

Cytodiagnosis for Angio-immunoblastic Lymphadenopathy with Dysproteinaemia*

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Angio-immunoblastic lymphadenopathy with dysproteinaemia (AILD) is recognized nowadays as a clinical and histopathological entity.^{1,5} Studies on several hundred patients show that the condition often mimics malignant lymphoma clinically with evidence of immunological derangement; almost all patients show localized or generalized lymphadenopathy. Auto-immune haemolytic anaemia and polyclonal hypergamma-globulinaemia are also frequent findings.^{2,3,6} Other immunological abnormalities include mixed and monoclonal cryoglobulinaemia, high titre of cold agglutinin, and the presence of auto-antibodies (platelet antibodies, rheumatoid factor, antismooth muscle antibodies, LE cells).⁷⁻¹¹ T-cell deficiency has been reported.¹² Skin test for tuberculin, mumps and trichophyton sensitivities are usually negative.^{4,13}

Although the aetiology of AILD remains undetermined, it has been attributed to prolonged antigenic stimulation by drugs,^{10,14,15} and infectious agents such as viruses¹⁶⁻¹⁸ or parasites.¹⁹

Formerly, the diagnosis of AILD was made solely by pathologists and based traditionally on a specific histopathological triad of lymph node changes: (1) the effacement of lymph node architecture with pleomorphic cellular infiltration comprising immunoblasts (transformed lymphocytes and plasmacytoid immunoblasts) and plasma cells; (2)

the proliferation of small arborizing blood vessels; and (3) the interstitial deposition of amorphous acidophilic material.

The clinical course of AILD has been observed to undergo three general patterns: (1) long-term survival with spontaneous remission;^{3,4,20} (2) long-term remission with chemotherapy; and (3) rapid deterioration with fatal outcome despite vigorous therapy. The latter pattern manifests itself as immunoblastic sarcoma,^{3,5,20} malignant lymphoma,²¹ Hodgkin's disease²² and Burkitt-like lymphoma.²³

The purpose of this communication is to present our experience with the cytological examination of peripheral blood, buffy-coat preparation, bone marrow aspirate, effusion and lymph node imprint as supplements for the rapid diagnosis of AILD.

OBSERVATIONS

During the past seven years, 30 patients (16 males and 14 females; aged 21 to 84 years) had been diagnosed as having AILD; they were studied at the Haematology Division of the Department of Medicine, Siriraj Hospital, Bangkok. In all cases, the diagnosis was confirmed by histological examinations.

The findings were as follows:

Peripheral blood (Figs. 1&2)

Anaemia of varying degrees was constantly present, with some

anisocytosis. Polychromasia and nucleated red cells were found in Coombs' positive cases and those with negative haemolytic anaemia. Auto-agglutination of red cells was observed in some Coombs' positive cases and in cases with high titre of cold agglutinin. There was no significant red cell fragmentation in blood smears.

Thrombocytopenia was observed in seven patients (23.3 per cent of the total). White-cell counts ranged from 2.9×10^9 /litre to 30.0×10^9 /litre in 29 out of the 30 cases; the one case not within that range had a count of 78.7×10^9 /litre.

Immunoblasts were present in the blood smears of 28 (93.3 per cent) of the 30 patients. Twenty-two (78.5 per cent) of them exhibited immunoblasts numbering less than 10 per cent; only six patients (21.4 per cent) had higher counts. Types I, II and III were most commonly found (description of immunoblasts will be given later). Types I and II together were seen in six cases; types II and III (with a few Type IV cells in some cases), in 21 cases (75 per cent of the 28 cases); and Types II and IV, in one case.

Electron microscopy showed certain features characteristic of cell types (Fig. 2).

