell lymphoma of AILD type	
	T-zone lymphoma	
	pleomorphic small cell T cell lymphoma	HTLV-1 ±
high grade	pleomorphic medium-sized and large cell T cell lymphoma	HTLV-1 ±
	immunoblastic lymphoma	HTLV-1 ±
	large cell anaplastic lymphoma, CD30+	HTLV-1 ±

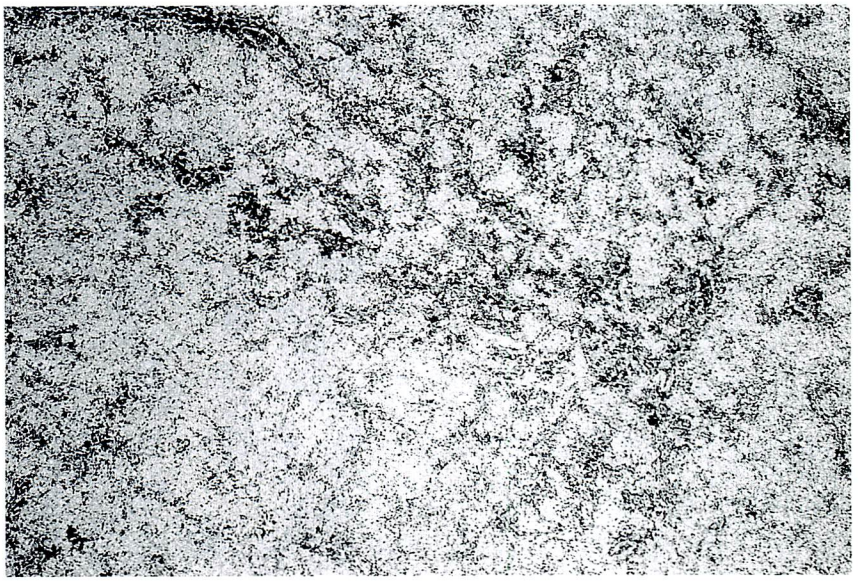


Fig. 7. Lymphoepithelioid lymphoma (LeL). Giemsa, ×31.

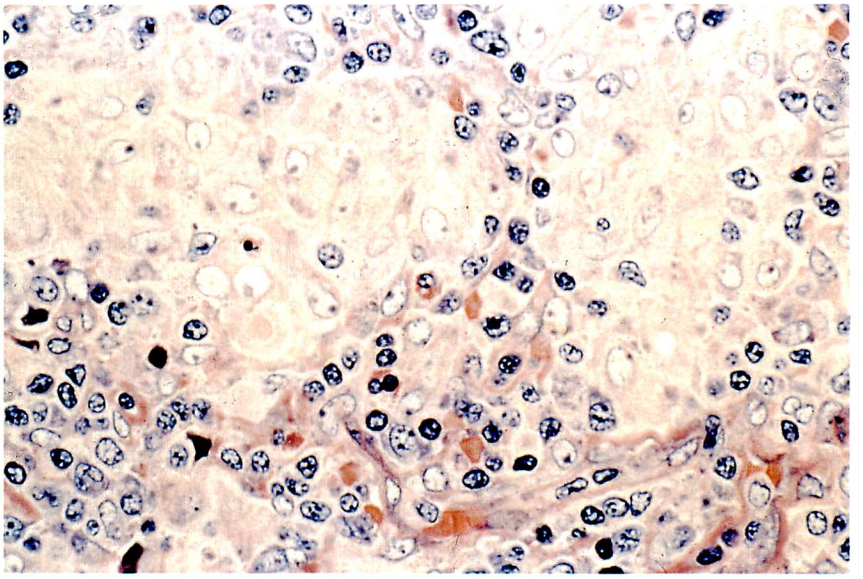


Fig. 8. Lymphoepithelioid lymphoma (LeL).Two foci of large oxyphilic epithelioid cells. Relatively few tumor cells (T lymphocytes). Giemsa, ×512.

The most important of the other T cell lymphomas is the AILD type[11]. It shows, in contrast to lymphoepithelioid lymphoma, a marked increase in venules (Fig. 9 a, b) and the other special features noted below (often increased numbers of follicular dendritic cells!). Epithelioid cells may also be found in immunocytomas, especially of the salivary glands[12], and rarely in other types of B cell lymphoma, Epithelioid cell clusters are regularly found in toxoplasmosis, frequently in infectious mononucleosis and rarely in special types of lymphadenitis like Whipple's disease (Fig. 10b). The diagnosis of LeL therefore requires, *inter alia*, a corresponding cytology: predominantly small monomorphic (to slightly pleomorphic) lymphocytes, several classic immunoblasts and some medium-sized cells between the two extremes[13].

In *T cell lymphomas of AILD type* various lymphokines are presumably produced, which sometimes lead to an increase in epithelioid cells Fig. 10a), but which more often lead to a focal, often extensive proliferation of follicular dendritic cells (Fig. 11a). This proliferation is specific to AILD, though it cannot be detected in every case. The increased high endothelial venules and also the few arteries and arterioles show perivascular deposits of (PAS+, amyloid-) hyaline. Often one sees a marked infiltration of the pericapsular tissue, frequently bypassing the capsule. There are often numerous eosinophils and a few basophils. The basophils are hard to see in sections, but can be found in small but significant numbers in imprints of some cases. The neoplastic T cells (Fig. 11b) vary greatly in morphology: small - medium - sized - large T cells, monomorphic or pleomorphic nuclei, sometimes clear cells, often single very large mononuclear or multi

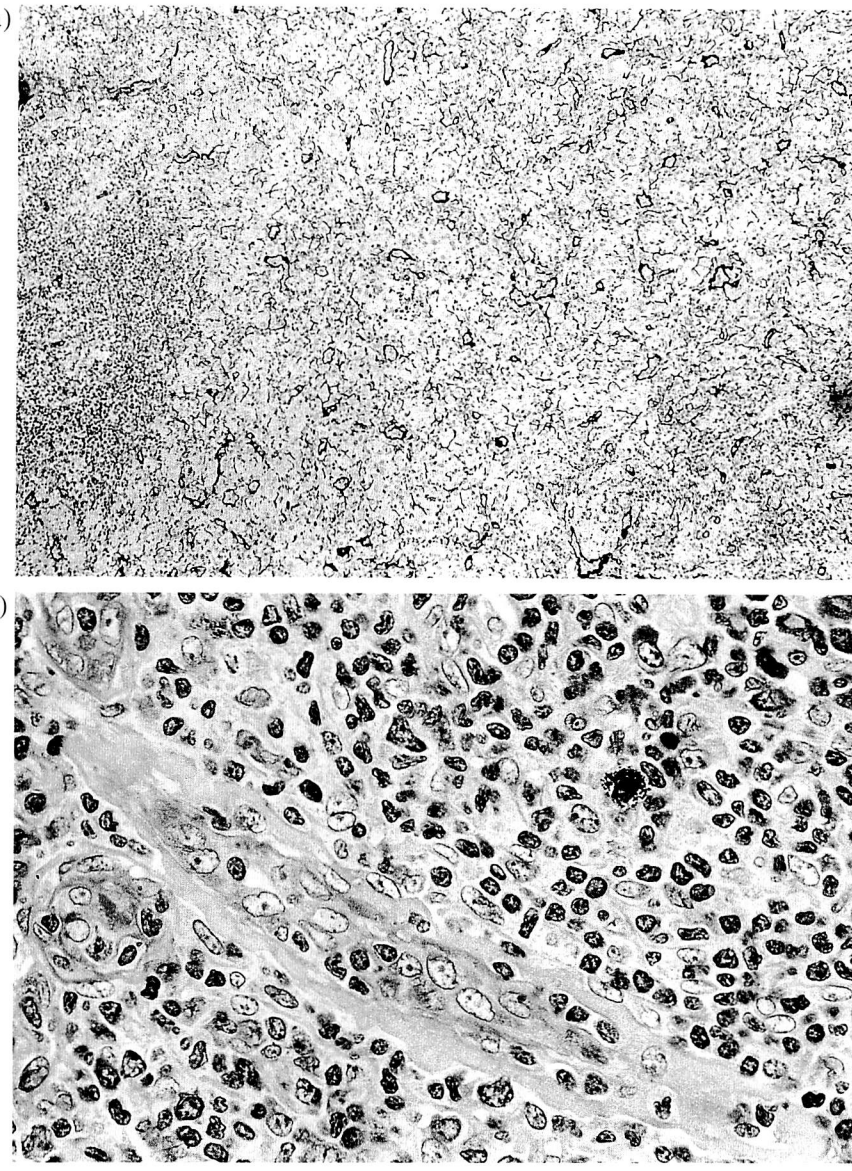


Fig. 9. (a) T cell lymphoma of AILD type with a high content of epithelioid cells (LeL-like). Note the large number of high endothelial venules! Gomori silver impregnation, ×110.
(b) Hyalinization of the high endothelial venules. Giemsa, ×256.

nucleate cells with some similarity to Sternberg-Reed cells.

The question of lymphokine production in *T-zone lymphoma* has not yet been resolved. This entity was originally described[4] as a T cell neoplasm in the T zones with hyperplastic germinal centers. In the meantime it has been better defined cytologically[14]. It corresponds to what the Chinese know as the "mixed type" of T cell lymphoma, i.e., it is composed of small, relatively monomorphic T lymphocytes, large, basophilic T immunoblasts, and various transitional forms of different sizes. Clear cells are often found (Fig. 12). Suchi and his group[15] now distinguish a T zone lymphoma with and without follicles, i.e., their definition is based solely on cytology. The cytological definition is important, inasmuch as T cell lymphomas are localized in the T zones when they begin to infiltrate, regardless of which cell type is present. What presents histologically as a T cell proliferation in the T zones between hyperplastic follicles can therefore be a T-zone lymphoma, or it can just as well be an early T cell lymphoma of another cellular composition. Consequently a cytology of the so-called "mixed type" is essential for the diagnosis of T-zone lymphoma, probably independent of the existence of follicles.

