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Angioimmunoblastic Lymphadenopathy

Fine Structure of the Lymph Nodes by Correlation of Light and Electron Microscopical Findings *

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Summary. Angioimmunoblastic lymphadenopathy was studied prospectively in 5 patients by correlation of light and electron microscopy of biopsy material obtained from lymph nodes, prior to any substantial therapy. The fine structure of this lymphoproliferative disease revealed various patterns of cellular composition: there was a predominance of lymphocytes, immunoblasts, epithelioid or plasmacytoid cells or mixed cellularity in the lymph nodes. The conspicuous vascular changes consisted or arborization of postcapillary venules, a thickening of the basement membranes and swelling of the endothelial cells.

The remarkable eosinophilic or acidophilic debris-like interstitial and pericapillar deposits showed filamentous finely dispersed material containing wide-spacing collagen fibers intermingled with normal collagen, but no fragments of disintegrated cells.

Two of these 5 patients developed malignant lymphomas of the Hodgkin-type after 13 months, and of the Non-Hodgkin-type after 7 months. At the time of first biopsy, however, no characteristic alteration of the fine structure of the lymph nodes disclosed evolution towards malignancy.

Key words: Angioimmunoblastic lymphadenopathy – Lymph nodes – Light and electron microscopy – Cellular composition – Vascular changes – Interstitial material.

Introduction

Angioimmunoblastic lymphadenopathy (AILAP) is nowadays defined as a generalized disease, characterized by lymphomas, allergic cutaneous reactions, fever

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and hepatosplenomegaly; polyclonal hypergammaglobulinaemia and haemolytic anaemia are often observed (Nathwani et al. 1978). Following the first descriptions of this disease by Westerhausen and Oehlert (1972) as a "chronic and pluripotential immunoproliferative syndrome" or as "lymphogranulomatosis X" by Lennert (1973), Frizzera et al. (1974, 1975) introduced the term "angioimmunoblastic lymphadenopathy", whereas Lukes and Tindle (1975) called this lesion "immunoblastic lymphadenopathy" with the additional characterization of a hyperimmune reaction similar to Hodgkin's disease. Although the definitions of lymphogranulomatosis X by Lennert and coworkers (1979) and angioimmunoblastic lymphadenopathy by Rappaport and his group (Frizzera et al. 1974, 1975; Nathwani et al. 1978) are different in some aspects, they are basically similar. In this study we follow the substantial histomorphological criteria of both groups with some modification.

It is uncertain whether AILAP represents a peculiar hyperimmune reaction of lymphatic tissue due to various stimuli (Frizzera et al. 1977) or a potentially neoplastic condition which may terminate as malignant lymphoma (Lennert et al. 1979, Rappaport et al. 1979, Schnaidt et al. 1979). A very clearcut description of this entity has been given by Lennert et al. (1979) classifying the nodal lesions, according to their cellular composition, into 5 subtypes. The assumption that AILAP may represent a prelymphoma is supported by the frequently encountered chromosomal abnormalities observed in this disease (Volk et al. 1975, Hossfeld et al. 1976, Schnaidt et al. 1979). Using the new classification, as proposed by Lennert et al. (1979) and based on the cellular components of the involved lymph nodes, we investigated 5 cases of AILAP by light and electron microscopy. A report of prospective ultrastructural investigation prior to any substantial therapy in close correlation with light microscopy seems to be of some importance, since only 10 such observations have previously been made (review by Neiman et al. 1978).

Table 1. Principal clinical and histomorphological findings of the five patients investigated. Histopathology of the lymph nodes was evaluated according to the predominant and characteristic cell type as proposed by Lennert et al. (1979)

	Initials	Sex	Age in years	Main clinical findings at onset of disease and follow up	Histopathology of lymph nodes with predominance of
1.	S.W.	M	67	Generalized lymphomas, polyclonal hypergammaglobulinaemia, transition into Hodgkin's disease after 13 months	Lymphocytes
2.	K.G.	F	74	Generalized lymphomas	Immunoblasts
3.	K.J.	M	51	Lymphomas of the right axilla and mandibula, hepatomegaly, transition into immunoblastic lymphoma after 7 months	Epithelioid cells
4.	B.C.	M	51	Inguinal lymphomas	Immunoblasts
5.	R.F.	F	65	Lymphomas of the neck and mandibula	Plasmacytic cells, immunoblasts

Patients and Methods

Patients. From about 40 cases in which a histopathological diagnosis of AILAP was established by clinical symptoms and findings, a prospective second biopsy was performed on lymph nodes in 5 patients prior to any substantial therapy. Combined histomorphological, ultrastructural, cytogenetic and immunological studies were done, of which the last two are described elsewhere (details see Schnaidt et al. 1979). Two of our patients later evolved a malignant lymphoma of the Hodgkin and Non-Hodgkin type (for further details see Table 1).

Methods. For light microscopy the specimens were fixed in 8% formalin and embedded in paraplast and a mixture of methylmethacrylate for semithin sectioning. Staining of the 1–3 μ sections included a haematoxylin-eosin, Giemsa, periodic-acid-Schiff (PAS), methyl-green-pyronin and silver impregnation (Gomori). Immunohistological investigations were done on paraplast embedded tissue, using peroxidase labelled antibodies to IgG, IgA, IgM and to light chains according to the method of Taylor and Burns (1974).

Results

Light microscopy displayed a total effacement of the normal follicular and sinus architecture of the lymph nodes by a varying population of different cells in most cases. In two cases we found preserved germinal centers, but one of these cases showed complete destruction of the nodal architecture in a follow-up biopsy. Cellular infiltrates included lymphocytes, mature plasma cells as well as plasmacytoid cells, epithelioid histiocytes and so called immunoblasts, accompanied by a prominent proliferation of arborizing vessels (Figs. 1a, 2a, 3a, 5a). Along the striking capillary-sized vessels or post-capillary venules, so called Schulze venules, and their numerous, often right-angled branchings, acidophilic and PAS-positive deposits of amorphous material were noticed (Figs. 6d, 7a).