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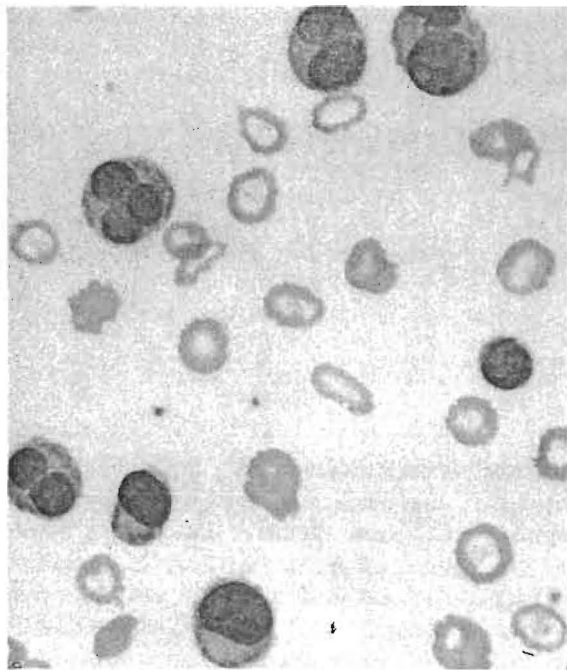


Fig. 1 Peripheral blood smear showing Type II or plasmacytoid and Type V or lobulated immunoblasts. (Wright's stain, x 800).

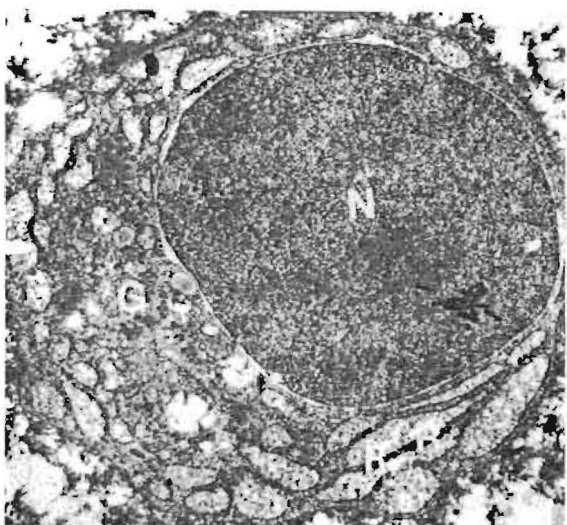


Fig. 2 Peripheral blood smear showing an immunoblast with distended, rough endoplasmic reticulum (R), homogeneous nucleus (N) and small Golgi area (G). (Uranyl acetate & lead citrate stain, x 10,560).

Buffy-coat preparation (Figs. 3 & 4)

Examination of the buffy-coat preparation is of great value in establishing a diagnosis for AILD because the small number of abnormal cells in a routine blood smear may be overlooked. The technique was conducted on 24 patients and immunoblasts were found in all 24 (100 per cent), including two undiagnosed cases using peripheral blood smear examination.

Immunoblasts of Types I, II, and III were commonly observed in the same patient; the single cell type may also be present. Type predominance was the same as that found in peripheral blood smears.

Plasma cells were sometimes present in the peripheral blood of patients with AILD; they may be hardly distinguishable from Type II immunoblasts, although the latter have a higher nucleocytoplasmic ratio and a less well-demonstrated perinuclear halo.

Bone marrow (Fig. 5)

Although bone marrow findings are not as diagnostic as they would be in cases of acute leukaemia, they may nonetheless be used as a complement. At the same time that numerous immunoblasts were readily observed in peripheral blood, frequently the number present in bone marrow totalled less than 10 per cent although the range may be from only few to 40 per cent. Only two out of the 30 patients with an immunoblastic leukaemic blood picture had more than 50 per cent immunoblasts in their bone marrow smears. This discordance between peripheral blood and bone marrow findings, together with the clinical picture mimicking malignant lymphoma with evidence of haemolysis and immunological abnormalities, is highly suggestive of AILD.

The number of plasma cells increased in most cases but their total was less than 15 per cent. There were no specific changes in other cell series. Erythroid hyperplasia with some megaloblastoid changes were seen in patients with haemolytic anaemia.

