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Lymphoreticular Tissue Lesions in Steinbrinck-Chediak-Higashi Syndrome

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Summary. Surgical and postmortem specimens of lymphoreticular tissue (organized and diffuse) from three patients with Steinbrinck-Chediak-Higashi syndrome were investigated by the light and electron microscope. Material before and after cancer chemotherapy was available. An extensive generalized hyperplasia of lymphoreticular tissues was observed in which several cell lines participated, including lymphocytes, histiocytes, and reticulum cells. Although this hyperplasia resembled neoplasia, histologic and cytologic details suggested it was only a reactive process. Therapy with prednisone and vincristine reduced the well differentiated cells in the lymphoreticular tissues, resulting in a more anaplastic population of immature lymphoid and reticulum cells. It is postulated that proliferation of the lymphoid and histiocytic stem cells is a reaction to the accumulation of materials normally degraded by phagocytes. This proliferation initially may be compensatory, but owing to persistent stimulation by non-degraded foreign materials it progresses to simulate neoplasia.

Zusammenfassung. Organisiertes und nicht organisiertes lymphoretikuläres Gewebe von 3 Patienten mit Steinbrinck-Chediak-Higashi Syndrome vor und nach Behandlung mit Prednison und Vincristin wurden licht- und elektronenoptisch untersucht (Biopsie- und Autopsiematerial). Dabei fand sich eine generalisierte Hyperplasie dieser Gewebe unter Beteiligung verschiedener Zellreihen, wie z. B. Lymphocyten, Histiocyten und Reticulumzellen. Obgleich das Ausmaß dieser Hyperplasie dem einer Neoplasie gleichkam, ähnelten histologische und cytologische Details eher einem reaktiven Prozeß. Behandlung mit Prednison und Vincristin war gefolgt von einer Abnahme differenzierter Zellen, so daß eine mehr anaplastische Population von Lymphoidzellen und Reticulumzellen das Bild beherrschte. Es wurde die Möglichkeit diskutiert, daß die Anhäufung von normalerweise in Phagocyten abgebauten Materials eine Proliferation von Lymphoidzellen und histiocytären Stammzellen anreize. Diese Zellproliferation, anfänglich kompensatorisch, mag wegen persistierender Stimulierung ein Ausmaß annehmen, das von dem einer Neoplasie nicht zu unterscheiden ist. Chemotherapie kann zu diesem anaplastischen Bild infolge Zerstörung differenzierter Zellen und Herabsetzung der immunologischen Reaktionsfähigkeit weiter beisteuern.

Introduction

The Steinbrinck-Chediak-Higashi syndrome (SCH) is characterized by an autosomal recessively inherited defect in lysosomal function, which interferes with the processing of extraneous and autologous substances by these organelles (White, 1966). This leads to atypical cytoplasmic granulation which is most prominent in cells with highly developed lysosomal activity under normal conditions (cells of excretory and partially endocrine glands). Atypical coarse granulation of eosinophilic granulocytes was one of the first signs of SCH described

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(Steinbrinck, 1948; Bequez, 1943). Consequences of the widespread defect in lysosomal function include disturbances in melanin metabolism and altered distribution characterized by hyper- as well as hypopigmentation and by melanin clumping in certain cells (Bedoya *et al.*, 1969), and disturbances in the reaction to breakdown of extraneous infectious agents at the cellular level leading to repeated widespread infections often causing the death of the patients at an early age. In others surviving for a longer period, hyperplastic changes in the lymphoreticular tissues were observed and interpreted as reactive lymphadenopathy, lymphoproliferative disorder, or even malignant lymphoma (Dent *et al.*, 1966; White, 1966; Efrati and Jonas, 1958; Page *et al.*, 1962). The present study describes lymphoreticular tissue changes as observed in three complete autopsy cases of Steinbrinck-Chediak-Higashi syndrome by use of light- and electron microscopy, as well as phase contrast microscopy. The reactive versus the neoplastic nature of the lymphoreticular tissue lesions is discussed, for which the case material appears especially valuable since investigation was possible with and without the influence of cancer chemotherapy.

Materials and Methods

Tissues were obtained from autopsies done at the Laboratory of Pathology, National Cancer Institute, National Institutes of Health, United States of America (Case 1) and at the Department of Pathology, University of Antioquia School of Medicine, Medellin, Columbia, South America. Fixation was done in 10% neutral formalin for light microscopy and, in addition, with phosphate buffered 1% osmium tetroxide for electron microscopy, embedding in paraffin or epoxy resin. Staining for light microscopy was performed with H & E, Masson's trichrome, Azan, Giemsa, PAS and digested PAS, phosphotungstic acid—hematoxylin, Methyl green pyronine-Y, Lillie's ferrous sulfate reaction for melanine, Sudan black, Nile blue, Luxol blue, Turnbull's reaction for iron, and Congo red with polarization for amyloid. Sections were cut for light microscopy at 2–5 μ, and, for electron microscopy, ultrathin sections were stained with 10% uranyl acetate. Microscopy was done using the Reichert "Zetopan" with a Zeiss automatic camera attached, and using the RCA-EMU 3F electron microscope.