The T cell lymphomas *without visible signs of lymphokine production* generally consist of a *relatively* monotonous proliferation of various cell types. *Chronic (pro)lymphocytic leukemia of T cell type* does not affect the lymph nodes as often as chronic lymphocytic leukemia of B cell type does. Unlike the latter it shows almost no immunoblasts, but rather a slightly pleomorphic but monotonous, dense infiltrate consisting of lymphocytes that are slightly larger than normal

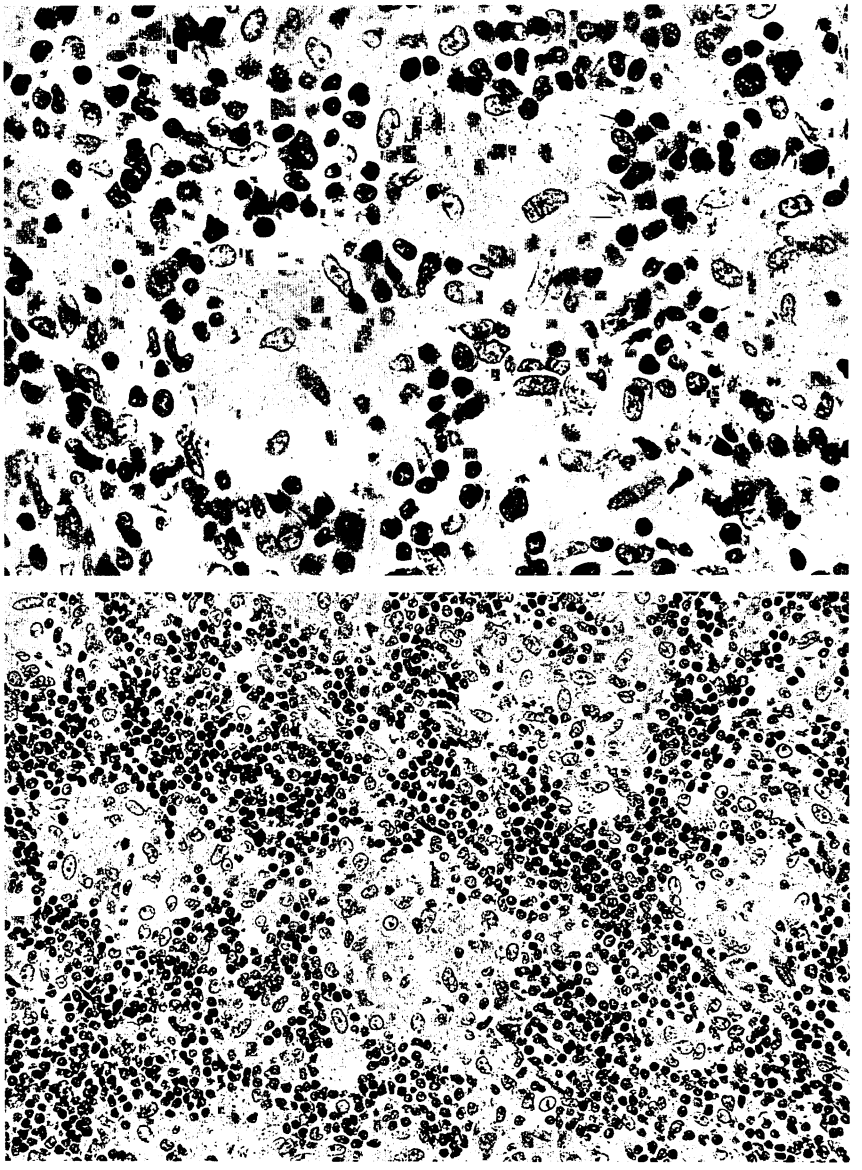


Fig. 10. (a) Same case as Fig. 9. b. Classical epithelioid cell clusters like LeL.
(b) Epithelioid cell clusters (LeL-like!) in a case of Whipple's disease.

lymphocytes and destroy the entire lymph node structure. There is a conspicuous increase in epithelioid (high endothelial) venules, in the walls of which outmigrating leukemic cells are frequently found.

Mycosis fungoides and *Sézary's syndrome* initially reveal infiltrations by small lymphocytes with cerebriform nuclei ("Lutzner cells"). This nuclear structure is often difficult to recognize in paraffin sections; it is seen better in plastic-embedded material and very well under the electron microscope. Intermingled among these cells are some large atypical cells, which bear a certain resemblance to Sternberg-Reed cells ("mycosis cells"), and some Langerhans cells. The skin infiltrate typically shows pronounced epidermotropism, often with Pautrier's pseudoabscesses. This epidermotropism is not specific, however; it also occurs in ATLL. In later stages ("tumor stages") the tumor cells become larger, are pleomorphic (pleomorphic medium-sized to large cell T cell lymphoma) or monomorphic (large cell anaplastic lymphoma, immunoblastic lymphoma), so that they can no longer be distinguished from other medium-sized to large cell T cell lymphomas.

The *pleomorphic T cell lymphomas* (small, medium-sized and/or large, Fig. 13, 14) show a relatively monotonous pattern, but the nuclei are pleomorphic in both shape and size. The cytoplasm appears gray with Giemsa staining. The diagnosis small/medium-sized/large is made according to the size of the prevalent cells. Usually we do not find large blast cells except in pleomorphic large cell lymphoma, which sometimes contains cells that can hardly be distinguished from immunoblasts. The patients can be HTLV-1 positive (in endemic areas). It is not possible to state with certainty whether one is dealing with a

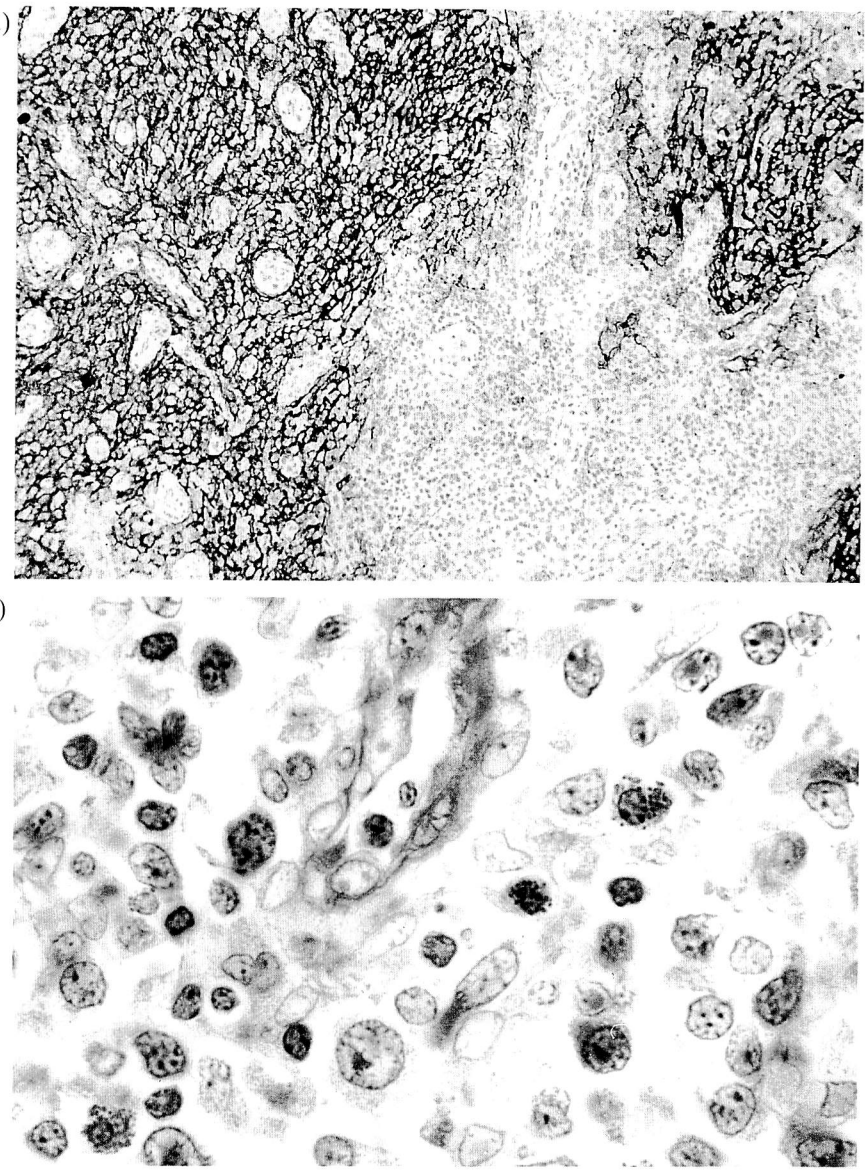


Fig. 11. (a) T cell lymphoma of AILD type. Large sheets of follicular dendritic cells (black) with many high endothelial venules in between. CD35, ×90.
(b) T cell lymphoma of AILD type. Polymorphic cytology, loosely packed. High endothelial venule in the upper center. Giemsa, × 1024.

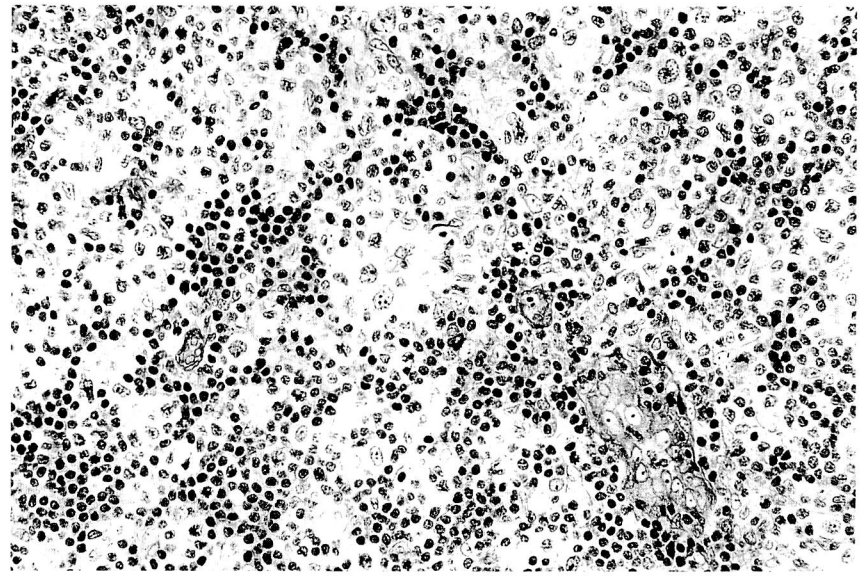


Fig. 12. T zone lymphoma with many clear cells. One high endothelial venule can be seen. No follicle in this area. Giemsa, ×256.

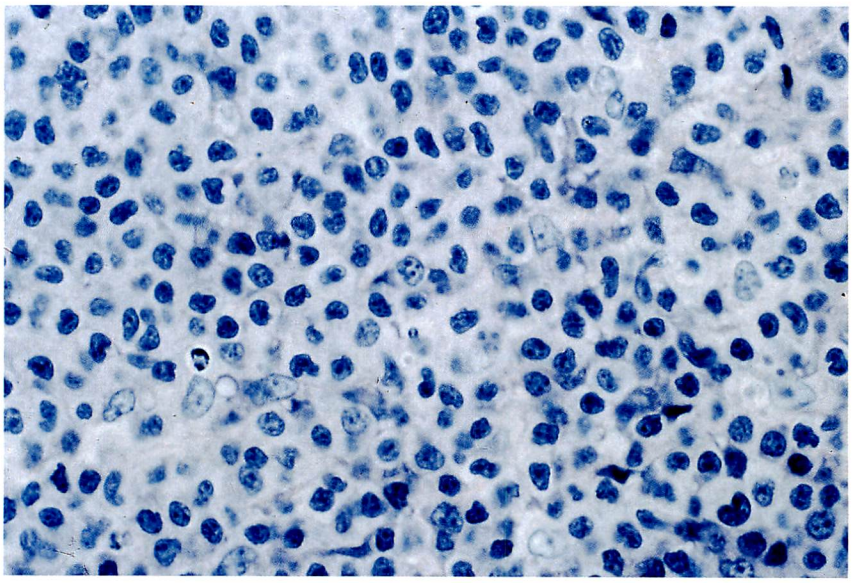


Fig. 13. Pleomorphic, small cell T cell lymphoma. No blast cells. Giemsa, ×512.

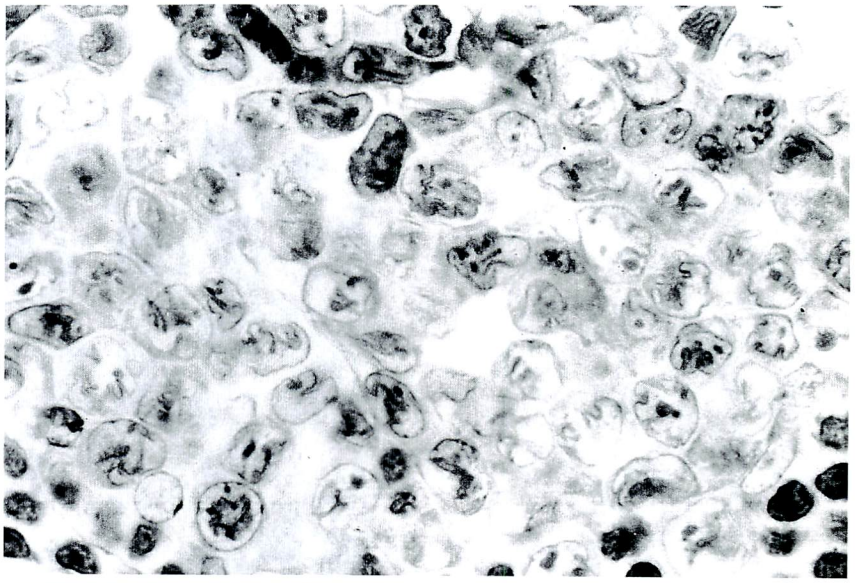


Fig. 14. Pleomorphic, large cell T cell lymphoma. European case, hence most probably HTLV-1 negative. Giemsa, ×1024.