Immunohistological investigation with the direct peroxidase method exhibited a patchy pattern of positive cytoplasmatic reaction for IgG, IgA, IgM and light chains of k- and λ-type in plasma cells and sometimes in immunoblasts. There was a close relationship of positive cells to the central parts of the lymph node. Epithelioid cells showed negative results.

A rough calculation of these varying cell populations showed that the lymph nodes of each patient displayed a predominance either of lymphocytes (case S.W., Fig. 1a), immunoblasts (case K.G., Fig. 2a) or epithelioid histiocytes (case K.J., Fig. 3a), apart from a varying admixture of plasma cells, and plasmacytoid elements.

Electron microscopy (case S.W., Fig. 1b) exhibited very few phagocytic (histiocytic) reticulum cells in addition to numerous small mature lymphocytes. Further, some large cells with a poor differentiation of their organelles, a large nucleus with dispersed chromatin and an extended nucleolus, consistent with so called immunoblasts were seen (Figs. 1b, 4b). In the second patient (case K.G., Fig. 2b) there was a predominance of cells which resembled these immunoblasts, with clusters of mitochondria and a few cisternae of the rough endoplasmic reticulum and abundant polysomes in their cytoplasm. Surveys of the third patient (case K.J., Fig. 3b) showed small assemblies of epithelioid histiocytes dispersed among lymphocytes and fibroblastic elements.

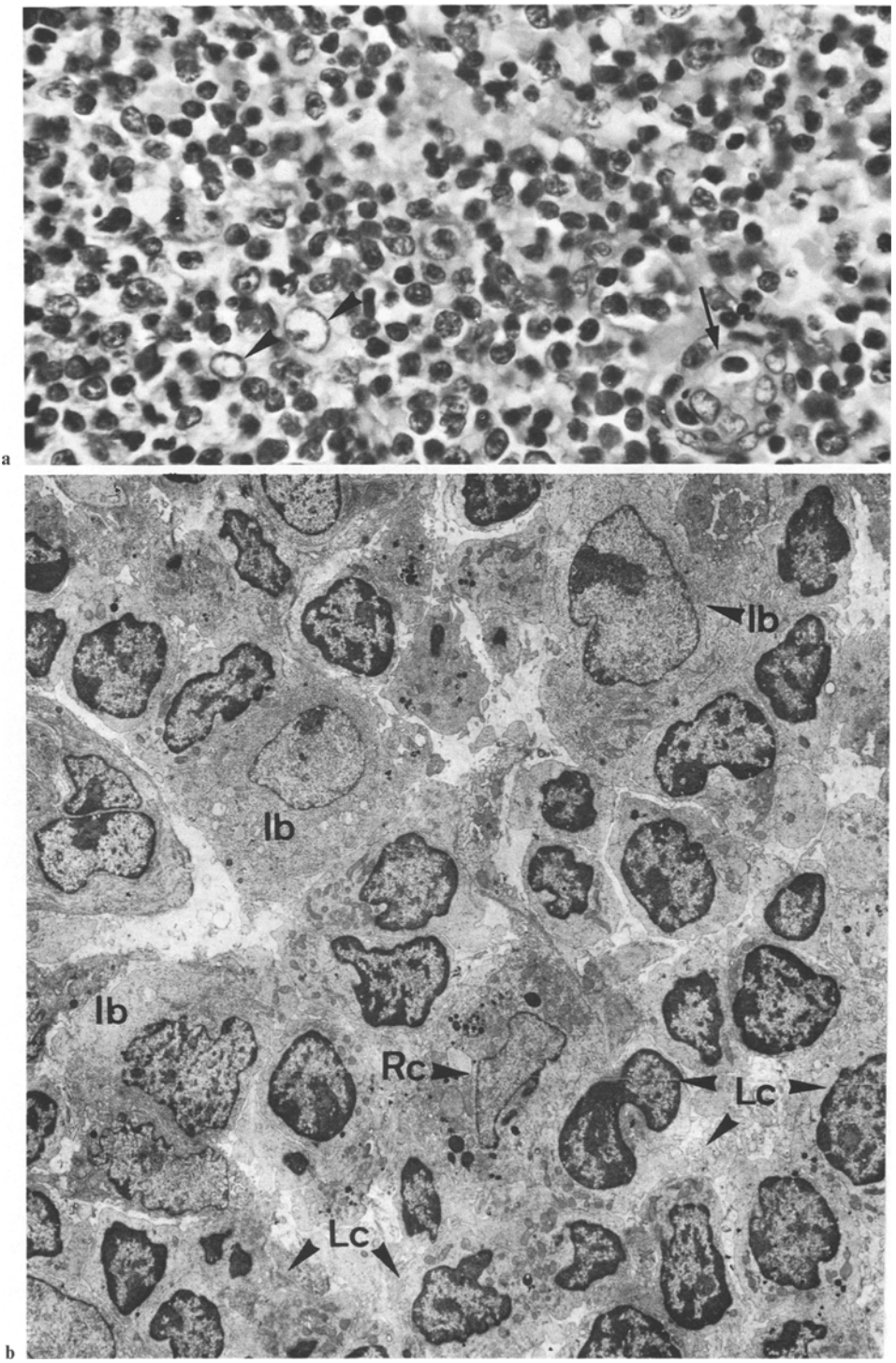

Fig. 1a and b. AILAP with lymphocyte predominance (patient S.W.). **a** Light microscopy with abundant small mature lymphocytes clustering around single immunoblasts (*arrow heads*) and a small vessel with an epithelioid like hypertrophy of the endothelial cells containing an erythrocyte in the lumen (*arrow*). **b** Electron microscopy with immunoblasts (*Ib*), lymphocytes (*Lc*) and a phagocytic (histiocytic) reticulum cell (*Rc*). **a** × 560, **b** × 2,800