I. Case Reports

Case 1 (S.E.P., A69–297). The eight year old white boy suffered from repeated infections of ears and respiratory tract almost from birth. These were usually controlled with antibiotic treatment. A peculiar grayish cast of his light brown hair and an incomplete albinism with extensive hypopigmented areas of the skin led to the diagnosis. Four months before death generalized lymphadenopathy was noted and diagnosed as "lymphomatous stage" of Chediak-Higashi disease. Treatment was started with prednisone and vincristine. During his final clinical admission, he developed cranial and peripheral neuropathy, vomiting with aspiration, and he died clinically of aspiration pneumonia. The gross and histological diagnosis made at autopsy was as follows:

1. Chediak-Higashi syndrome.
2. Hepato-splenomegaly (liver 980 g, spleen 280 g).
3. Generalized lymphadenopathy.
4. Bilateral necrotizing bronchitis and peribronchitis.
5. Bilateral necrotizing bronchopneumonia with giant cell reaction (foreign body type).
6. Acute nephrosis.
7. Bilateral myocardial dilatation (heart 130 g).

Family History. Grandparents and parents unremarkable. His mother has had thirteen pregnancies, two of which ended as spontaneous abortions, one child was delivered premature, three children were albinotic and died in early childhood, and two children (including this case) had Chediak-Higashi syndrome.

Case 2 (N.C., *A68-63*). The four and one half year old mestizo girl suffered, for 8 months before death, from repeated infections of the respiratory tract, of the ears, the eyes, the nailbeds, and the veins. As in the first case, a silvery-gray cast of the hair and hypo- as well as hyperpigmentation of the skin led to the diagnosis. In addition photophobia and nystagmus were observed. During the subsequent course of the disease generalized lymphadenopathy and hepatosplenomegaly as well as hyperplastic tonsils were noted. She was finally hospitalized for symptoms of hepatitis and died of severe bronchopneumonia and empyema (this patient received no cancer chemotherapy). The gross autopsy diagnosis was as follows:

1. Chediak-Higashi syndrome.
2. Hepatosplenomegaly (liver 750 g, spleen 200 g).
3. Generalized lymphadenopathy.
4. Aspergillus pharyngitis and esophagitis.
5. Acute purulent pericarditis.
6. Bilateral segmental necrotizing pneumonia.

Family History. Granulocytic abnormalities noted in parents, grand-mother and several sisters. One brother with albinotic skin and hair changes died shortly after birth.

Case 3 (*M.R.V.*, *A68-62*). The two and one half year old mestizo girl suffered from a series of infections of the respiratory and intestinal tract, and was hospitalized three months before death because of generalized lymphadenopathy and hepatosplenomegaly. A changed skin pigmentation, a silvery-gray color of the hair, nystagmus and photophobia suggested Chediak-Higashi syndrome which was further proved by demonstration of typical cellular cytoplasmic inclusions. In the further course of the diasease, infections could be only transiently controlled by medical treatment, and the girl died of widespread bronchopneumonia. The gross autopsy diagnosis listed:

1. Chediak-Higashi syndrome.
2. Hepatosplenomegaly (liver 750 g, spleen 280 g).
3. Generalized lymphadenopathy.
4. Bilateral acute necrotizing bronchitis and bronchiolitis.
5. Bilateral diffuse interstitial pneumonia.

Family History. One brother died in early age with Chediak-Higashi syndrome.

II. Extract of Laboratory Findings

Case 1 (before treatment). *Blood.* Hb 5.4–8.8; hematocrit 30; reticulocytes 1.7%; leukocyte count 1200–2200; differential 72–86% lymphocytes, 7–17% mature granulocytes; thrombocytes 41000–55000. *Bone marrow.* Microblastic erythroid hyperplasia, focal lymphocytosis, Chediak-Higashi inclusions. *Immunoglobulins.* IgG 3.5 mg/ml, IgM 2.0 mg/ml, IgA 0.52 mg/ml, haptoglobulin 272 mg-%. *Serology.* Coombs direct and indirect negative, LE cell phenomenon negative, ASO 50 Todd units, Toxoplasmin test negative, *Bacteriology.* Routine bacteriological investigations including for acid-fast organisms and fungi were negative.

Case 2 (as obtained from submitted clinical report). *Blood.* Mild anemia and neutropenia (34%), lymphocytosis (63%). *Bone marrow.* Lymphocytosis. *Serum proteins.* Total 7.8 g, albumin 3.11 g-%, α_1 globulin 0.26 g-%, α_2 globulin 0.51 g%, β globulin 0.64 g%, and α globulin 2.96 g-%. *Serology.* Coombs test direct and indirect negative. *Bacteriology.* No information.

In Case 3 no information about special laboratory studies were obtained from submitted protocols.