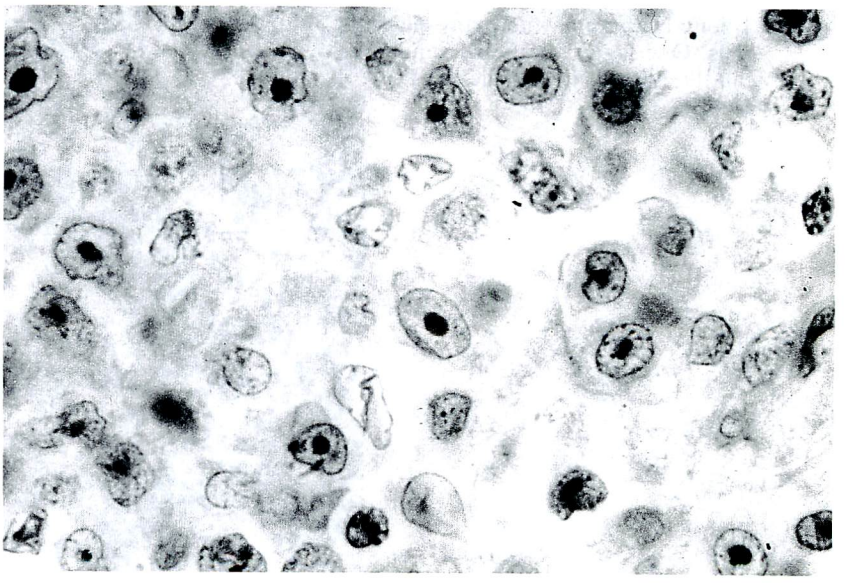


Fig. 15. Immunoblastic lymphoma, T cell type. Secondary in a T cell lymphoma of AILD type. Note the pale cell with two nuclei in the lower center. It is an interdigitating reticulum cell. The neoplastic immunoblasts show large central nucleoli. Giemsa, ×1024.

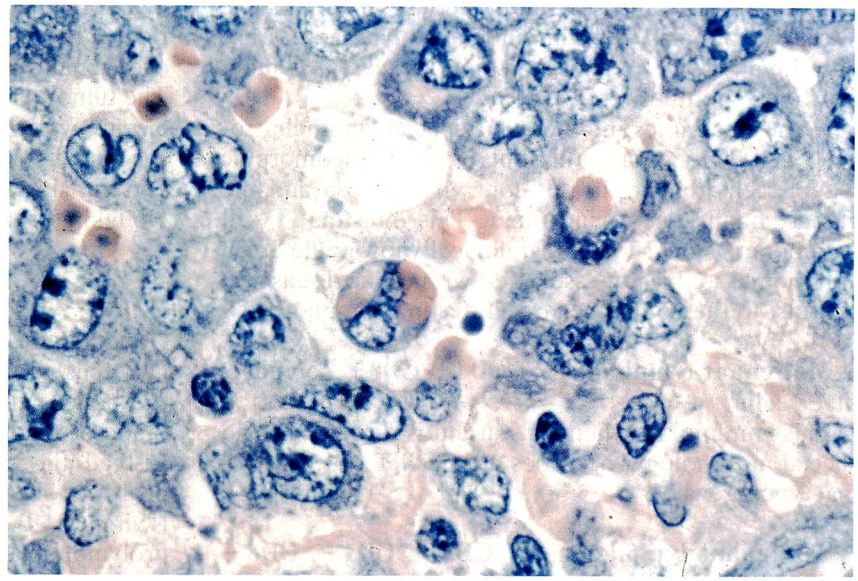


Fig. 16. Large cell anaplastic lymphoma of T cell type. Erythrophagocytosis in the center. Giemsa, ×1024.

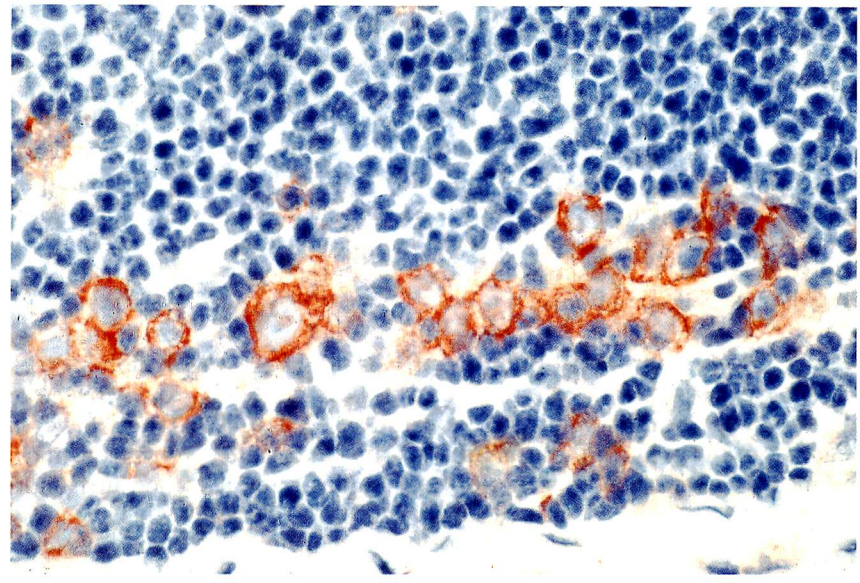


Fig. 17. Large cell anaplastic lymphoma. Tumor cells in the marginal sinus. CD30, ×512.

case of HTLV-1-positive ATLL by morphology alone, but experienced pathologists may recognize up to 80% of virus-positive cases[16]. The most remarkable feature of virus-positive cases is the pronounced anisocytosis (variation in cell size), including the occurrence of giant cells of Sternberg-Reed and Kikuchi type[17]. Immunohistochemistry is useful in verifying the diagnosis of ATLL. It is usually CD25 positive, contrary to the HTLV-1-negative T cell lymphomas[16].

T-immunoblastic lymphomas consist of large cells with ovoid nuclei that are not very pleomorphic and contain one large nucleolus or a few medium-sized nucleoli (Fig. 15). The cytoplasm is usually grayish blue when stained with Giemsa and not as basophilic as in the cells of B-immunoblastic lymphoma. No plasmacytoid differentiation can be seen.

5. Malignant lymphomas of CD8+ peripheral T cells

Most of the T cell lymphomas listed under 4 can also be CD8+, although the percentage of CD8+ lymphomas is lower in each group than that of CD4+ lymphomas. They probably do not occur in lymphoepithelioid lymphoma (LeL). Mycosis fungoides is composed only very rarely of CD8+ cells. In the AILD type a certain percentage of CD8+ cells is always observed along with the CD4+ cells. Occasionally they predominate and may contain large azurophil granules. Additionally, a large proportion of the cases of "large granular lymphocyte leukemia" have CD8 antigens in addition to CD3 antigens and therefore cannot be considered to be a NK cell leukemia in the true sense. Rarely is chronic lymphocytic leukemia of T cell type without azurophil granules CD8 positive; usually the

CD4 antigen is expressed simultaneously. Pleomorphic T cell lymphomas and immunoblastic lymphomas are occasionally CD8+ and then, in rare cases, contain azurophil granules.

In the small intestine there is a special "epitheliotropic T cell lymphoma" consisting of small, pleomorphic CD8+ cells that infiltrate along the mucosa and the glands, finally destroying them. This intestinal T cell lymphoma belongs to the histologically low grade T cell lymphomas and is not associated with celiac disease, in contrast to the double negative intestinal lymphoma[18].

6. Malignant lymphomas of CD4+ CD8+ peripheral T cells

This immunohistochemical variant is rare and has no special morphology, nor does a special T cell lymphoma type prevail.

7. Malignant lymphomas of CD3+, CD4−, CD8− peripheral T cells

These "double negative" T cell lymphomas are often localized in the intestine and there they are associated with celiac disease or gluten-sensitive enteropathy and are therefore called enteropathy-associated T cell lymphoma ("EATCL"[19]). The morphology is extremely varied, ranging from a pleomorphic small cell type to a large cell anaplastic lymphoma. Characteristic is the positive reaction with the monoclonal antibody HLM-1[20], which is negative with practically all other T cell lymphomas.

8. Large cell anaplastic lymphoma, CD30+

Large cell anaplastic lymphoma can bear T cell markers, but its immunophenotype can also be T cell negative (null type). In these cases it is usually possible by means of molecular genetics to demonstrate a rearrangement of the T cell receptor genes[21]. There are, however, rare cases that cannot be recognized as being T cell derived even with molecular methods, and there are cases of large cell anaplastic lymphoma of B cell type[21].

The essential point in the diagnosis of large cell anaplastic lymphoma is not the CD30 reaction, although it is positive in 99% of the cases. It is the *morphology* together with the positive CD30 reaction, for there are other high grade T and B cell lymphomas that differ morphologically and clinically from large cell anaplastic lymphoma.

Morphologically the typical case of large cell anaplastic lymphoma shows cells ranging in size from large to giant with pleomorphic nuclei and relatively abundant, moderately basophilic cytoplasm (gray with Giemsa staining!). There are often multiple large nucleoli, which may be elongated. They can also be very large and round. The cells often grow cohesively, so that the initial impression may be that of a carcinoma or melanoma. Sometimes the appearance is cribriform, in which case the tumor cells are interspersed with many nonneoplastic macrophages (this used to be referred to as reticulosis!). The reactive macrophages occasionally phagocytose some blood cells (Fig. 16). The tumor tissue may show prominent extravasation of erythrocytes. A feature of the tumor that is almost specific is a carcinomalike intrasinusoidal growth pattern (Fig. 17), like that previously described in Hodgkin's sarcomas[22].

B. B cells and their lymphomas

Normal and reactive B cells (Fig. 18)

B cells originate, like T cells, from the stem cells of the bone marrow, but they do not emigrate into the blood or other lymphoid organs in the precursor state. Instead they mature in the bone marrow from the prolymphoblastic phase until they become naive ("virgin") B lymphocytes. After the Ig negative prolymphoblastic phase they first develop mu chains (without light chains) in the cytoplasm and at the membrane (pre-B lymphoblasts). Afterwards they show complete IgM molecules at the cellular membrane (intermediate lymphoblasts). This is also the case in the B_1 lymphocyte. During the pre-B lymphoblast phase a rearrangement of the IgH (mu chain) takes place, and in the intermediate B lymphoblast phase the L chains are rearranged (first kappa, then lambda chains). The most frequently applied B cell antibody is that against the CD20 antigen, which is expressed in a rather early phase (between pro- and pre-lymphoblast).

As in the T cell system there are two types of mature lymphocytes: CD5− and CD5+ ones. The CD5+ ones overwhelmingly predominate in the newborn. They have been studied in cord blood under the electron microscope[23,24]. Their nuclei were found to be much more pleomorphic than in the CD5− type, which makes up more than 95% of the peripheral B lymphocytes in healthy adults. The CD5+ lymphocytes show certain analogies to the T lymphocytes with gamma/delta receptors. They appear to have become diverted in an early phase of B cell development and show much fewer IgH rearrangements than the CD5− lymphocytes. In addition to the CD5 antigen they bear the antigen CD23. They colonize the primary follicles of the newborn and are an important part of the follicle mantle zone after germinal centers develop.