Effusions (Fig. 6)

The examination of four peritoneal, four pleural and one pericardial effusions from five of our patients revealed that all the effusions were exudate, containing from a few hundred to over 1,000 nucleated cells/mm³, but rarely exceeding 3,000 cells/mm³; only one case had 7,000 cells/mm³. Immunoblasts were seen in all cases (100 per cent); commonly found were Types II and III. Other cells included red blood corpuscles, lymphocytes and occasional mesothelial cells. Non-degenerated neutrophils could be found after repeated tapings.

Under these conditions, the use of Wright's stain preparation furnished more information than Papanicolaou stain. Methyl green pyronin stain was used in some cases for better details of immu-

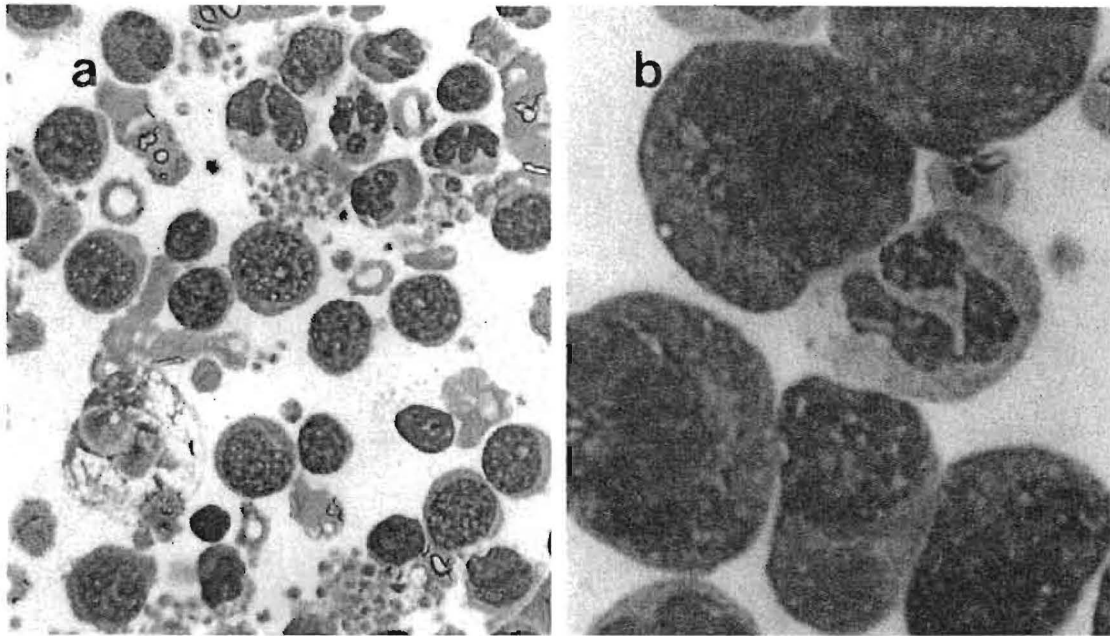


Fig. 3 Buffy-coat preparation: (a) showing immunoblasts Type I as large mononuclear cells with prominent nucleolus, coarse chromatin network and greyish blue cytoplasm; (Wright's stain, x 800); (b) showing Type III or transformed lymphocyte-like immunoblasts with pleomorphic nucleus and deep blue cytoplasm. (Wright's stain, x 2,000).