During the course of the disease, above given values showed repeated unpredictable changes attributed to progressive disease and effect of treatment. Especially bacteriological cultures from the throat revealed a varying growth of Candida albicans, hemophilus parainfluenza and pneumonococcus.

Results (Table)

I. Biopsy Materials

Biopsy materials consisted of several bone marrow aspirates. They showed persistent hypercellularity partly with decreased numbers of megakaryocytes.

Table. *Microscopic Findings at Autopsy*

	Thymus	Lymph nodes	Spleen	Peyer's patches	Tonsils	Bone marrow	Other organs
Case 1 (S.E.P.)	Severe atrophy; marked medullary hyalinization; absence of epithelial cells and of Hassals corpuscles	Homologous atrophy and replacement of normal cells by loosely arranged population of atypical lymphoid cells, reticulum cells and histiocytes	Homologous atrophy and replacement of normal cells by atypical reticulum cells and histiocytes with prominent granules Extramedullary hemopoiesis	Atrophy	Atrophy	Diffuse lymphocytosis. Maturation arrest of granulopoiesis. Atypical granulated histiocytes	Generalized lymphocytic infiltration with participation of immature lymphoid cells. Necrotizing bronchitis and bronchopneumonia. Acute tubular necrosis. Sepsis.
Case 2 (N.C.)	Homologous atrophy of thymus; occasional atypical Hassals corpuscle	Diffuse population of lymphocytes, plasma cells, and a few granulocytes. Indistinct lymphoid follicles; no secondary follicles. Increased number of reticulum cells	Small unremarkable lymphoid follicles; hyalinized remnants of secondary follicles. Marked histiocytic activation in red pulp. Increase in undifferentiated reticulum cells	Dense population of inconspicuous small lymphocytes no secondary follicles	Moderate atrophy	Hypercellularity with increase in immature myeloid cells; abundant megakaryocytes. Multiple lymphocytic aggregates	Necrotizing lobular pneumonia. Mild generalized lymphocytic infiltration with many immature reticulum cells. Abundant intraepidermal melanocytes with coarsely granular melanin pigment. Abnormally condensed and irregularly distributed pigment of choroid and iris of eyes
Case 3 (M.R.V.)	Homologous atrophy, hyalinization of thymic medulla, no Hassals corpuscles recognized	Diffuse population of small and large lymphocytes and atypical small round cells resembling erythroid precursors. No distinction between cortex and medulla; absence of secondary follicles. Phagocytosis of melanin by histiocytes	Follicular atrophy with hyalinization of secondary follicular remnants. Histiocytic activation in red pulp. Extramedullary hemopoiesis	Unremarkable	Not investigated	Hypercellularity and lymphocytosis (diffuse); maturation arrest of granulopoiesis; sparse megakaryocytes. Granulated histiocytes partly containing melanin clumps	Generalized lymphocytic infiltration with many immature reticulum cells. Bronchitis and bronchopneumonia. Periportal fibrosis and extramedullary hemopoiesis, liver. Abundant epidermal melanin with prominent enlargement of melanin granules. Histiocyte increased in periportal area and sinusoids. Sepsis.

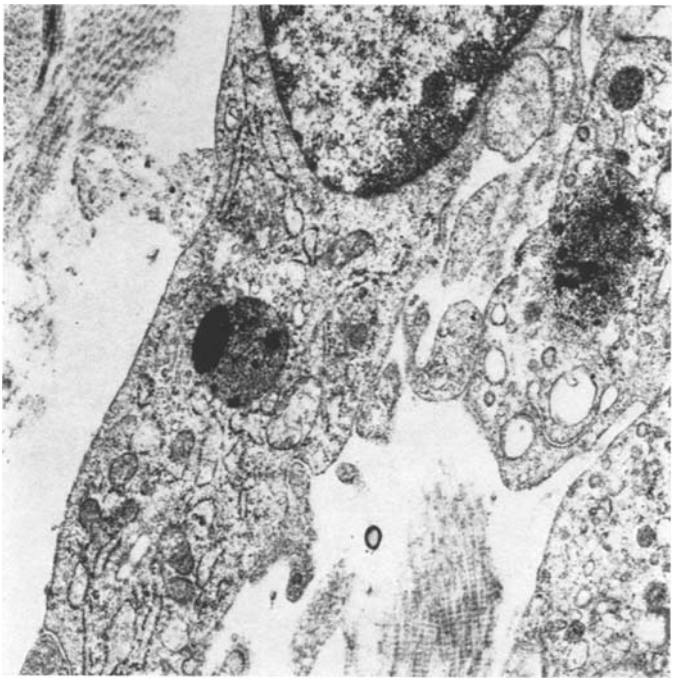

Fig. 1. Histiocytes from a dermal infiltrate of patient N. C. containing a cytoplasmic inclusion and a melanosome (Uranyl acetate, 16800 ×)

There were diffuse and focal aggregates of lymphoid cells cytologically representing small and medium sized lymphocytes, lymphoblasts, and atypical lymphoid reticulum cells. Many of these cells as well as histiocytic reticulum cells contained coarse eosinophilic intracytoplasmic granules, melanin pigment in some instances, and other unidentified granular material. These intracytoplasmic inclusions appeared indicative of SCH. (Fig. 1).