The CD5− B_1 lymphocytes of the blood migrate either into the follicles or into the pulp. In the pulp they transform via B cell blasts (cf. below) into B immunoblasts and on into plasma cells. This is the case in the primary immune response and can be observed extensively in infectious mononucleosis, in which the smaller "blood plasma cells" are formed and enter the peripheral blood. The larger, so-called Marschalko type plasma cells also develop directly ("metaplastically")from centrocytes and B_2 lymphocytes. They colonize primarily the bone marrow and the intestine via the peripheral blood.

The CD5 − B_1 lymphocytes enter the primary follicles or the follicular mantle of secondary follicles, i. e., follicles with germinal centers. The development of germinal centers has been studied in the past few years especially by MacLennan and his group[25]. We will basically follow his ideas (Fig. 19). In the germinal center the CD5− B_1 lymphocytes transform into large basophilic cells, MacLennan's B-cell blasts (cf. Fig. 4). These cells proliferate extremely actively. This cell type grows exponentially; a cell cycle is completed in 6 hours. Here too the mutation of the cells begins. They still possess sIg. After a number of divisions they transform into centroblasts, in which sIg is no longer demonstrable. These centroblasts only divide one time. Then they continuously transform into centrocytes. The centroblasts are the main site of mutation (recombination of Ig genes). Unsuitable cells (centroblasts and centrocytes) are selected and perish by apoptosis (Flemming's "tingible bodies") because of the lack of *bcl*-2 in the germinal center cells. Centrocytes again contain sIg, which has often switched to IgG or IgA. Centrocytes do not divide any more, but instead develop into memory cells (B_2 lymphocytes) on the one hand and long-lived (Marschalkó) plasma cells on the other hand.

The morphology of the germinal center cells changes in correspondence with their development: the nuclei of the B cell blasts have multiple medium-sized, central nucleoli. Centroblasts usually have marginal, medium-sized to large nucleoli; centrocytes have only very small, central nucleoli. The nuclei of B cell blasts and centroblasts are more less round; those of centrocytes are irregular, occasionally cleaved or multilobated. The cytoplasm of B cell blasts and centroblasts is basophilic, in centrocytes it stains so weakly that it is barely visible with Giemsa or H&E staining.

Germinal centers additionally contain T lymphocytes, follicular dendritic cells, B immunoblasts, plasmablasts and the already mentioned macrophages. At the beginning of their development, germinal centers consist almost exclusively of B cell blasts, centroblasts and starry sky cells. A few days later the characteristic development of a dark zone (with many blast cells and few follicular dendritic cells) and a light zone (with many centrocytes and follicular dendritic cells) takes place. From the light zone the B_2 lymphocytes migrate into the follicular mantle zone.

The follicular *mantle zone* is not homogeneous, although it usually makes a monotonous impression as though consisting entirely of "small lymphocytes." These lymphocytes comprise CD5− B_2 lymphocytes, CD5+ and CD23+ B lymphocytes (=follicle mantle cells) and T lymphocytes. In the spleen, and occasionally in the lymph node as well, there is additionally a light outer zone, whose cells are somewhat larger and react as follows with monoclonal antibodies: CD5 − , CD76 − , Ki-B3 − , MT3 + , Ki-M4p(+). They are known as *marginal zone* cells, as they were called by

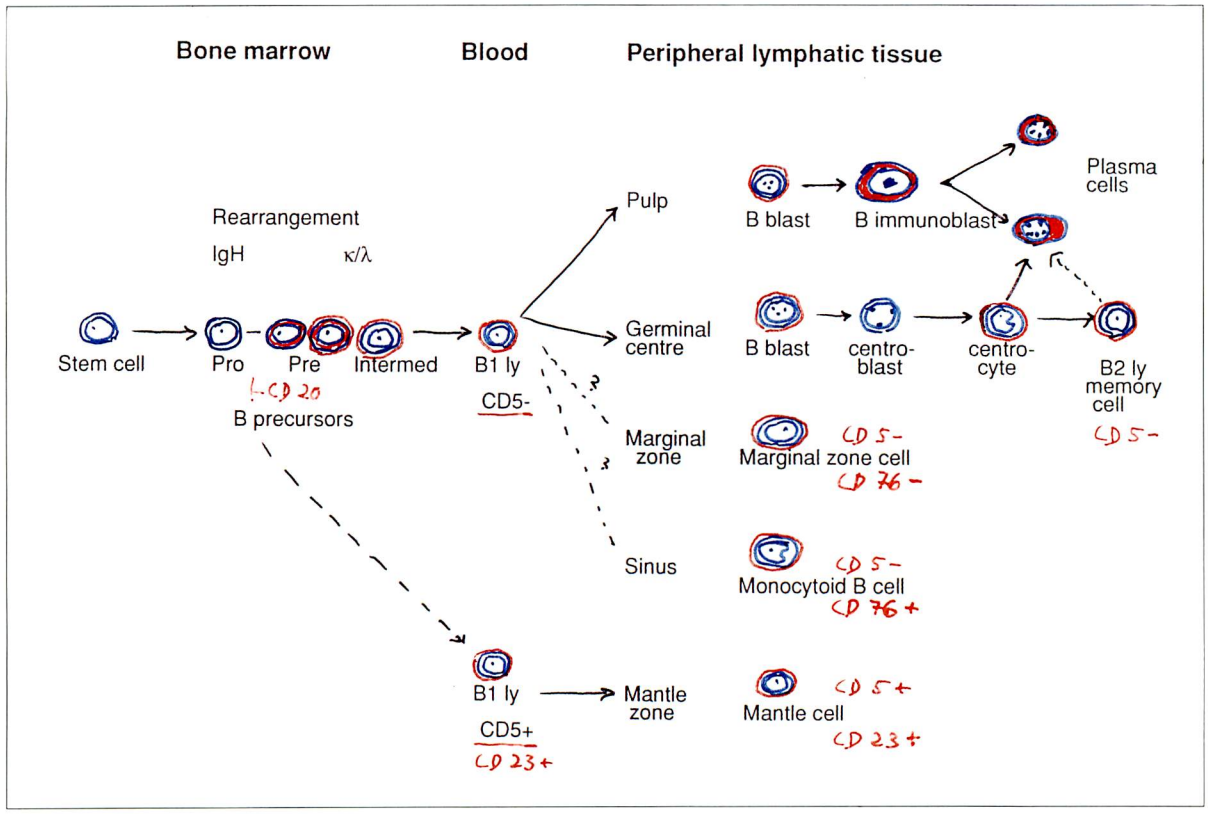


Fig. 18. B cell system, arranged according to morphology and immunophenotype.

Keuning. They must be clearly distinguished from the follicle mantle cells, and this has not always occurred in the literature.

Figure 18 shows another CD5−B cell, whose origin is, however, not yet clarified; the monocytoid B cell of the sinus. It shows certain similarities to the marginal zone cell. It is somewhat larger, its nucleus is more irregular and it is Ki-B3+ and often CD76+. In the cytoplasm we found a *granular* reaction with the antibody Ki-M1p, a macrophage marker[26]. They probably develop out of B lymphocytes of the peripheral blood [6] or the afferent lymph (Paulsen, personal communication), but their immunophenotypical similarity to the marginal zone cells should not be overlooked. Could both have the same precursor?

The malignant lymphomas of the B cell system

Malignant lymphomas of B precursor cells = lymphoblastic lymphoma

Lymphoblastic lymphomas are more often associated with a leukemic blood picture (acute lymphoblastic leukemia of B cell type) than they are solid tumors. They consist of medium-sized moderately basopilic cells (Fig. 20). The nuclei are usually roundish, but cases can occur in which there are convoluted nuclei[27]. The chromatin is fine, the nucleoli are small to medium sized and central.

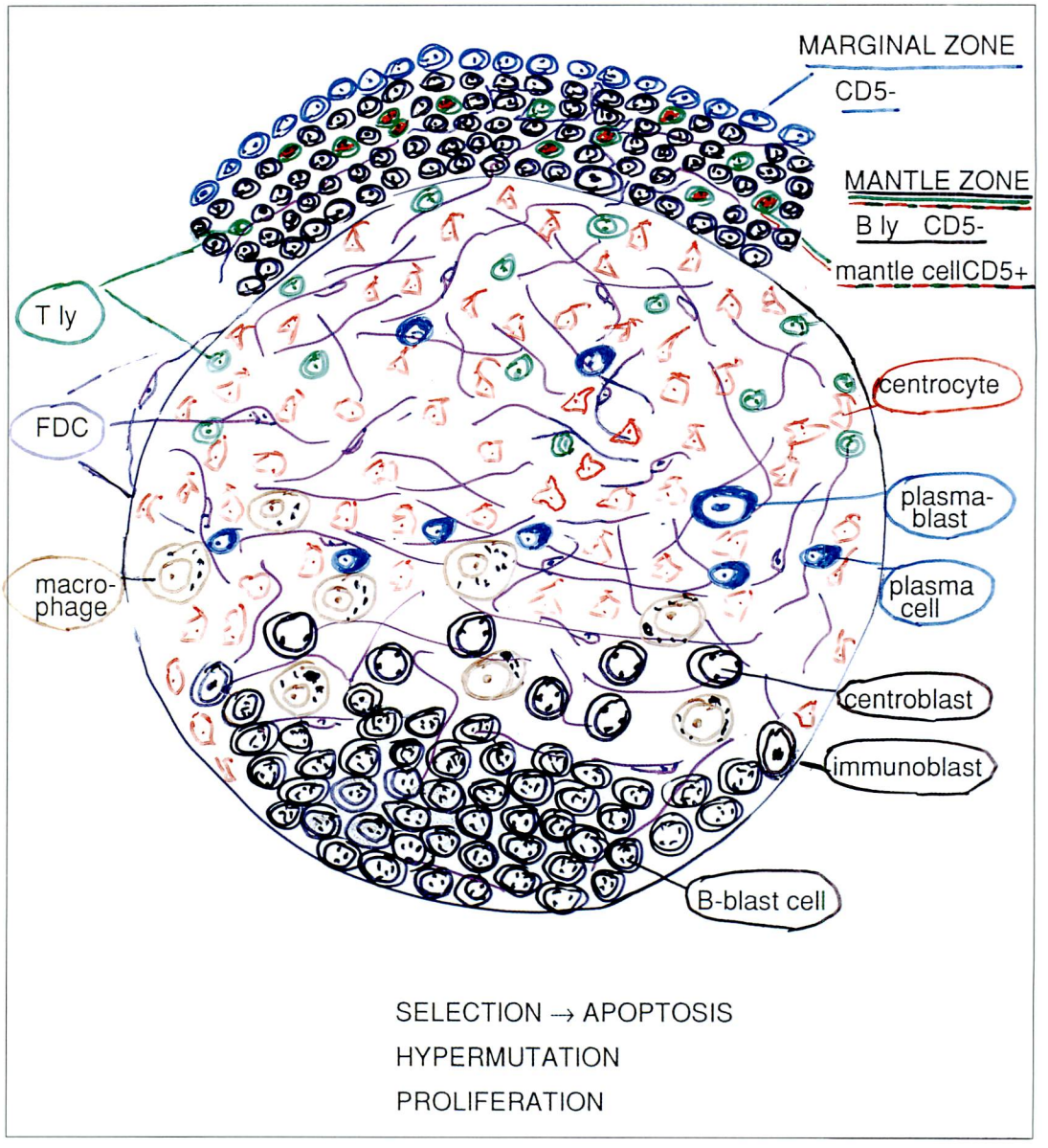


Fig. 19. Scheme of a germinal center with lymphocyte mantle ("secondary follicle") and a marginal cell zone.