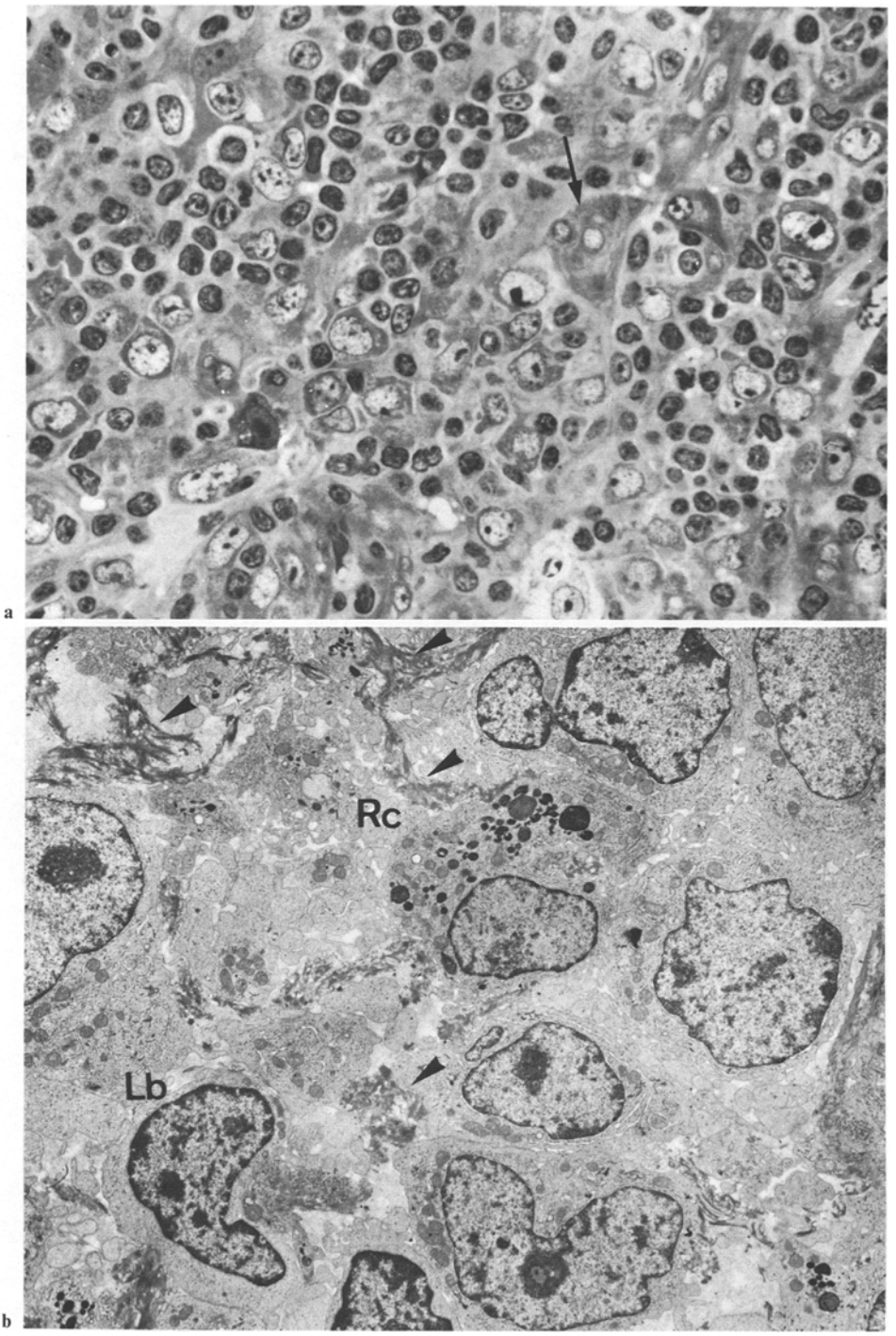

Fig. 2a and b. AILAP with immunoblast predominance (patient K.G.). **a** Light microscopy with numerous large immunoblastic cells showing a large nucleus, prominent nucleolus and basophilic cytoplasm intermingled with small lymphocytes. The arrow points to a vessel with hypertrophy of the endothelial cells. **b** Electron microscopy with many immunoblasts surrounding a phagocytic reticulum cell with dense inclusions (*Rc*) and a lymphoblast (*Lb*), inbetween are small bundles of filamentous material (*arrow heads*, compare with Fig. 7a). **a** × 560, **b** × 5,000