II. Autopsy Materials

1. Organized Lymphoreticular Tissues

a) Thymus. There was a severe atrophy of the thymic medulla with extensive hyalinization in one case. Between these pale pink amorphous hyaline masses, which stained negative for amyloid, only a few small lymphocyte remnants were noted. No epithelial cells or Hassals corpuscles were identified (Fig. 2). The thymic cortex was occupied by an unusually small number of small and medium-sized lymphoid cells and strands of hyalinized material reached into the cortical end. The nuclear chromatin of these cells as judged by light microscopy appeared normal. Many cells had small nucleoli. Their cytoplasm was sparse, and the intracytoplasmic granules noted in other tissues were not seen. The diameter of cortical cells measured 12–14 μ. Mitoses were not seen. There were diffusely distributed small pyknotic nuclei scattered in medulla and cortex. This thymic tissue was

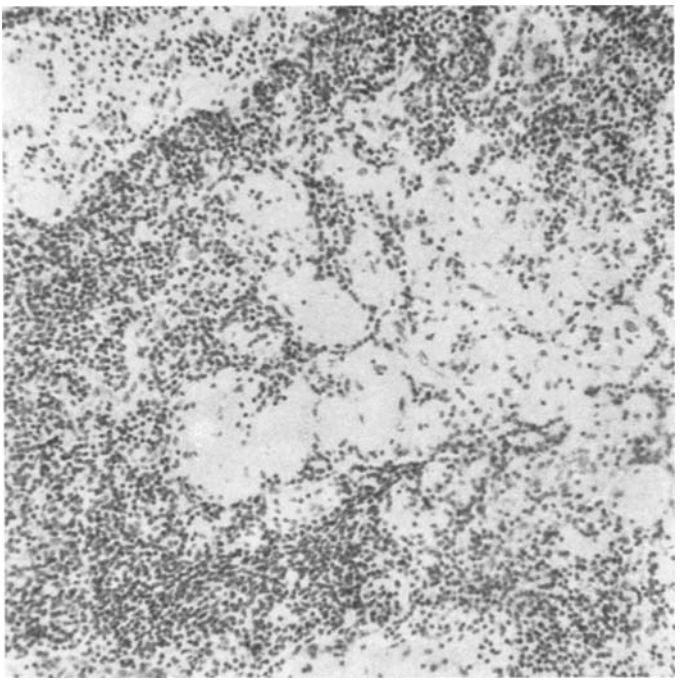

Fig. 2. Thymus of patient S.E.P. treated with prednisone and vincristine. Note atrophy of cortex and medulla, absence of Hassals corpuscles and epithelial cells, and hyalinization of the medulla (H and E, 150 ×)

investigated after cancer chemotherapy with prednisone and vincristine. The thymuses of the other two patients were similar but less extensively changed (see Table).

b) Lymph Nodes. Lymph nodes *before treatment* showed a diffuse increase in lymphoid cells obscuring the differentiation between cortex and medulla. Occasional primary follicles were noted, and some of these were centrally hyalinized. No secondary follicles (germinal centers) were noted. Post capillary venules were coated by a flat inactive endothelium, and the sinus endothelium cells showed a histiocytic differentiation. Lymphoid cells populating the lymph nodes belonged to a small and medium sized lymphocyte with sparse cytoplasm measuring between 10–12 μ in diameter. Their cytologic details are indistinguishable from those of regular lymphocytes when the light microscope is used (Figs. 3, 4). Also no peculiarities were noted by phase contrast microscopy. Occasional plasma cells were seen in the medullary cords. Lymph nodes of all three cases showed moderate erythro- and leucophagocytosis by sinus endothelial cells and histiocytes (Fig. 5). Histiocytes in one case (M.R.V.) in addition markedly ingested melanin pigment. The basic structure of all lymph nodes in all three cases was well preserved despite a mild to moderate infiltration by small lymphocytes of capsule and perinodal tissue.