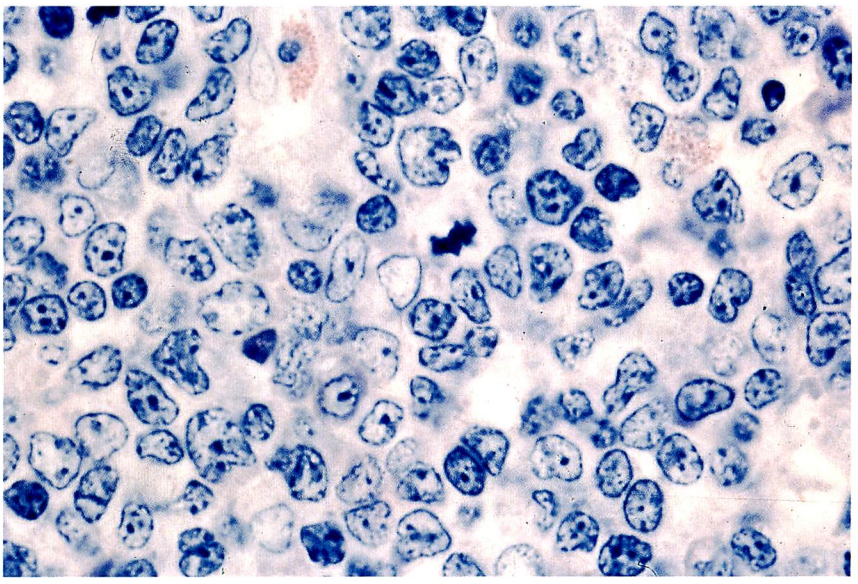


Fig. 20. Lymphoblastic lymphoma, pre-B type. Giemsa, ×1024.

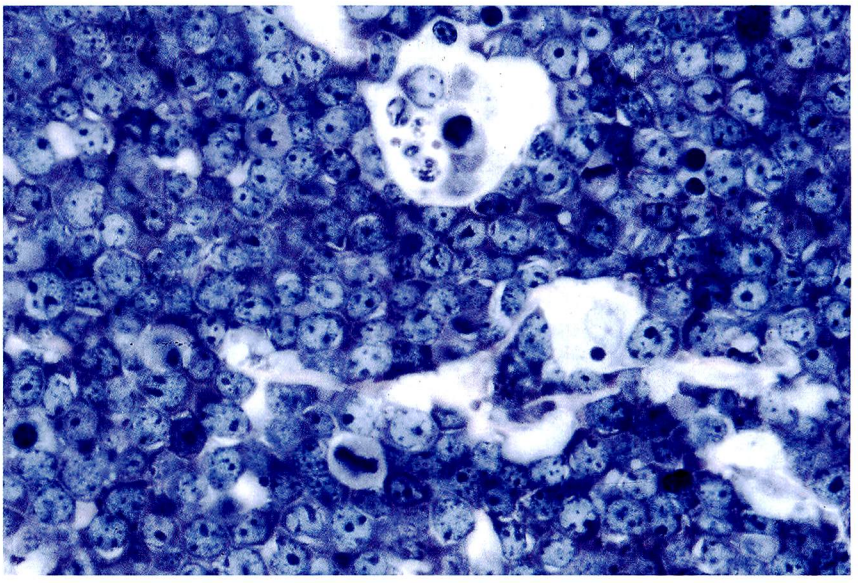


Fig. 21. Burkitt's lymphoma, EBV positive. Giemsa, ×695.

Malignant lymphomas of CD5 − lymphoid cells

1. Malignant lymphomas of B cell blasts: Burkitt's lymphoma

Burkitt's lymphoma usually consists of a monotonous population of B cell blasts, i.e., they consist of medium-sized to large cells with multiple, central, medium-sized nucleoli (Fig. 21). The cytoplasm is basophilic, often contains some fat vacuoles and is *cohesive*. This cohesiveness is particularly important diagnostically. It is only visible in well fixed slides, often only in outer parts of the slide. Mitotic figures and starry sky cells (~ apoptosis!) are abundant. The cell cycle is completed, like in normal B cell blasts, within 6 hours[28].

In addition to this typical Burkitt's lymphoma there are cases that are reminiscent of immunoblastic lymphoma ([Fig. 22] large central nucleoli!, *but*: cohesive!) or centroblastic lymphoma ([Fig. 23] marginal, medium-sized nucleoli, *but cave* fixation artefacts with bubbles in the nuclei!). Or there is a certain differentiation into plasmacytoid cIg-positive cells (Fig. 24). The repeatedly described "Burkitt lymphoma-like" lymphoma may perhaps be classified in this group.

It is certain that Burkitt's lymphoma can develop from the B cell blasts of the germinal center, probably there are also cases that are derived from the B blast cells of the pulp. Whether the somewhat variable appearance of Burkitt's lymphoma depends on the possible different origins of the tumor is a question that cannot be decided today.

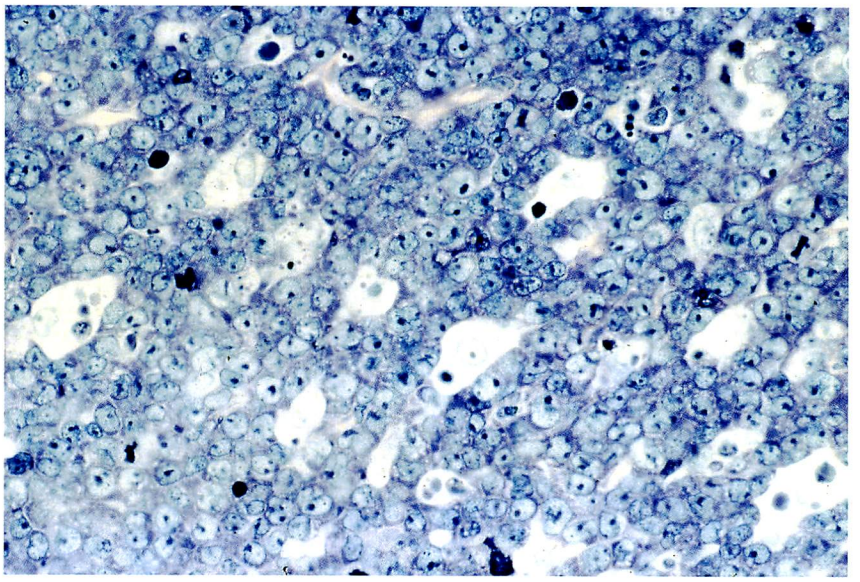


Fig. 22. Burkitt's lymphoma, large cell (immunoblastic lymphoma-like). Giemsa, ×450.

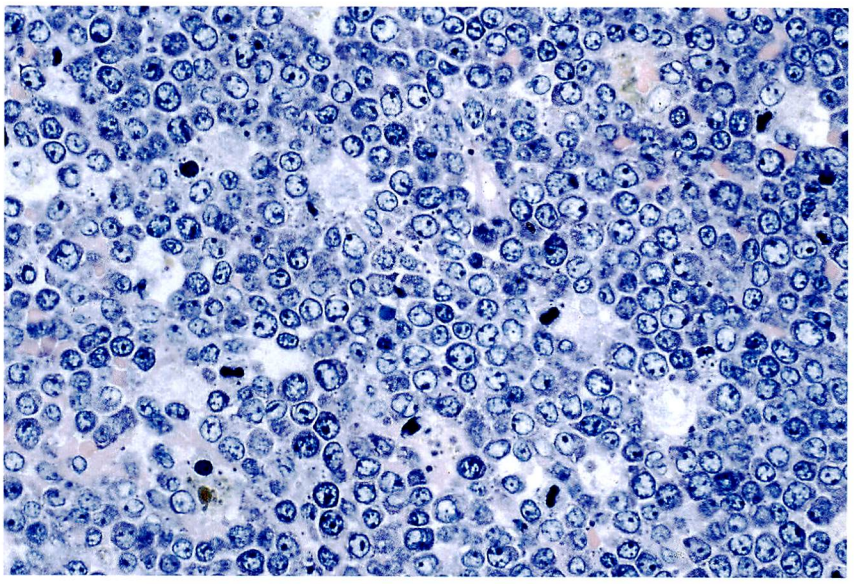


Fig. 23. Burkitt's lymphoma, centroblastic lymphoma-like. Giemsa, ×440.

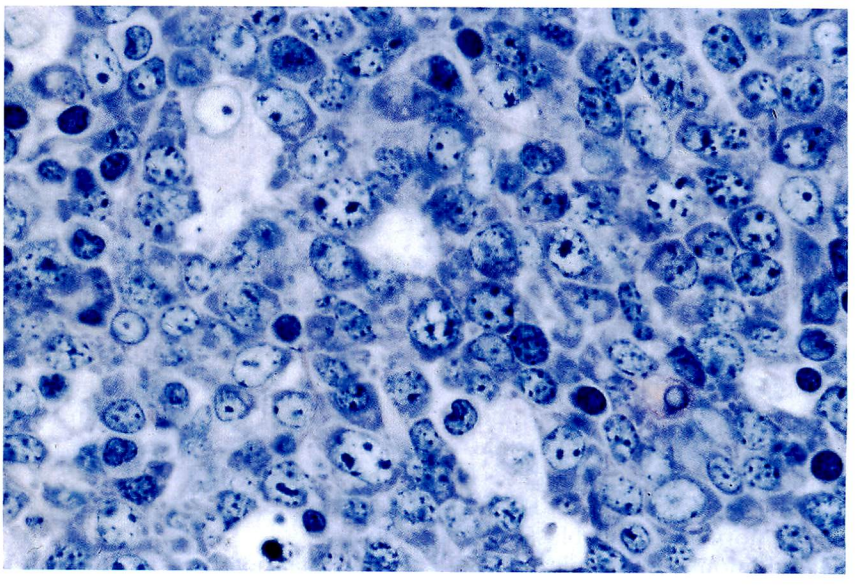


Fig. 24. Burkitt's lymphoma-like lymphoma, with plasmacytic differentiation. cIg+, EBV−. Giemsa, ×695.

2. Malignant lymphomas of centroblasts: centroblastic lymphoma

Centroblasts, which occur only in the germinal center, can proliferate alone (Fig. 25) or in combination with multilobated variants or immunoblasts (Fig. 26). Correspondingly, we can speak of a monomorphic, multilobated or polymorphic subtype. In rare cases the tumor begins with a follicular growth pattern, but within a short period of time the growth pattern becomes diffuse. Sometimes a starry-sky pattern is observed.

Like normal centroblasts, the cells typically show medium-sized nucleoli, which are often situated at the cellular membrane (Fig. 25). Poor processing of the paraffin blocks may also cause the nucleoli to have this appearance. For this reason centroblastic lymphomas are usually overdiagnosed. By reembedding tissue specimens in resin it is easier to recognize centroblastic lymphoma[27]. The borderline between the polymorphic type of centroblastic lymphoma and immunoblastic lymphoma is not sharp because centroblastic lymphomas may contain up to 80% non-centroblastic cells, especially immunoblasts. In these cases the presence of multilobated cells helps to confirm the diagnosis of centroblastic lymphoma (polymorphic subtype).

Differentiating between monomorphic and polymorphic centroblastic lymphoma is important because the prognosis of monomorphic centroblastic lymphoma is clearly better.