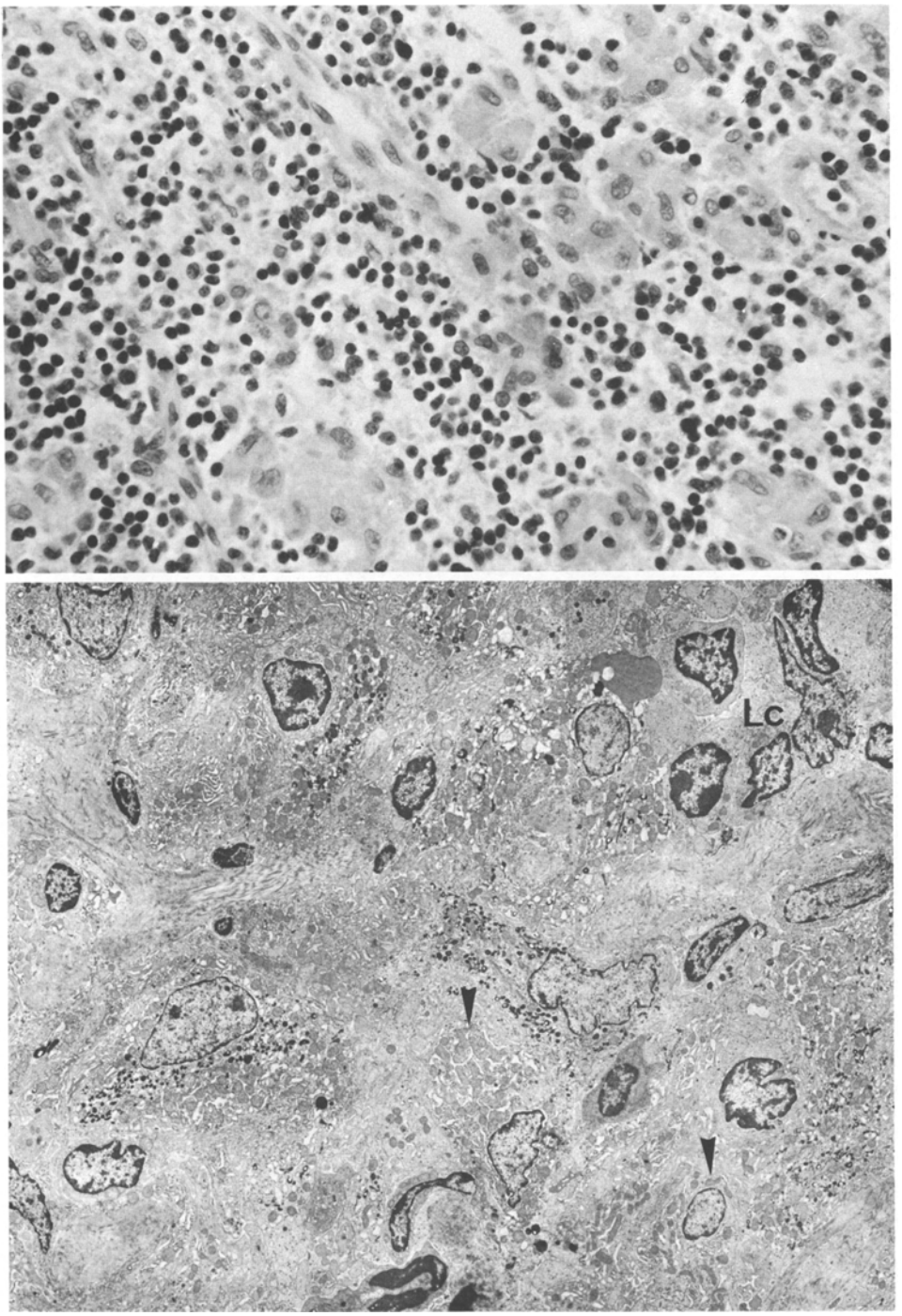

Fig. 3a and b. AILAP with epithelioid cell predominance (patient K.J.). **a** Light microscopy with clusters of large epithelioid cells surrounded by small lymphocytes. **b** Electron microscopy with such a cluster of epithelioid cells partially with dense granules in the cytoplasm and many mitochondria intermingled with some lymphocytes (*Lc*). A few epithelioid cells display a paucity or even a lack of those granules (*arrow heads*). **a** × 300, **b** × 3,800