Treatment with prednisone (8–30 mg/day) and vincristine (2 mg/m²/day) in one case (S.E.P.) was followed by a moderate to marked hypocellularity of lymph

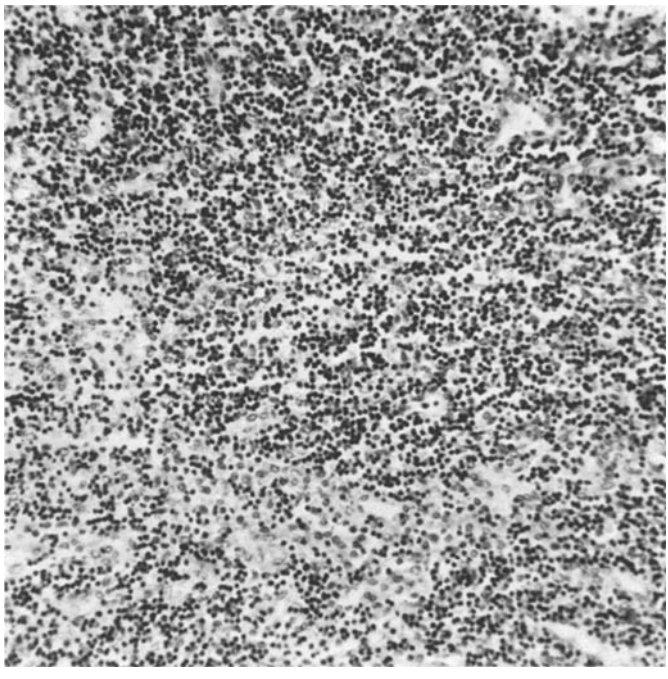

Fig. 3. Lymph node of patient S.E.P. showing a diffuse lymphocytic and histiocytic population and no gross destruction (H and E, 150 ×)

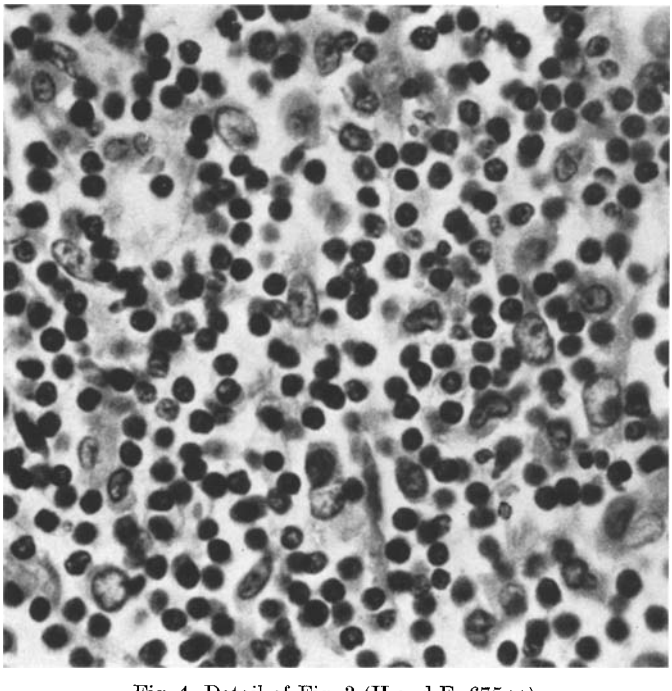

Fig. 4. Detail of Fig. 3 (H and E, 675 ×)

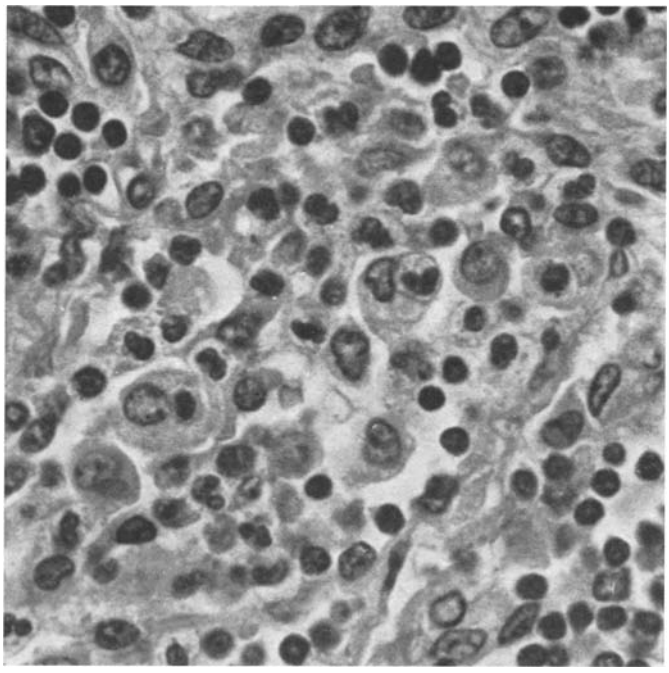

Fig. 5. Lymph node of patient S.E.P. with prednisone and vincristine therapy. Note depletion of small lymphocytes, increase of histiocytes, erythro- and leukophagocytosis (H and E, 675 ×)

nodes, showing a decrease primarily of small lymphocytes. After several courses of therapy, histiocytes were the most prominent cell types showing still active phagocytosis and atypical cytoplasmic granulations (Fig. 6). At autopsy, one patient (S.E.P.) showed focal and diffuse proliferation of atypical lymphoid cells comparable to cases with lymphoma, yet the picture was still not monomorphic (Fig. 7).