We used to distinguish a fourth type of centroblastic lymphoma, called the centrocytoid subtype. In the meantime we have learned from Feller (personal communication) and Weisenburger (personal com-

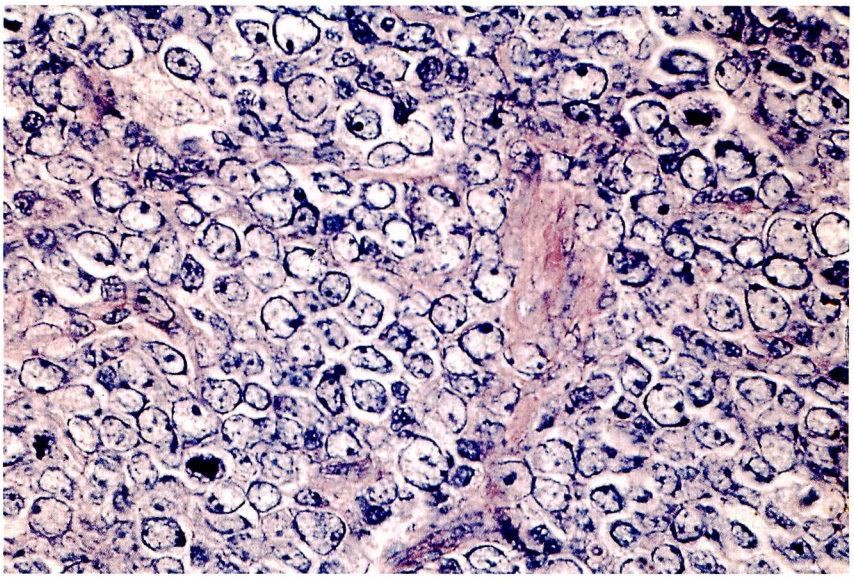


Fig. 25. Centroblastic lymphoma, monomorphic subtype. Giemsa, ×512.

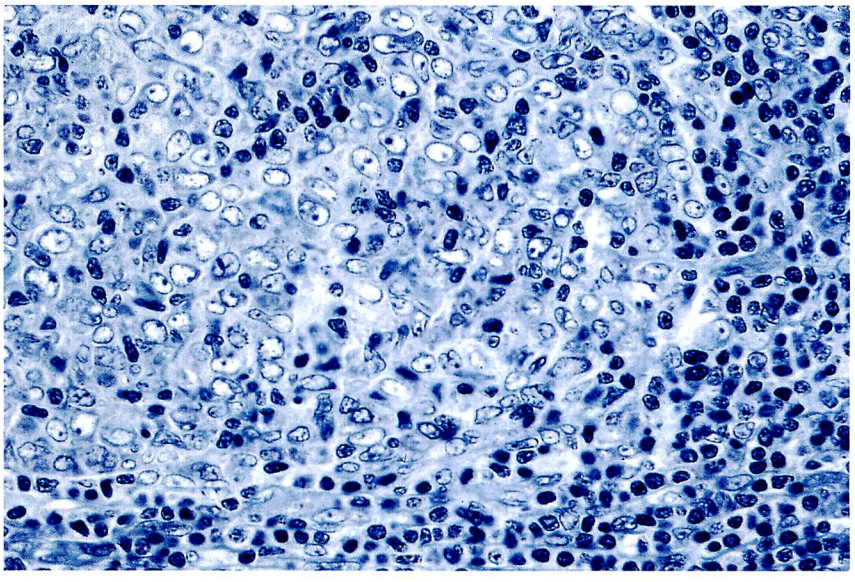


Fig. 26. Centroblastic lymphoma, polymorphic subtype, initially growing in a germinal center. Here follicular dendritic cells are seen. Giemsa, × 440.

munication) that the centrocytoid type apparently may also represent the high grade equivalent of mantle cell lymphoma, because few cases that have been investigated have shown a t(11; 14), as mantle cell lymphoma usually does.

3. Malignant lymphomas of centroblasts and centrocytes: centroblastic-centrocytic lymphoma

The tumor usually corresponds to the follicular lymphoma of the literature. Its growth pattern is follicular or follicular and diffuse. Only few cases show a purely diffuse growth pattern. Centrocytes are always the dominant kind of cells. They may be small or medium sized.

If we wish to subclassify the centroblastic-centrocytic lymphomas, we may distinguish ones:

(a) with small centrocytes and only a few centroblasts
(b) with small centrocytes and moderate numbers of centroblasts
(c) with medium-sized centrocytes and moderate numbers of centroblasts

About one third of the cases show varying degrees of sclerosis, which appears to be almost specific to centroblastic-centrocytic lymphoma. It has a certain resemblance to the nodular sclerosis of Hodgkin's lymphomas[29].

bcl-2 is useful in differentiating between follicular lymphoid hyperplasia and follicular lymphomas. It is negative in reactive germinal centers, but positive in neoplastic ones. Correspondingly, in neoplastic germinal centers there are no starry sky cells (with apoptotic cells!), which are usually seen in reactive ones.

Centroblastic-centrocytic lymphoma may evolve into a high grade lymphoma, especially centroblastic lymphoma. This occurs rather frequently, but the percentage of transformed cases is higher (e.g., 44%) in our autopsy collection than in our biopsy collection ($<5\%$[4]). The prognosis of secondary centroblastic lymphoma is much poorer than that of primary centroblastic lymphoma.

4. Malignant lymphomas of B immunoblasts: immunoblastic lymphoma

The large basophilic B cells of the pulp (and of the germinal centers?) may develop a tumor consisting of pure populations of immunoblasts. They mostly have a solitary large central nucleolus and intensely basophilic, noncohesive cytoplasm. Monotypic cIg may or may not be found. The monoclonal antibody CD20 usually shows a positive reaction. In some of the lymphomas there may be a differentiation into plasma cells with all transitional cell forms. They show the same immunophenotype as the immunoblasts, if immunoglobulins are expressed, but they strongly express monoclonal cIg, whereas the immunoblasts sometimes show only monoclonal sIg or no immunoglobulins at all.

If a given case of immunoblastic lymphomas is a secondary lymphoma that has developed out of a low grade lymphoma (chronic lymphocytic leukemia of B-cell type, immunocytoma, T cell lymphoma of AILD type) remnants of the preceding low grade lymphoma can usually be seen between the B immunoblasts.

5. Malignant lymphomas of lymphocytes and Marschalkó plasma cells: lymphoplasmacytic immunocytoma

This lymphoma always consists *mainly* of small CD5− lymphocytes and contains some or many more or less typical Marschalkó plasma cells with eccentric nuclei and a perinuclear halo (Golgi body). The lymphocytes express sIg (mostly IgM) at the membrane; the plasma cells contain cIg of the same type. In addition there are a few B immunoblasts. The number of mast cells is usually increased. Intranuclear PAS positive globular inclusions are often found.

The blood picture is mostly aleukemic. In many cases the tumor corresponds to the clinical syndrome of Waldenström's macroglobulinemia, but there are cases without macroglobulinemia and cases in which there is increased expression of other immunoglobulins, H or L chains. Therefore the term macroglobulinemia does not cover the entire spectrum of lymphoplasmacytic immunocytoma.

6. Malignant lymphoma of Marschalkó plasma cells: plasmacytoma

This lymphoma consists *only* of more or less typical Marschalkó plasma cells, which may show some anaplasia in later stages: the cells become larger, the plasmacytic nature of the cells is not well recognizable. The tumor cells always contain monotypic cIg, mostly IgG or IgA, less often IgM.

We have separated extraosseous ("extramedullary") plasmacytoma, especially of the lymph nodes, from plasmacytoma of the bone marrow (multiple myeloma). We had two reasons for this, one being the different clinical behavior and the other that our basic principle is to include only nodal lymphomas in our classification, as far as possible.

7. Malignant lymphomas of marginal zone cells: marginal zone cell lymphoma

Marginal zone cells are not usually found in *lymph nodes*, only sometimes as a reactive feature, especially in mesenteric lymph nodes (Isaacson, personal communication, Fig. 27, 28). They are always found in the *spleen*, however, where they are often hyperplastic. These splenic marginal zone cells may develop a specific tumor known as marginal zone lymphoma. It is sometimes associated with a leukemic blood picture in the peripheral blood showing "villous" lymphocytes[30].

Low grade B cell lymphoma of the mucosa associated lymphoid tissue (MALT)[19,31] consists in most of the cases predominantly of "centrocyte-like" cells, which most probably are neoplastic marginal zone cells (Fig. 29). There are also B cell lymphomas of MALT type

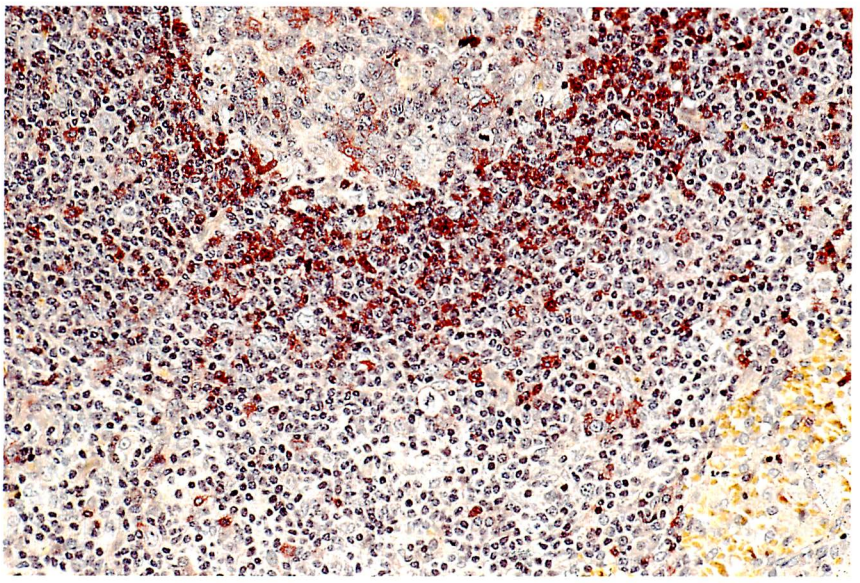


Fig. 27. Marginal zone hyperplasia in a mesenteric lymph node. Ki-B3, ×220.

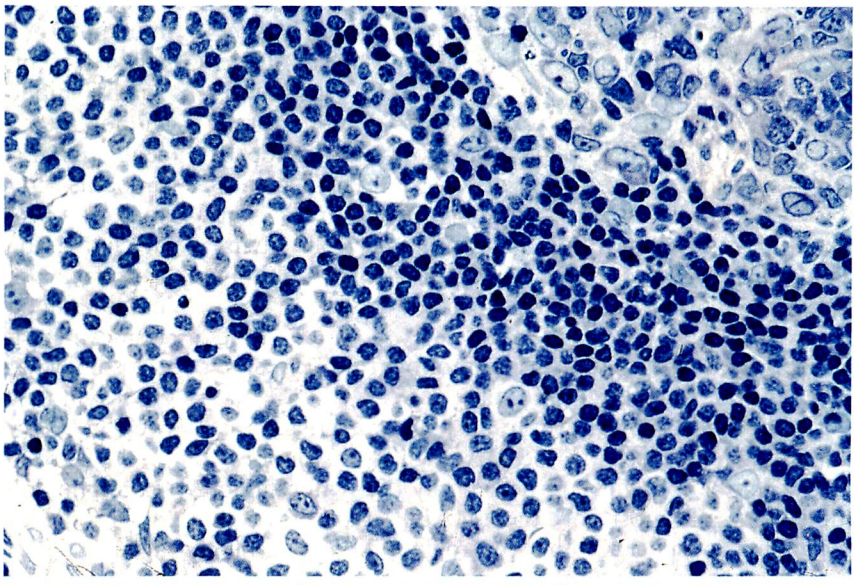


Fig. 28. Same case as Fig. 27. Giemsa, × 440.