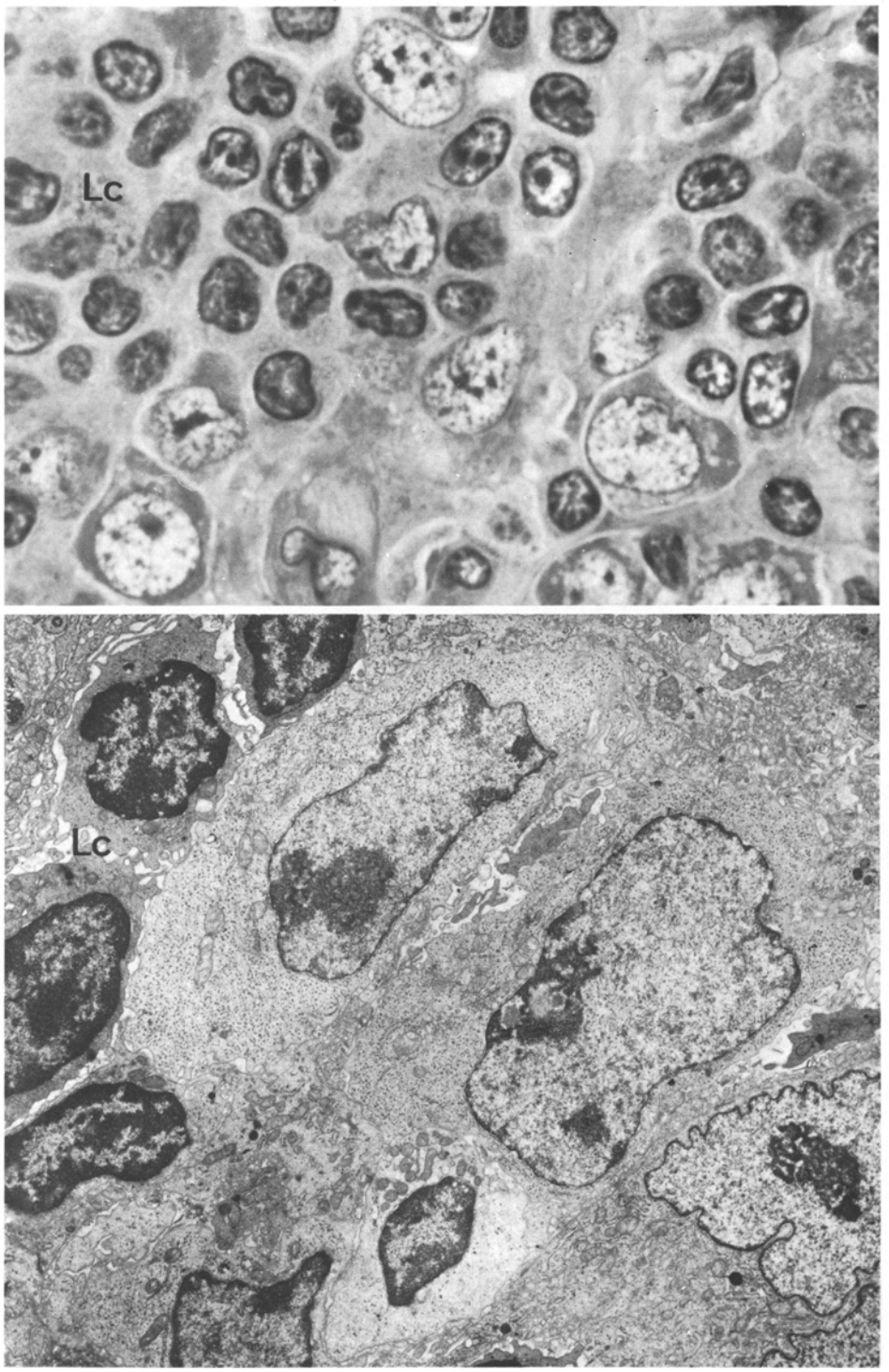

Fig. 4a and b. Immunoblasts in AILAP (patient K.G.). **a** Light microscopy with large immunoblastic cells displaying a slightly indented nucleus with prominent nucleoli and a basophilic cytoplasm, inbetween are many small lymphocytes (*Lc*). **b** Electron microscopy with immunoblasts showing extensive nucleoli in the finely dispersed chromatin of the nucleus. The large portion of cytoplasm contains numerous polysomes and a few cisternae of the rough endoplasmic reticulum besides mitochondria. These immunoblasts are surrounded by mature small lymphocytes (*Lc*). **a** × 1,250, **b** × 7,500

Immunoblasts and epithelioid histiocytes warrant further morphological analysis because they may be confused either with each other or with lymphoblasts or plasmablastic elements. Light microscopy displayed large cells with prominent nuclei and a slightly elongated, sometimes ellipsoid outline, with shallow indentations of the nuclear envelope (Fig. 4a). One or several nucleoli were always prominent features in the otherwise dispersed chromatin. Ultrastructure corroborated the results of light microscopy, showing numerous polysomes of the cytoplasm which may account for the basophilia (Fig. 4b). There were several immunoblastic cells with a varying amount of rough endoplasmic reticulum which was sometimes augmented, pointing towards a plasmablastic differentiation. The so called reticulum cells which may exhibit several ultrastructural forms of differentiation among the other cell populations were plentiful. They appeared, apart from typical phagocytic histiocytes (Figs. 1b, 2b), as interdigitating as well as dark reticulum cells. Epithelioid histiocytes also exhibited a variable amount of their peculiar electron dense granules (Fig. 3b). Severe paucity or even an almost complete lack of those granules may lead to an erroneous interpretation as immunoblastic or plasmacytoid cells, despite an epithelioid differentiation.

A review of survey pictures of the lymph nodes of the 5 patients did not disclose any giant cells compatible with Hodgkin- or Reed-Sternberg cells.

The second peculiar feature of AILAP was the enormous growth of vessels with their remarkable branchings (Fig. 5a).

Light microscopic findings were consistent with post-capillary venules (so called Schulze venules) which depending on their caliber displayed an almost normal structure in many areas (Figs. 5a, b, c). Some of these vessels showed a slight thickening of their walls with PAS-positive material and surrounding interstitial amorphous material. Others displayed large swollen endothelial cells, forming small clusters, which may be confused with immunoblasts, but PAS-staining and immunoperoxidase give a negative reaction for these cells. In accordance with the PAS-staining the outer layer of those vessels contained immunoglobulins (mainly IgG and light chains) with the peroxidase reaction.

Electron microscopy revealed some normal vessels and a minimal to prominent thickening along the basement membrane in others (Figs. 5d, 6b, 6d). These alterations were also detected in PAS- and silver impregnated specimens by light microscopy (Figs. 5a, b, 6a, c).

Most vessels showed a remarkable epithelioid-like hypertrophy and swelling of their endothelial cells by light and electron microscopy (Figs. 1a, 2a, 6a), causing an occlusion of the lumen (Fig. 6b). In addition with electron microscopy there was a frequently occurring increase and broadening of the basement membrane and interstitium (compare Figs. 6b and d with 6c) by a dense layer which contained dispersed bundles of collagen fibers. These extracellular basement membrane like structures were compatible with the eosinophilic and PAS-positive material laying between the various cells and along the vessels, which is frequently seen in light microscopy (Fig. 7a).

Ultrastructural evaluation showed filamentous finely dispersed material (Fig. 2b) with a conspicuous wide-spacing or ribbon like period intermingled with single collagen fibers of a normal structure (Figs. 7b, c).