c) Spleen. The spleen *without treatment* showed regular primary follicles made up of small and medium sized lymphocytes. Number and size of the follicles appeared normal or slightly reduced. Hyaline foci were present in some follicles at the usual site of secondary follicles. The red pulp appeared hyperplastic and populated by free reticulum cells (Fig. 8) many of which showed obvious histiocytic differentiation and phagocytosis of pigmented granular material. Some of this material gave positive reactions for iron, some for melanin; other pigments were unidentified. The sinuses of the red pulp were well recognizable and coated by unremarkable endothelial cells. In their lumina occasionally free histiocytes showing erythrophagocytosis and leucophagocytosis were noted. Trabecles and capsule were unremarkable. Treatment with cancer *chemotherapy*, as in lymph nodes, led to a cellular depletion affecting primarily small lymphocytes in the follicles. The hyalinized foci in these became more prominent while the follicle size decreased. The red pulp was less affected showing only a moderate decrease of differentiated lymphoid cells. Terminal sepsis in two cases (S.E.P. and M.R.V.)

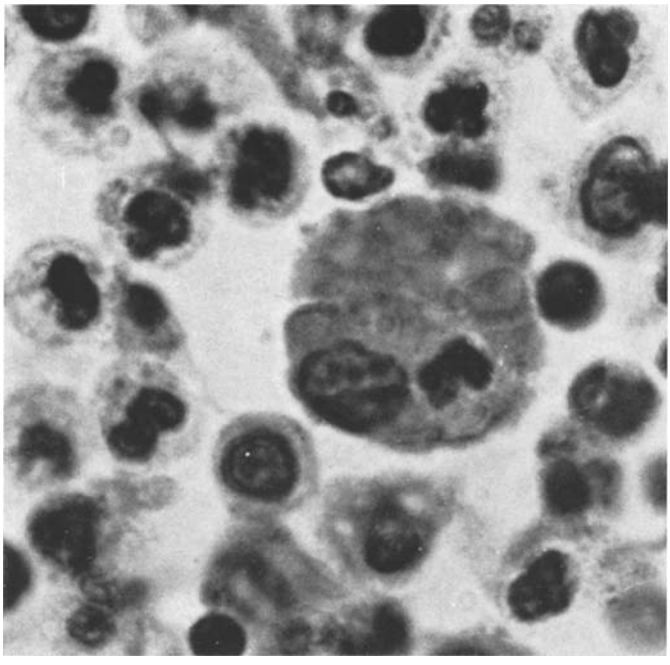

Fig. 6. Lymph node of patient S.E.P. treated with prednisone and vincristine. Development of atypical large histiocytes (H and E, Oil, 1500 ×)

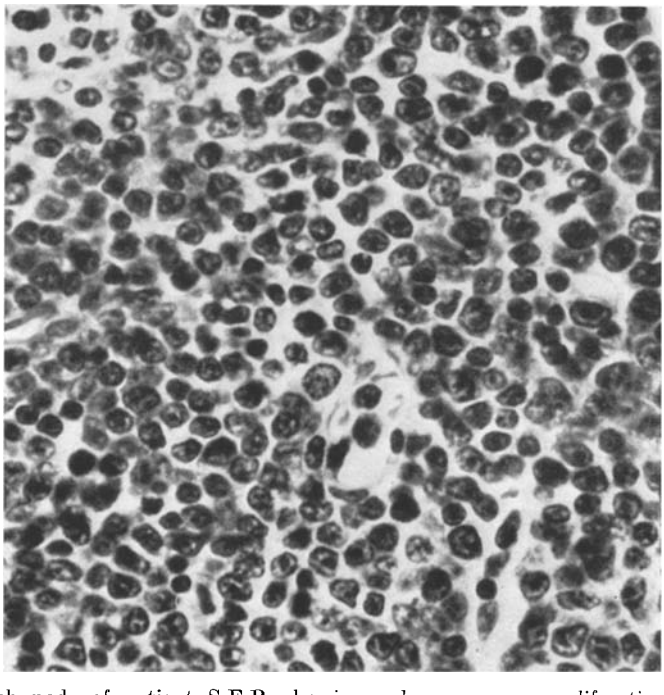

Fig. 7. Lymph node of patient S.E.P. showing a homogeneous proliferation of atypical lymphoid cells after prednisone and vincristine therapy; compare with Fig. 4 (H and E, 675 ×)