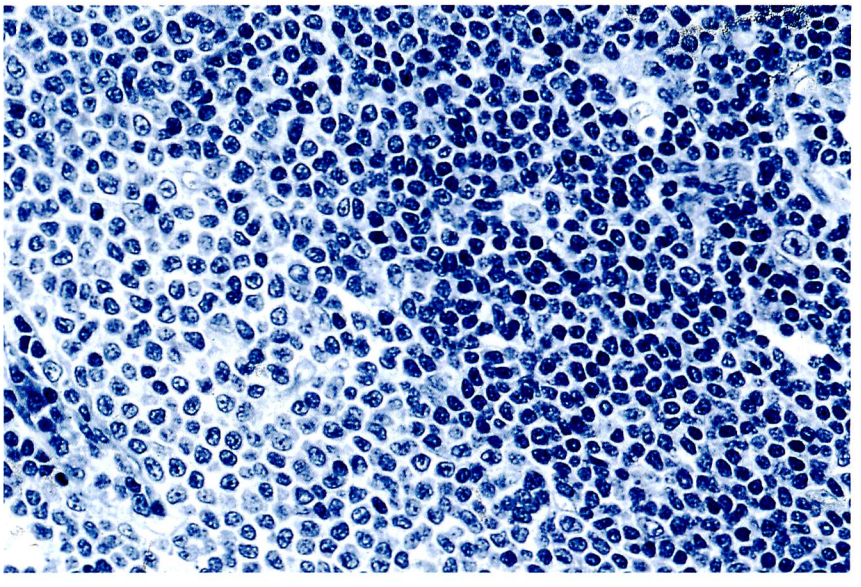


Fig. 29. Metastasis of a "centrocyte-like" MALT lymphoma of the stomach. The tumor cells are identical in localization and morphology to those in Fig. 28. Giemsa, ×440.

that consist mainly of lymphocytes and of some plasma cells (immunocytoma type) and MALT-type lymphomas that correspond to the malignant lymphomas of monocytoid B cells. Finally, there are high grade variants that mostly develop from low grade B cell lymphomas of MALT type.

In its early phases low grade B cell lymphoma of MALT type contains active germinal centers with polyclonal germinal center cells. They may be colonized by the neoplastic clone (centrocyte-like cells, etc.) and then they become monoclonal (L chain restriction). In MALT-type lymphomas with centrocyte-like cells there may also be admixtures of plasma cells belonging to the same clone. The reactions with Ki-B3 and CD76 are negative in most of the cases of centrocyte-like MALT lymphoma, but there are exceptions. The monocytoid B cell type shows a positive reaction with both antibodies.

Malignant B cell lymphomas of MALT type occur predominantly in the stomach. Most of them are apparently induced by an infection with *Helicobacter pylori*. These lymphomas occur in many parts of the body in which MALT is present (e. g., lung, conjunctiva), but there are localizations without mucosa that may nevertheless develop a low grade B cell lymphoma of *MALT type* (e.g., thyroid gland, skin). They all have in common an infiltration of glandular epithelium by the lymphoma cells (lymphoepithelial lesions), but these are not absolutely specific and may be lacking in a few cases.

8. Malignant lymphomas of monocytoid B cells: monocytoid B cell lymphoma

Monocytoid B cells develop only on a reactive basis as marginal zone cells in the MALT system. Monocytoid B cell lymphomas are not simply the lymph node equivalent of most of the MALT type B cell lymphomas, especially the centrocyte-like type, because they differ morphologically and immunohistochemically. The tumor cells are larger; the nuclei are more irregular (Fig. 30); they grow at first in the sinus, not the marginal zone (this is not always clearly demonstrable!) and are Ki-B3+ (Fig. 31) and mostly CD76+. In the cytoplasm the typical granular Ki-M4p reaction can always be detected (Fig. 32). Sometimes plasma cells belonging to the same Ig clone are seen in the adjacent lymphoid tissue. The tumor cells may express monoclonal IgM, IgG or even IgA.

9. Malignant lymphomas of unknown origin

(a) Hairy cell leukemia

So far we do not know the normal equivalent of hairy cells. Probably they are in the red pulp of the spleen. Morphologically leukemic hairy cells in the lymph node are somewhat larger than lymphocytes, often have a bean-shaped nucleus and abundant nonbasophilic cytoplasm. Blast cells are not found. Mitotic figures are extremely rare. Mast cells and polyclonal plasma cells are often interspersed. The hairy cells begin to grow between the follicles and must be postfollicular cells because they have always switched immunoglobulins: IgG or IgA. They are positive for CD20, Ki-B3, CD76, HLM1 and Ki-M1p.

(b) Large cell anaplastic lymphoma of B-cell type

The morphology is similar to that of large cell anaplastic lymphoma of T-cell and null type, especially a cohesive growth pattern may also be seen. They may originate from any stimulated B cell of the follicles or pulp.

Malignant lymphomas of CD5+ B cells

1. Malignant lymphomas of CD5+ small lymphocytes: chronic lymphocytic leukemia

Small lymphocytes are by far the predominant cell type. Their nuclei are usually round, but occasionally somewhat pleomorphic. In lymph nodes some large, moderately basophilic blast cells with large, often solitary, central nucleoli are always found among the small lymphocytes (Fig. 33). We call them paraimmunoblasts. In typical cases of chronic lymphocytic leukemia of B-cell type they do not express appreciable amounts of cIg. According to our investigations[4] light foci (= proliferation centers) are often scattered around among the predominant small lymphocytes, causing a pseudofollicular impression. In addition to paraimmunoblasts we find interpersed in the proliferation centers a large number of prolymphocytes, which are somewhat larger and stain paler than lymphocytes. The lymphocytes express sIg (IgM and IgD) only weakly.

The proliferation centers and the existence of paraimmunoblasts are unmistakable evidence in favor of chronic lymphocytic leukemia of B-cell type and against mantle cell lymphoma. Unfortunately, for a long time this fact was not taken into account in American publications, so that false diagnoses were made. This is of practical significance, e.g., for the evaluation of chromosome anomalies in chronic lymphocytic leukemia of B-cell type. When cases of chronic lymphocytic leukemia of B-cell type with a t(11; 14) were described - this translocation seems to be specific to mantle cell lymphoma - the *histological* evidence was usually lacking. If we perform a histological examination of the lymph nodes in every case of chronic lymphocytic leukemia of B-cell type, we can avoid confusing it with mantle cell lymphoma.

1a. Malignant lymphoma of CD5+ small lymphocytes with differentiation into plasmacytoid cells: plasmacytoid immunocytoma

We originally classified cases of this type as belonging to the entity immunocytoma, but we consider it possible to classify them with chronic lymphocytic leukemia[32], because in the other variant of

Fig. 30. Malignant lymphoma of monocytoid B cells. Giemsa, ×695.

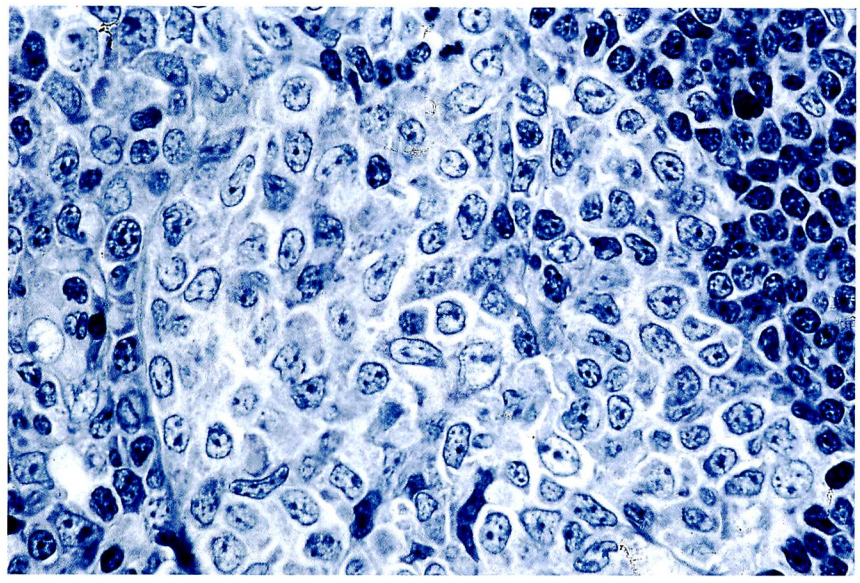


Fig. 31. Malignant lymphoma of monocytoid B cells. Strongly positive tumor cells in the central area. In between three high endothelial venules. Ki-B3, ×220.

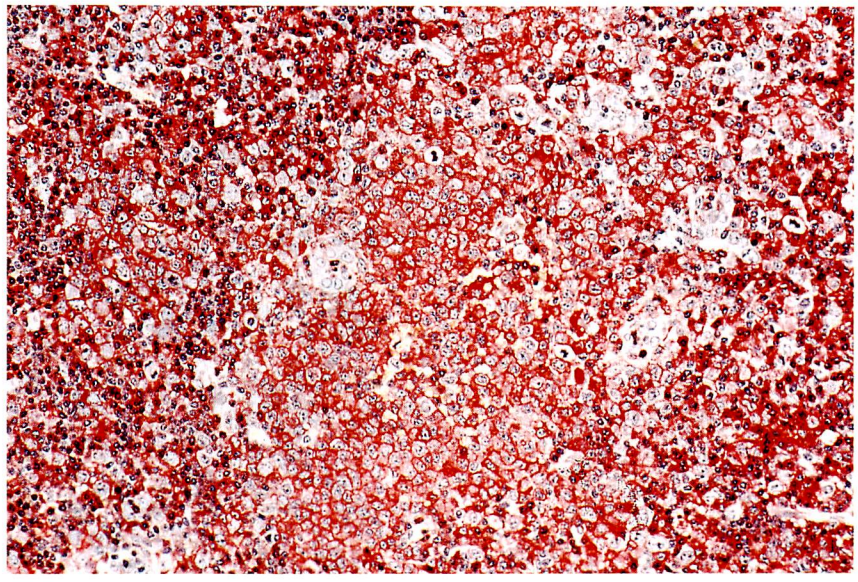
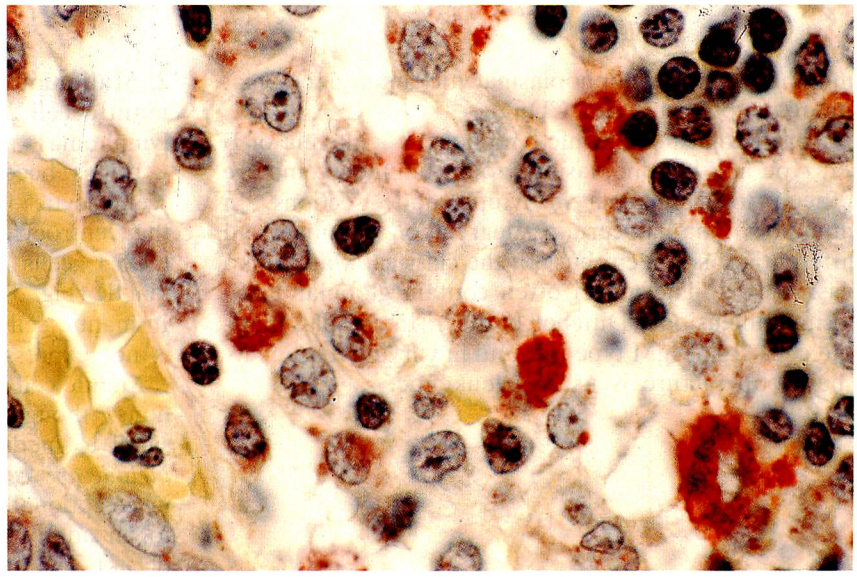


Fig. 32. Malignant lymphoma of monocytoid B cells. Ki-M1p reaction. Tumor cells show a granular reaction, macrophages a strong, diffuse reaction. ×1094.