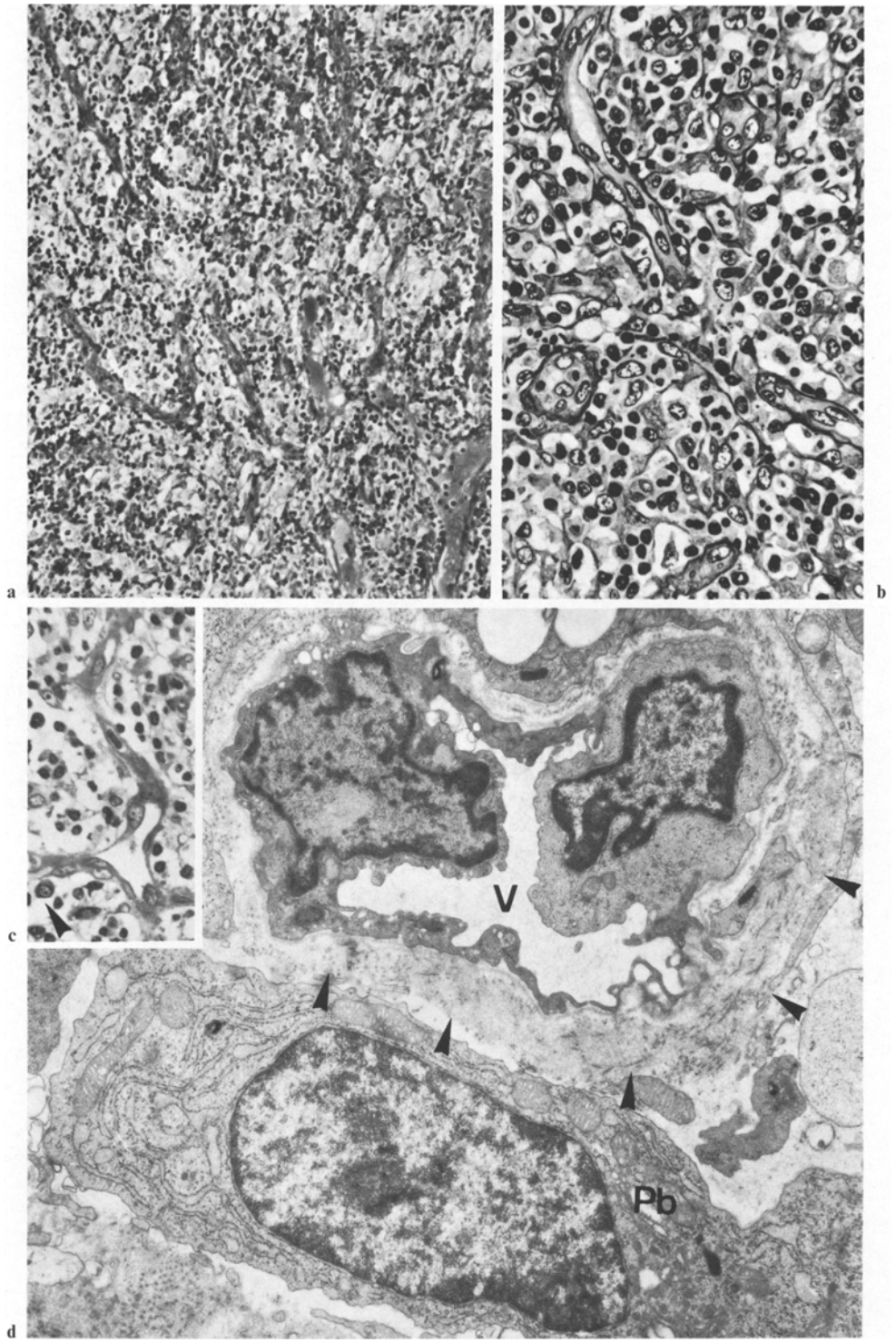

Fig. 5a–d. Vessels in AILAP. **a** Light microscopy with arborizing vessels surrounded by lymphoid cells. **b** Silver impregnation demonstrates prominent basement membrane and endothelium. **c** Postcapillary vessel surrounded by lymphocytoid cells and a plasma cell (*arrow head*). **d** Electron microscopy of corresponding vessel (*V*) with a fluffy basement membrane (*arrow heads*), large endothelial cells and an attached plasmablastic cell (*Pb*). **a** × 140, **b** and **c** × 300, **d** × 10,000