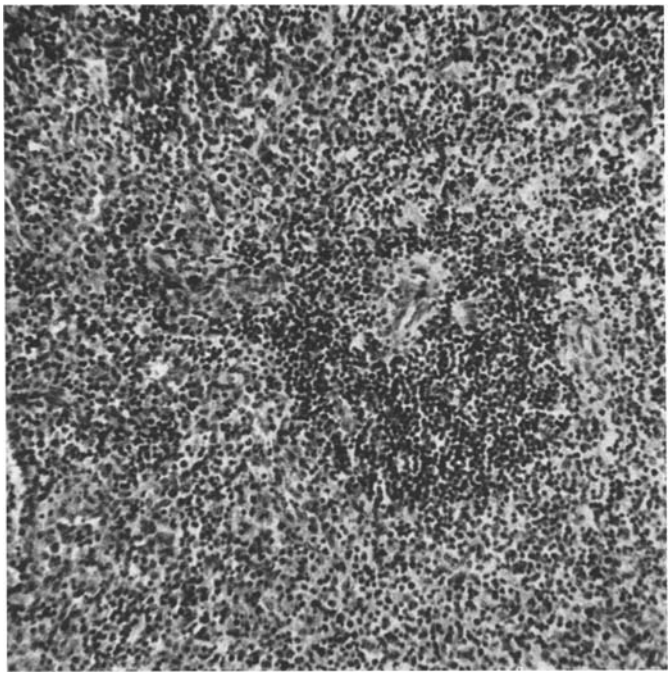

Fig. 8. Spleen of patient S.E.P. showing follicular atrophy and a diffuse lymphocytic and histiocytic population in the red pulp with no gross destruction; compare with Fig. 3 (H and E, 150×)

led to focal necroses which expanded to form geographic patterns (M.R.V.). In this case, depletion of cells in the red pulp also was marked leaving behind nearly exclusively a population of fixed reticulum cells.

d) Peyer's Patches and Tonsils. In *untreated* cases, Peyer's patches were densely populated by small lymphocytes which profusely infiltrated also the surrounding tissue and were most prominently seen in the mucosa and submucosa. Cytological details of these cells were those of normal small lymphocytes. Secondary follicles were not seen. The tonsils were unremarkable except for a very dense population of normal small lymphocytes which also invaded the oral mucosa. No histiocytic hyperplasia or abnormal cytoplasmic inclusions were noted. Chemotherapy led to a depletion of small lymphocytes, but did not affect the structure of these organs otherwise.

2. Diffuse Lymphoreticular Tissues in Other Organs

There was a diffuse lymphoreticular hyperplasia everywhere in the body in all cases which increased with the duration of the disease (i.e. the age of the child) in spite of chemotherapy. Small lymphocytes with admixtures of undifferentiated reticulum cells and histiocytes were seen interstitially in heart, lungs, kidney, pancreas, central and peripheral nervous system, genital organs, endocrine organs, salivary glands, striated muscle, and in the bone marrow. The number of well

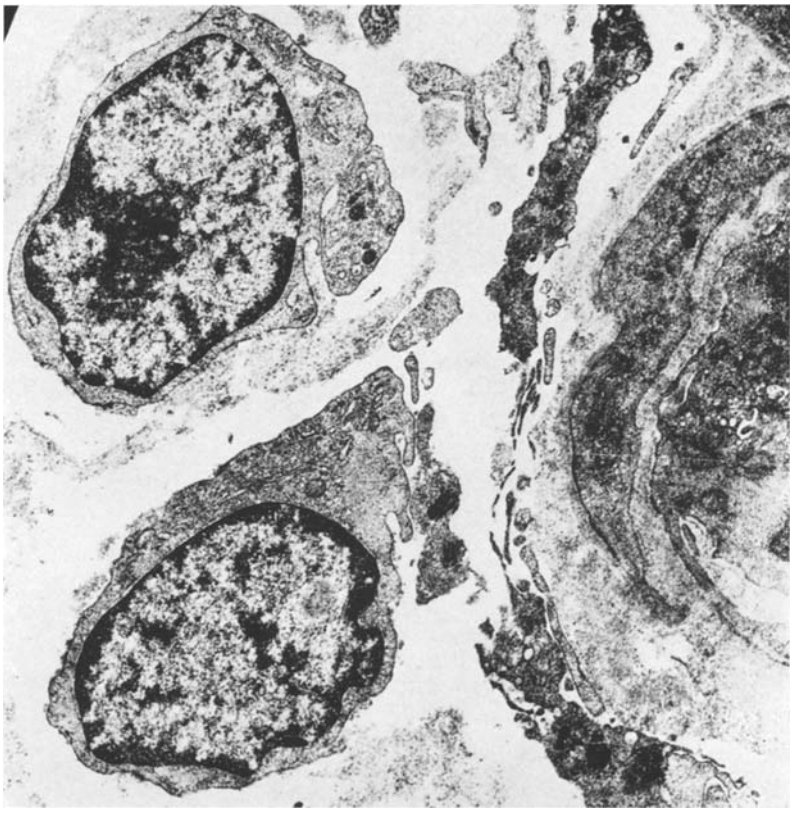

Fig. 9. Two typical lymphoid cells in a dermal infiltrate of patient N.C. representative of the cells observed in untreated patients (Uranyl acetate, 18400 ×)

differentiated histiocytes varied from organ to organ, it was highest, however, in the liver. Here, histiocytes were prominent in periportal areas and sinusoids, varying size up to the one of hepatocytes. Erythro- and leucophagocytosis was noted in all three cases. Infiltrates in endocrine organs and the central and peripheral nervous system consisted mainly of small lymphocytes. Chemotherapy, unlike in lymph nodes and spleen, apparently had no influence on this cell population.