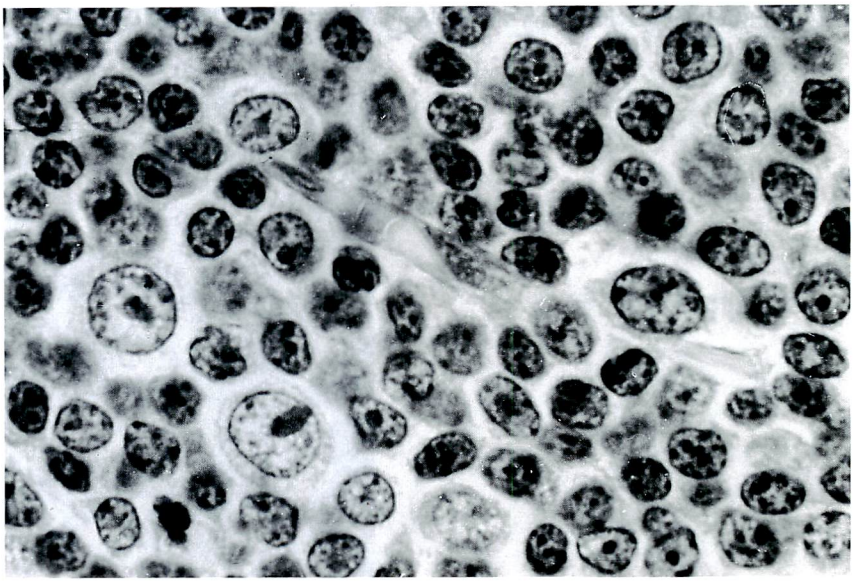


Fig. 33. Chronic lymphocytic leukemia. A few large paraimmunoblasts. H&E, ×1250.

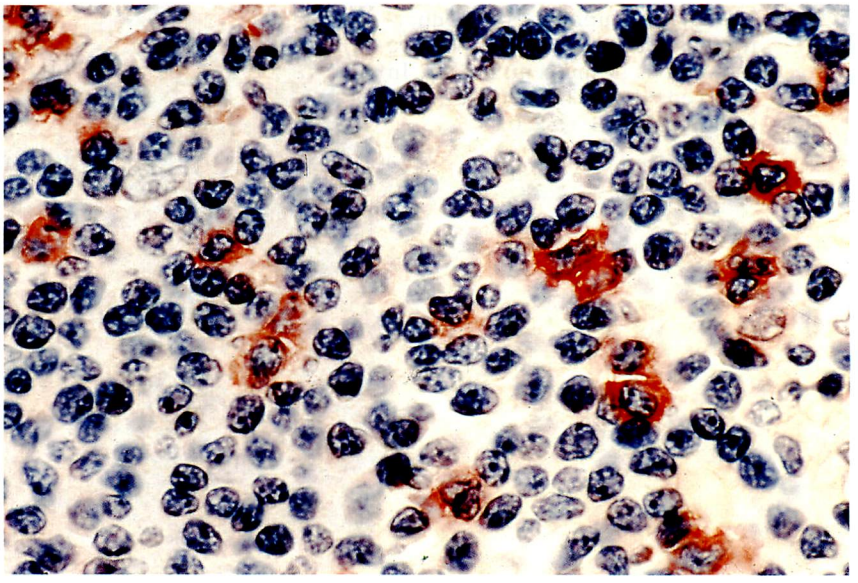


Fig. 34. Follicle mantle with CD5-positive mantle cells and T cells. The mantle cells stain somewhat more weakly and are somewhat larger than the T lymphocytes (slide kindly provided by Prof. Feller). Most lymphocytes are CD5-negative ! CD5 reaction (Leu-1) after microwave treatment. ×695.

immunocytoma, lymphoplasmacytic immunocytoma, the B lymphocytes are CD5-.

Morphologically chronic lymphocytic leukemia of B cell type and lymphoplasmacytoid immunocytoma are difficult to distinguish in lymph node sections. In immunocytoma a certain degree of plasmacytoid differentiation is seen, but not the classical Marschalkó plasma cells. The nuclei often contain globular PAS-positive inclusions (Dutcher bodies). In the plasmacytoid cells cIg of IgM type is found in varying frequency. The blood picture is usually leukemic.

2. Malignant lymphomas of (follicle) mantle cells: mantle cell lymphoma (formerly called centrocytic lymphoma)

It has become clear that the tumor cells of our "centrocytic" lymphoma[3] are CD5+[33], in contrast to the centrocytes of reactive germinal centers. These CD5+ cells occur, however, mainly in the follicle mantle (Fig. 34), where they are normally also CD23+. In mantle cell lymphoma, however, the CD23 antigen is not expressed.

Mantle cell lymphoma is characterized by a monotonous, though slightly pleomorphic proliferation of small to medium-sized cells (Fig. 35), which *do not include any centroblasts or neoplastic immunoblasts*. If in exceptional cases we do find a few blasts, they belong to an admixture of polyclonal plasma cells (plasmablasts). The tumor cells may grow in a nodular pattern,

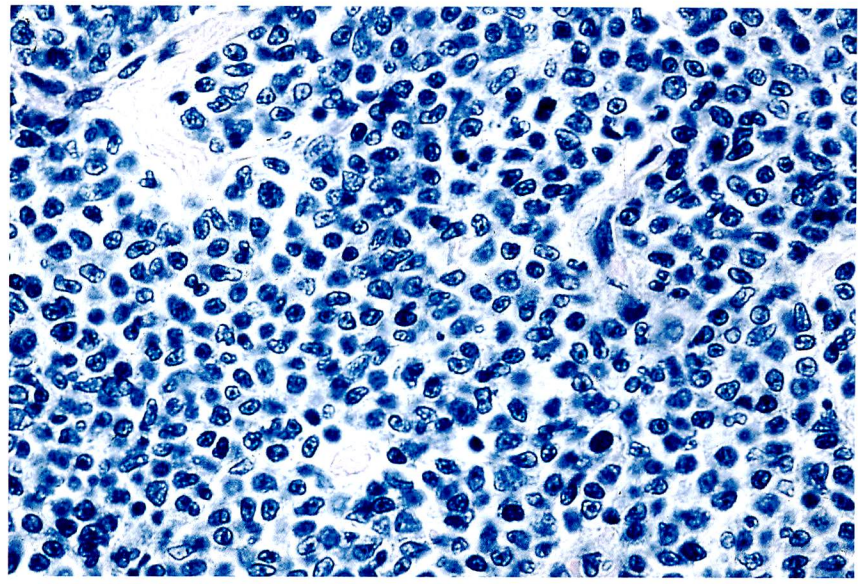


Fig. 35. Mantle cell lymphoma ("centrocytic lymphoma"). No blast cells. Note the hyalinization of capillaries. Giemsa, ×512.

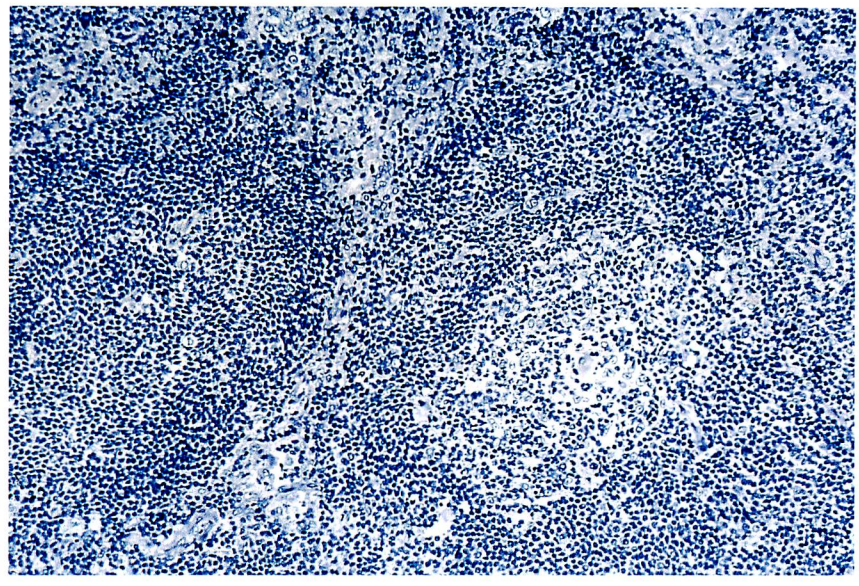


Fig. 36. Mantle cell lymphoma ("centrocytic lymphoma"). One germinal center is still preserved, one has been colonized by the tumor cells. Giemsa, ×280.

sometimes surrounding and finally replacing germinal centers (Fig. 36). About half of the cases, however, show a purely diffuse growth pattern with a few very thick fibers[34]. A characteristic feature is small hyaline deposits around small vessels (capillaries, arterioles) (Fig. 35).

The existence of small and medium-sized cell variants does not allow us to differentiate two separate subentities because, as Satodate showed (in [4]), there is no clear bimodal distribution, but rather a continuum. Nevertheless, one can see a gradual increase in cell size if the tumor exists for a longer period of time (called "anaplastic" mantle cell lymphoma).

The Kiel Classification

The entities described above were arranged in a special order in the Kiel classification[3,4], especially in its updated form[5,6] (Table 2). On the left side the B cell lymphomas are listed, on the right side the T cell lymphomas. The upper half is concerned with the "cytic" lymphomas = low grade malignancies, the lower half contains the "blastic" lymphomas = high grade malignancies.

We are convinced that small corrections and additions will be necessary, but the basic system should survive, especially because immunological markers and cytogenetics have confirmed these categories to a large extent. Perhaps some interpretations of cellular origin will need to be reconsidered, however. Maybe certain groups can also be combined. At present we should avoid overhasty simplifications, not least because the treatment could become more specific for certain cell types.

Table 2. Updated Kiel classification of non-Hodgkin's lymphomas (1988, modified in 1992, from Lennert K, Feller AC [1992] Histopathology of non-Hodgkin's lymphomas. Springer, Berlin Heidelberg New York)

B	T
Low-grade malignant lymphomas	
Lymphocytic	Lymphocytic
Chronic lymphocytic leukaemia	Chronic lymphocytic leukaemia
Prolymphocytic leukaemia	Prolymphocytic leukaemia
Hairy-cell leukaemia	Small cell, cerebriform
	Mycosis fungoides, Sezary's syndrome
Lymphoplasmacytic/cytoid (immunocytoma)	Lymphoepitheloid (Lennert's lymphoma)
Plasmacytic	Angioimmunoblastic (AILD, LgX)
Centroblastic-centrocytic	T-zone lymphoma
follicular diffuse	
diffuse	
Centrocytic (mantle cell)	Pleomorphic, small cell (HTLV−1 ±)
Monocytoid, incl. marginal zone cell	
High-grade malignant lymphomas	
Centroblastic	Pleomorphic, medium-sized and large cell (HTLV−1 ±)
Immunoblastic	Immunoblastic (HTLV−1 ±)
Burkitt's lymphoma	
Large cell anaplastic (Ki-1+)	Large cell anaplastic(Ki-1+, HTLV−1 ±)
Lymphoblastic	Lymphoblastic
Rare types	*Rare and ambiguous types*

P.S. For further references and a large number of illustrations cf. Lennert K, Feller AC. Histopathology of non-Hodgkin's lymphomas. Berlin: Springer 1992.

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