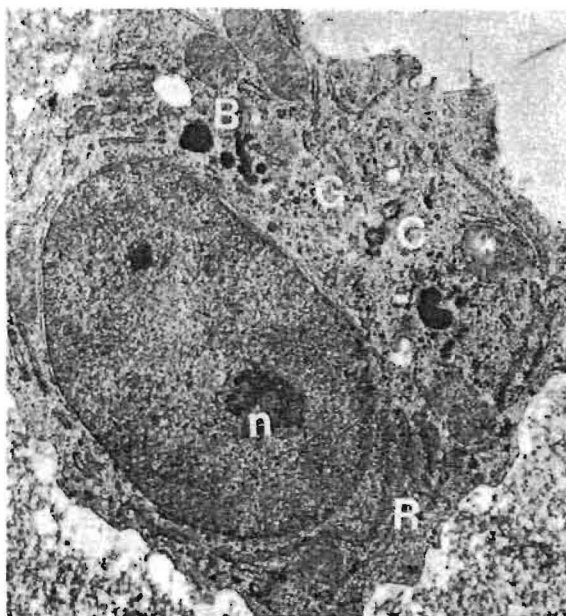


Fig. 4 Buffy-coat preparation showing an immunoblast with prominent nucleolus (n), well developed Golgi area (G), centriole (C) and (short and flat) rough endoplasmic reticula (R). (Uranyl acetate & lead citrate stain, x 10,560).

noblasts.

Lymph node imprint (Fig. 7)

Out of 22 patients whose peripheral lymph nodes were biopsied, 20 cases (90.9 per cent of the total) yielded suggestive findings. Of the two patients whose initial examination failed to furnish a

diagnosis, one subsequently had a revealing examination after repeated biopsies.

In cases of AILD, the cut surface of lymph nodes had the appearance of fish flesh similar to that seen in malignant lymphoma. The cell components, however, were rather pleomorphic with small and me-

dium-sized lymphocytes numbering 30 to 50 per cent of the total. Plasma cells were also common. Immunoblasts of types I to IV were most commonly found. The periphery of their cytoplasm was sometimes stained pink and flame-like as seen in flame plasma cells. Methyl green pyronin staining demonstrated immunoblasts very effectively. The imprint background of particulate material was greyish blue, in contrast with the clear, homogeneous background of reactive lymph nodes and those in malignant lymphoma.

Although the results of lymph node imprint in AILD have not been as pathognomonic as that obtained in cases of tuberculous lymphadenitis, Hodgkin's disease, non-Hodgkin's lymphoma and metastatic carcinoma, the procedure is of some value as a complement in establishing a diagnosis for AILD patients presenting lymphadenopathy.

Immunoblasts, which are present in aforementioned specimens taken from patients with AILD, could be