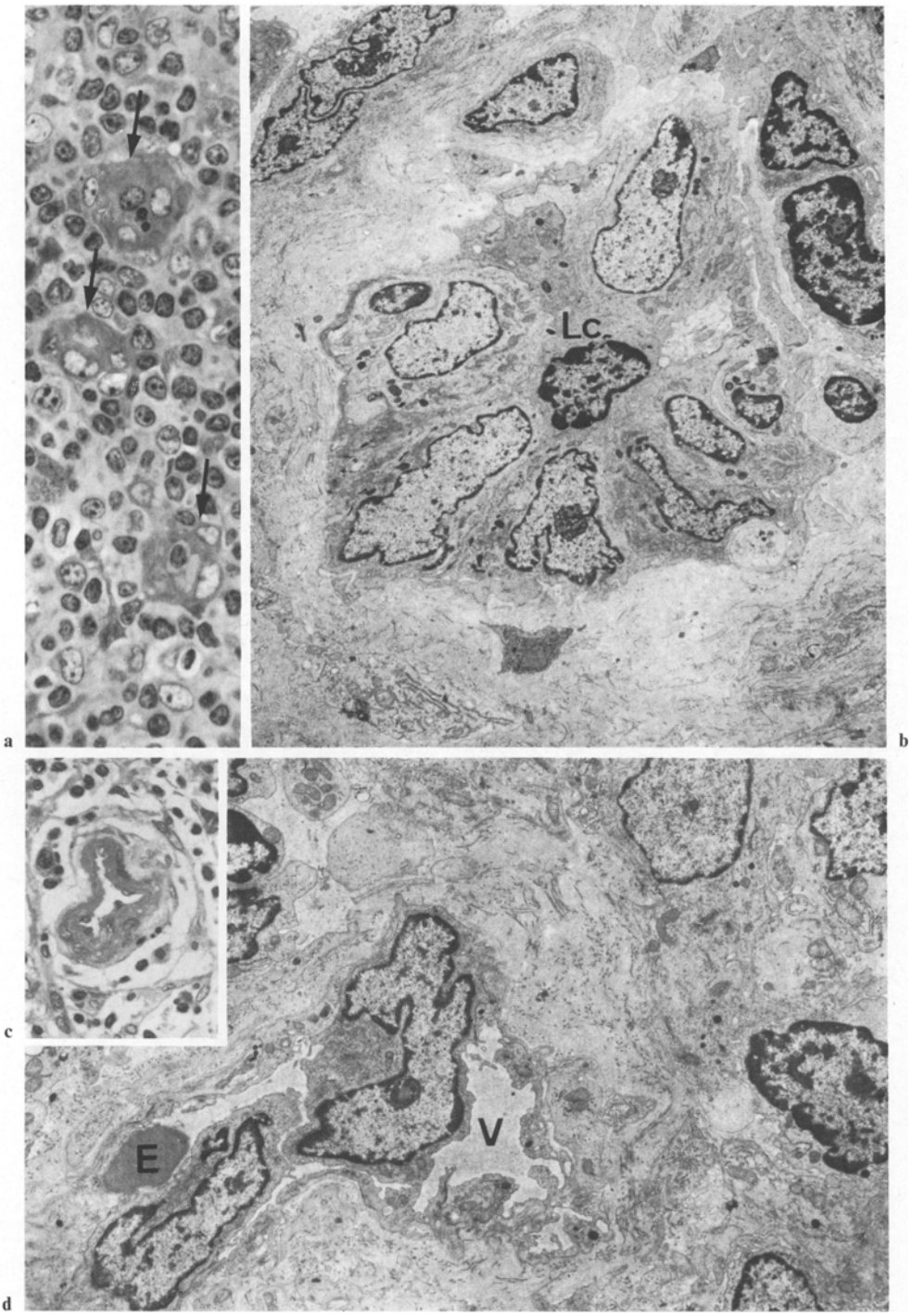

Fig. 6a–d. Vascular changes in AILAP. **a** Light microscopy of so called epithelioid like hypertrophy of post-capillary vessels with large swollen endothelial cells almost occluding the lumina (*arrows*). **b** Electron microscopy of a corresponding vessel with a lymphocyte in the lumen (*Lc*) and large clustering endothelial cells surrounded by a thickened basement membrane. **c** Light microscopy of the thickening of the basement membrane without endothelial edema. **d** Ultrastructure of corresponding vessels (*V*) shows an erythrocyte (*E*) in the lumen, large endothelial cells and a broad flocculent basement membrane containing small bundles of collagen fibers. **a** × 560, **b** × 5,000, **c** × 300, **d** × 6,000

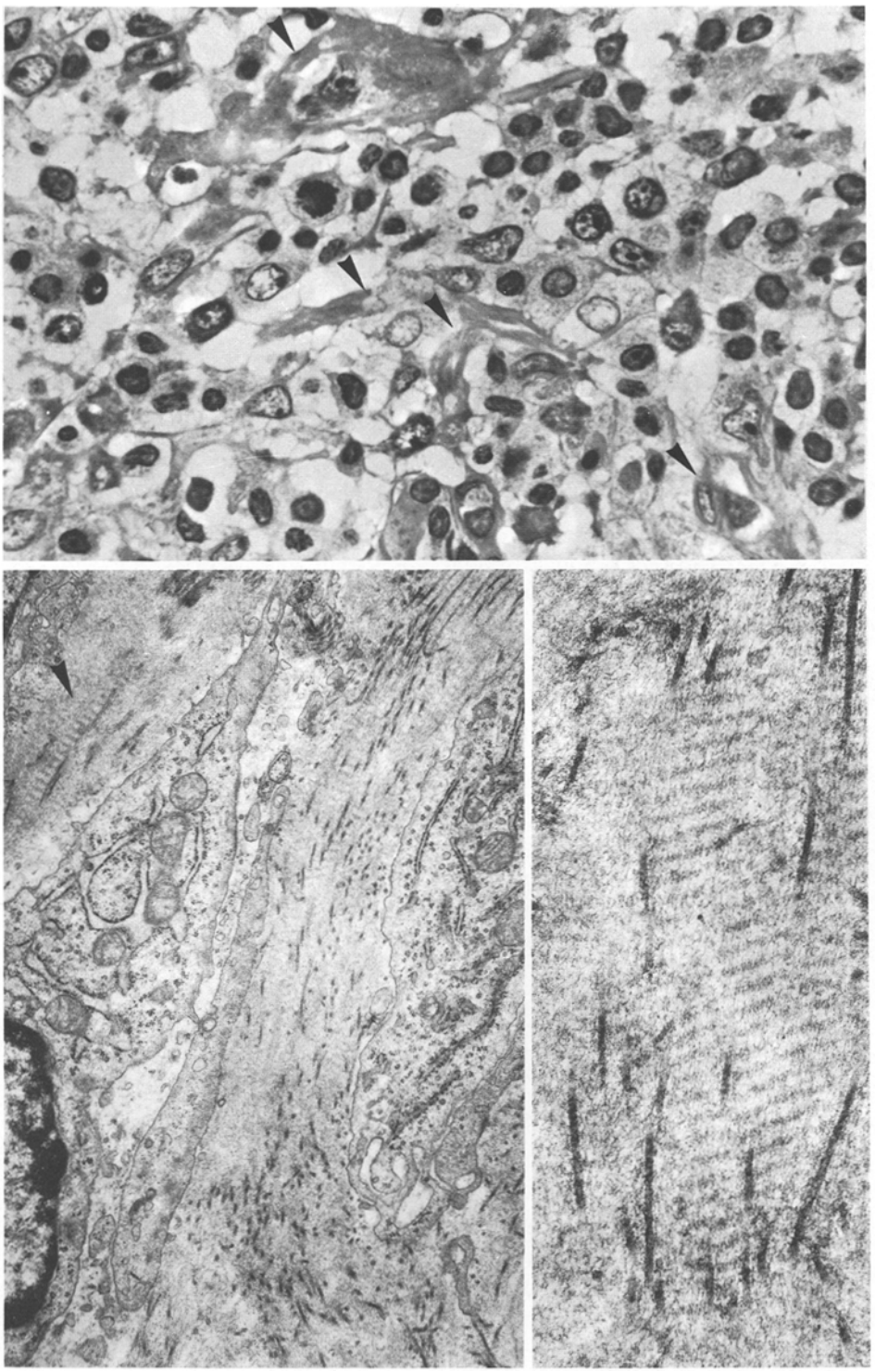

Fig. 7a–c. Interstitial material in AILAP. **a** Light microscopy with areas of a fluffy, PAS-positive material dispersed among the lymphoid cells and surrounding vessels (*arrow heads*). **b** Electron microscopy showing parts of fibroblastic reticulum cells (fibroblasts) surrounded by a broad filamentous material which contains single collagen fibers and areas with a conspicuous periodicity (*arrow head*). **c** Cross of ribbon banded material corresponding to so called long-spacing collagen besides single collagen fibers. **a** × 750, **b** × 12,000, **c** × 45,000

Discussion

Our results based on light and electron microscopy confirm and extend previous reports describing the histomorphology and ultrastructure of the lesions in lymph nodes caused by AILAP in a total of 10 cases (Fisher et al. 1976; Palutke et al. 1976; Valdes et al. 1976; Matz et al. 1977; Neimann et al. 1978). This applies particularly to the classification of AILAP into several subgroups, the problem of malignant transformation, immunoperoxidase reaction, the vascular changes and the interstitial material.