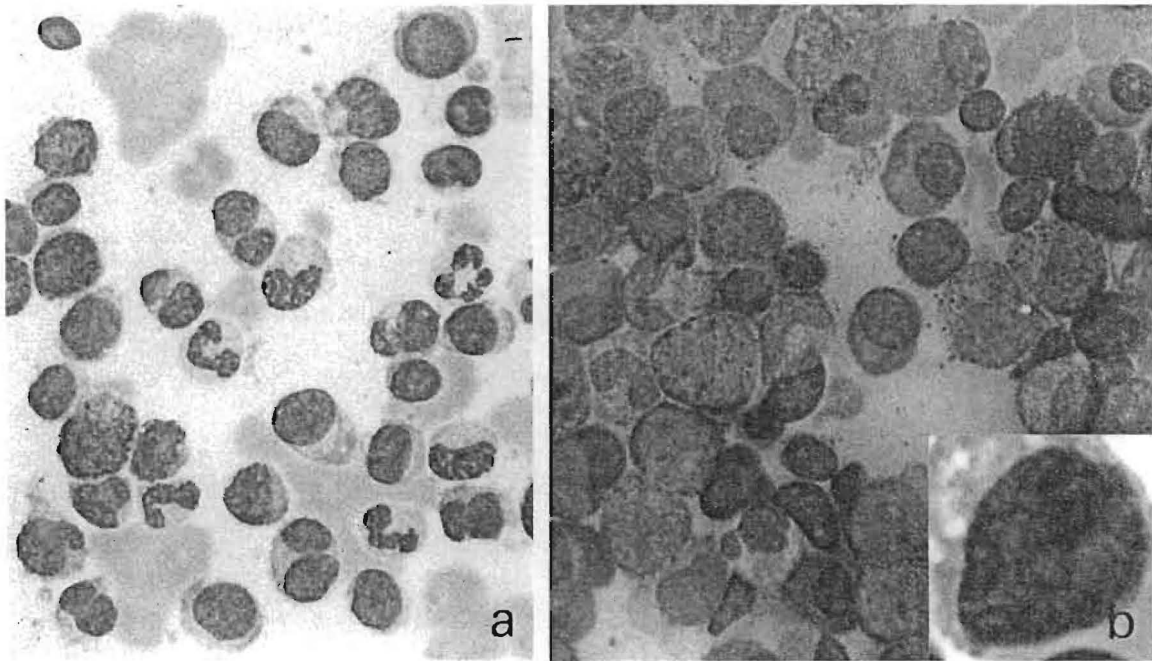


Fig. 5 Bone marrow aspirate showing: (a) infiltration with immunoblasts Types I, II and V. (Wright's stain, x 800); (b) infiltration with immunoblasts Type II. (Wright's stain, x 800). Inset, a vacuolated immunoblast (x 2,000).

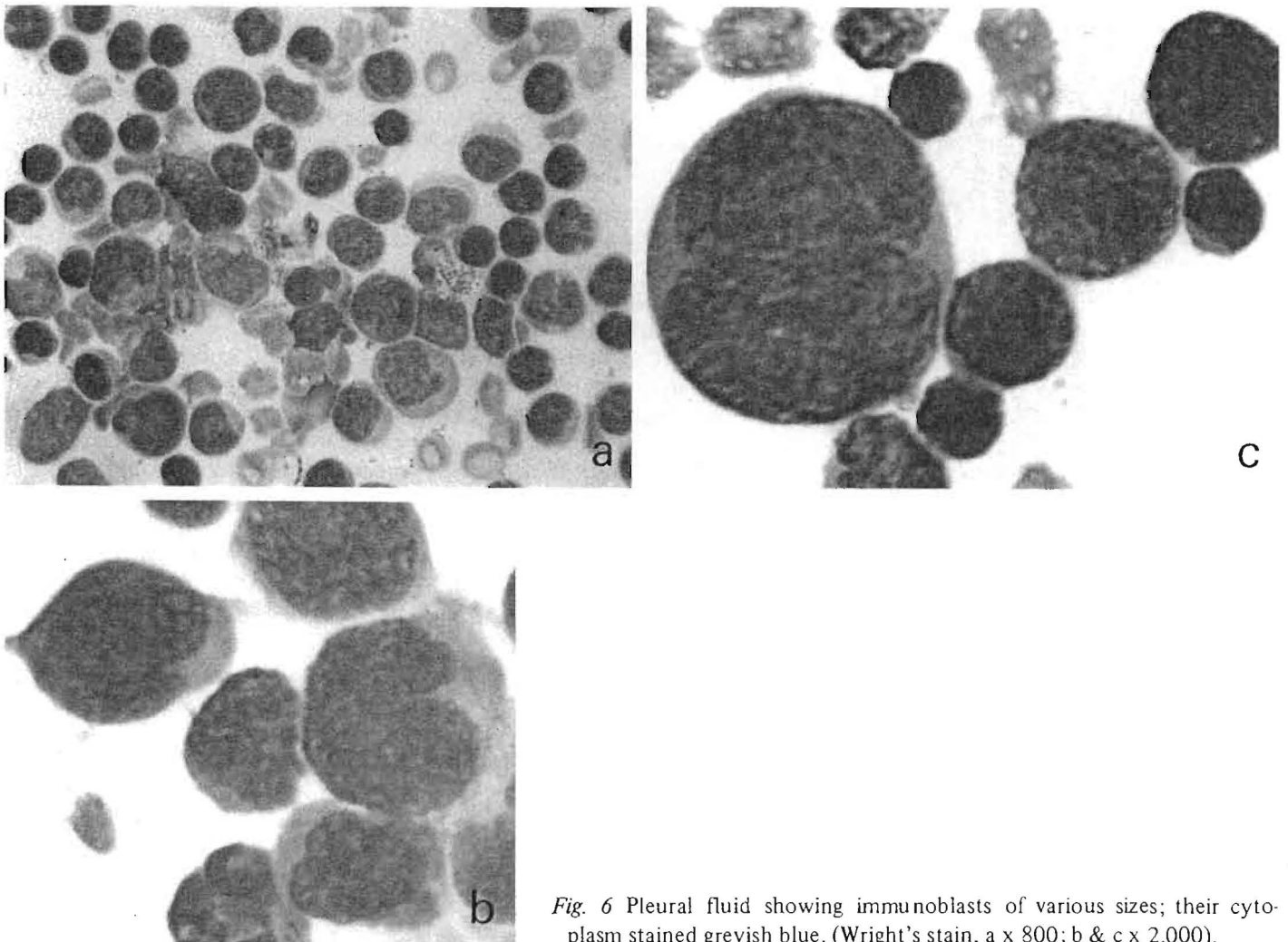


Fig. 6 Pleural fluid showing immunoblasts of various sizes; their cytoplasm stained greyish blue. (Wright's stain, a x 800; b & c x 2,000).

Fig. 7 Lymph node imprint showing pleomorphic cellular components with lymphocytes and immunoblasts against the greyish blue stained particulate background. (Wright's stain, x 800).

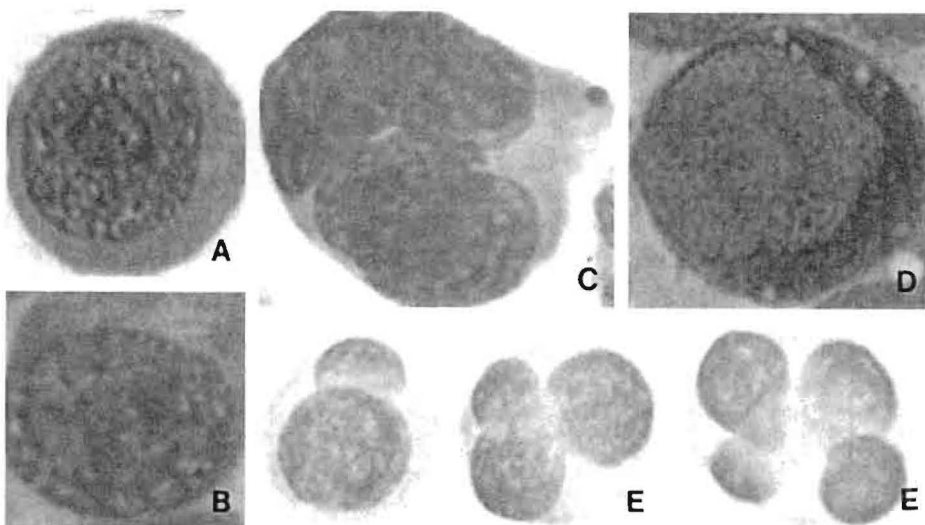
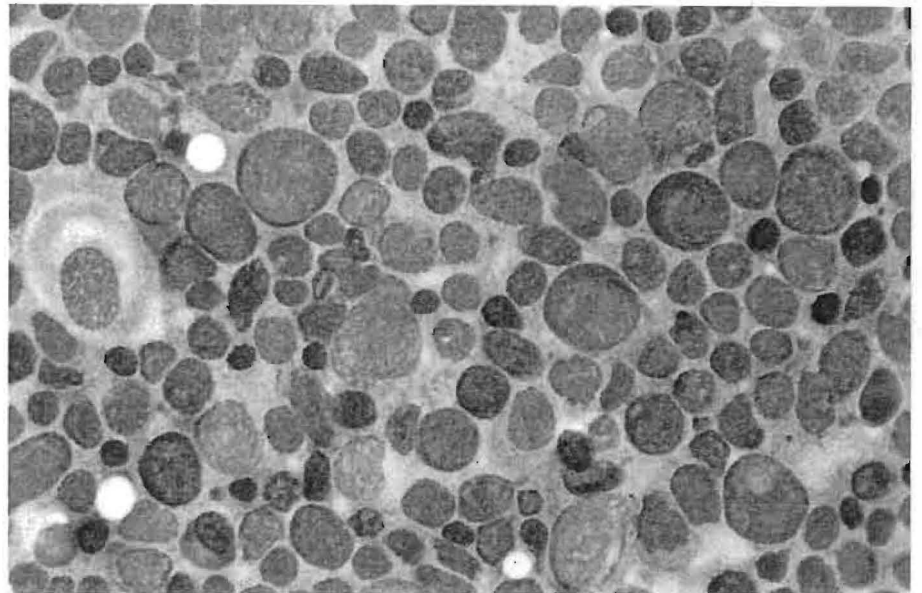