The value of classification of AILAP into several subgroups is emphasized at least into lymphocyte- immunoblast- epithelioid cell- plasma cell predominance, or mixed cellularity, corroborating the results of Lennert et al. (1979). This classification seems to be of importance in the view of the differential diagnosis with the other lymphomas of the Hodgkin- or Non-Hodgkin type: AILAP with large numbers of epithelioid cells has to be distinguished either from the so called Lennert's lymphoma (Lennert and Mestdagh 1968; Burke and Butler 1976) or from at least some cases of atypical lesions in Hodgkin's disease (Radaszkiewicz and Lennert 1975).

Pronounced proliferation with clusters of large lymphoid or immunoblastic cells may present the first evidence for evolving malignant lymphomas, which terminate AILAP in the following reported frequencies: about 35–50% (Nathwani et al. 1978; Rappaport et al. 1979) 6–13% (Lennert et al. 1979) and 9% (Lukes and Tindle 1975) in larger series. Morphological features accompanying the transformation of AILAP into immunoblastic sarcoma have also been recorded by Fisher et al. (1976) and Howarth and Bird (1976) and evolution into Hodgkin's disease by Yataganas et al. (1977) and Lennert et al. (1979). In our prospective study however, development of immunoblastic lymphoma was preceded by a predominance of epithelioid histiocytes (case K.J.) 7 months before appearence of immunoblastic lymphoma. 13 months after the first biopsy (case S.W.) Hodgkin's disease evolved in AILAP with a predominantly lymphocytic proliferation.

In addition to the clinical features resembling Hodgkin's disease (review by Lukes and Tindle 1975) dysproteinaemia seems to be one of the most characteristic laboratory findings in AILAP (Frizzera et al. 1974; Horne et al. 1974; Palutke et al. 1976; Iseman et al. 1976; Matz et al. 1977; Weisenburger et al. 1977; Nathwani et al. 1978; Pangalis et al. 1978).

As shown by the immunoperoxidase technique, intracytoplasmatic immunoglobulins of the light and heavy chain type were present in the plasma cells and also in some of the large lymphoid (immunoblastic) elements (Nathwani et al. 1978) according to our findings. Fluorescence studies on formalin fixed wet tissue have demonstrated almost the same types of immunoglobulins distributed in plasmacytoid and immunoblastic cells randomly scattered or assembled around the vessels (Moore et al. 1976). The presence of many peroxidase positive immunoblasts, developing and mature plasma cells in our cases with ultrastructural differentiation of cell organelles for immunoglobulin synthesis are in agreement with these results.

The different types of reticulum cells dispersed between the lymphoid, histio-

cytic and plasmacytoid cells, especially the so called dark reticular cell (Mollo et al. 1969), have been encountered in different forms of lymphadenitis and malignant Non-Hodgkin-lymphomas (review by Kaiserling 1977).

The remarkable vascular changes of the lymph nodes should not be regarded as a specific feature of AILAP since they may be detected in conditions like graft versus host reaction (Graham 1974) or post vaccination lymphadenitis (Hartsock 1968). As suggested by Neiman et al. (1978) this vascular proliferation may only be a relative one and much of the prominence of the vessels is due to the conspicuous lining by the thickened basement membrane like material. In animal experiments the function of the post-capillary or Schulze venules is clearly connected with a migration of T-lymphocytes from the circulation into the lymphatic tissue (review by Haferkamp et al. 1975). The basement membrane like pericapillary material in T-lymphocyte depleted lymphatic tissue of the mouse was shown to contain immunoglobulin deposits (IgG) in a large quantity (review by Syrjänen 1979) corresponding with our findings by immunoperoxidase reaction. Therefore the prominent eosinophilic or acidophilic and apparently amorphous material observed along the vessels and between the different cells of AILAP deserves special attention. Neiman et al. (1978) considered this material to be cellular debris consisting of a large accumulation of degenerating and dying cells and concluded that there must be a high rate of cell death in this condition. In addition, these authors showed a peculiar banded interstitial, mostly perivascular arranged material which is identical to the structures seen by Matz et al. (1977). Morris and Bird (1979) concluded that this amorphous interstitial material results from the oblique sectioning of elongated and branched cytoplasmatic processes of reticulum cells.

According to our results this material, often a diagnostic feature in AILAP, is composed neither of cellular debris nor of reticulum cells but of a basement membrane like material, which contains immunoglobulins. By electron microscopy the material consisted of a felt like arrangement of fine fibrils, scattered collagen fibers and cross or ribbon banded structures identical with the so called long-spacing collagen (review by Pillai 1964). Similar differentiation of intercellular hyaline or proteinaceous substances was recorded in Hodgkin's disease (Stiller and Katenkamp 1978; Costanzi et al. 1978) as well as in malignant lymphomas of the Non-Hodgkin-type and in lymphadenitis (Mollo and Monga 1971; Costanzi et al. 1978) but amyloid has never been detected. It is noteworthy, however, that by immunofluorescence technique no basement membrane deposits or antigen-antibody complexes were observed along the vessels (Moore et al. 1976; Neiman et al. 1978). This is in contrast with the findings of Haferkamp et al. (1975) who found immunoglobulins in the walls of venules by FITC-labelled antisera, and with our results with the direct peroxidase reaction. Thus the thickening of venule walls may be caused at least partially by an impregnation with immunoglobulins, which is compatible with the ultrastructural findings in this areas.

Reviewing the pertinent literature and our morphological results, we conclude that AILAP may be regarded as a lymphoproliferative disease which may either evolve into malignant lymphoma (so called pre-lymphoma) of the Non-Hodgkin and Hodgkin type or follow the course of a severe non-neoplastic lymphadenitis.

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