Fig. 8 Showing the five types of immunoblasts (Wright's stain, x 2,000)

identified as belonging to five types.

Type I or Blast-like immunoblast (Fig. 8A)

The size of the cells varies from 15-25 μ in diameter. The nucleocytoplasmic ratio is about 3:4. The cytoplasm is greyish blue containing no granules. The nucleus is round or slightly indented, and placed centrally or eccentrically, exhibiting coarse nuclear chromatin with prominent parachromatin. There is usually one distinct nucleolus. The Type I immunoblast may be differentiated from other blast

cells by its more mature nucleus and coarser nuclear chromatin.

Type II or Plasmacytoid immunoblast (Fig. 8B)

This type of immunoblast has similar morphology to plasma cells, measuring 12 to 25 μ in diameter, but has a higher nucleo-cytoplasmic ratio, finer nuclear chromatin and less distinct perinuclear halo. Nuclear chromatin may be compared with that of lymphocytes. This similarity is well demonstrated by electron microscopy (Fig. 2). A nucleolus may be found, and distended or flattened endoplasmic re-

ticula are always present. The cytoplasm is greyish blue. Small vacuoles (non-empty) from distended rough endoplasmic reticula are sometimes seen (Fig. 4).

Type III or Transformed lymphocyte-like immunoblast (Fig. 8C)

Varying in size (diameter 15-30 μ), the morphology of this type is similar to the atypical or transformed lymphocytes that are seen in viral, bacterial and parasitic infections. The nucleus may be round or oval, indented or lobulated, and it may contain one or two nucleoli. The cytoplasm is usually greyish or deep

blue in colour; it is not so variable in intensity as that of transformed lymphocytes. Small vacuoles (non-empty) are seen occasionally.

Type IV or Reticulum cell-like immunoblast (Fig. 8D)

The diameter of this type varies from 15-30 μ . Its morphology is similar to the primitive reticulum cells that are seen in reactive lymphadenopathy and Hodgkin's disease. The nucleus is round or oval with prominent parachromatin. The chromatin pattern may be either more or less dense than that of the Type I immunoblast. From one to three nonprominent nucleoli may be observed. The amount of cytoplasm, stained grey or deep blue, is variable. The perinuclear halo is not well demonstrated.

Type V or Lobulated immunoblast (Fig 8E)

The diameter of this type may vary from 12 to 25 μ . Both the nuclear chromatin and the cytoplasm are the same as those of the other four types of immunoblasts, but the nucleus appeared to be lobulated or cloven in a manner similar to the type of nucleus seen in Reider cell leukaemia.

In conclusion, it has been our experience that clues for the rapid diagnosis of AILD may be obtained from clinical pictures mimicking lymphoma with evidence of haemolytic anaemia and immunological abnormalities together with the presence of immunoblasts in the peripheral blood (especially in buffy-coat preparation), bone marrow, effusion and lymph node imprint. Prompt diagnosis of AILD using such haematological means is

imperative and of great benefit for patients with a rapidly progressive course who need early specific treatment.

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