III. Electron Microscopic Findings

Electron microscopic investigations of cellular infiltrates before cancer chemotherapy revealed a mixed population of small and medium sized lymphocytes, reticulum cells and histiocytes. Lymphocytes had the usual round, partially elongated shape, a well outlined cytoplasm with a few mitochondria, occasional lysosomes, and sparse ergastoplasmic structures. Many free unaggregated ribosomes were present in the cytoplasm. The nucleus was round or ovoid with membrane associated nuclear chromatin and inconspicious nucleoli (Fig. 9). Some lymphocytes exhibited deeply indented nuclei (Fig. 10). No elongated profiles

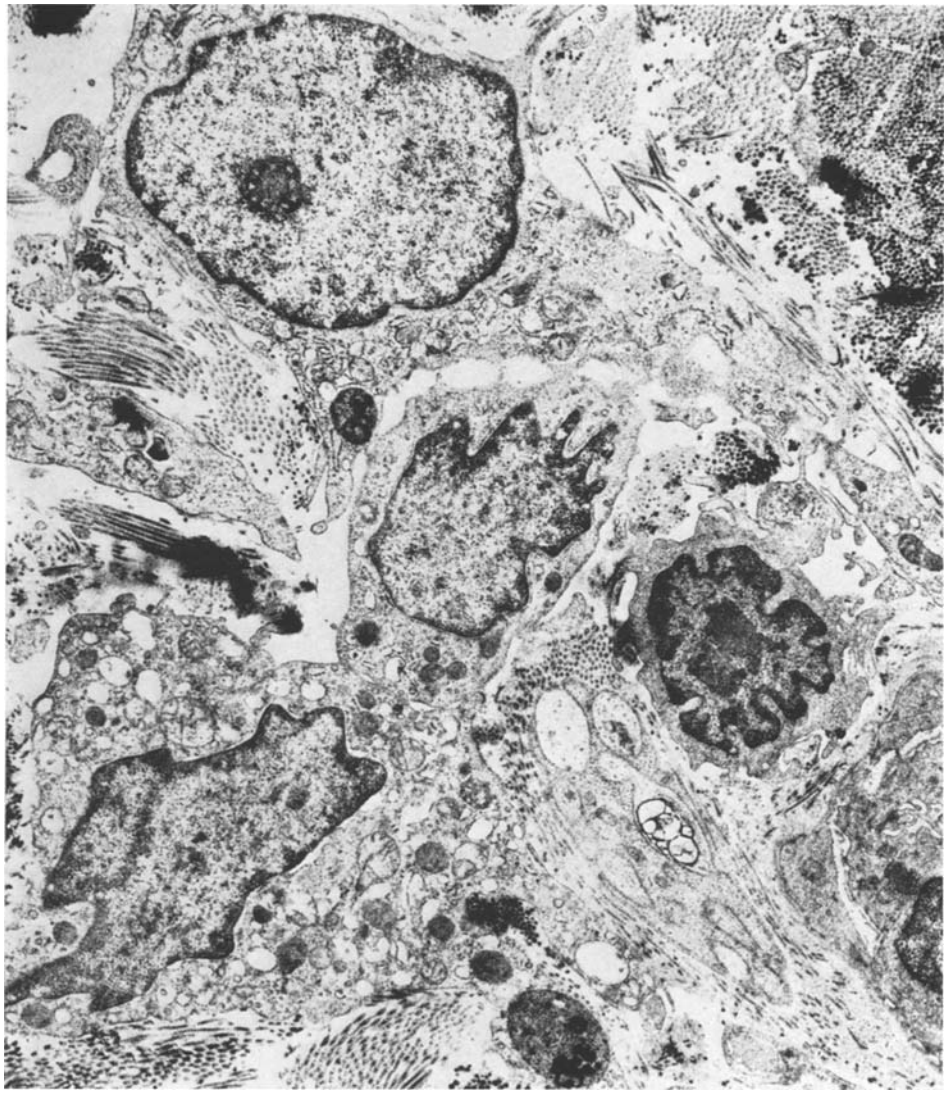

Fig. 10. Lymphocyte with indented nucleus and histiocytes in dermal infiltrate of patient N.C. as noted in untreated patients (Uranyl acetate, 16800 ×)

of endoplasmic reticulum are observed as described for lymphoma cells (Schumacher *et al.*, 1970).

Histiocytes (phagocytic reticulum cells), the second major component of the infiltrates, varied markedly in size and shape measuring up to 20 μ in diameter. The cytoplasm, showing sometimes many pseudopod-like extensions, contained a prominent Golgi apparatus, mitochondria, lysosomes and sometimes cystically dilated smooth endoplasmic reticulum. Phagosomes often contained coarse elec-

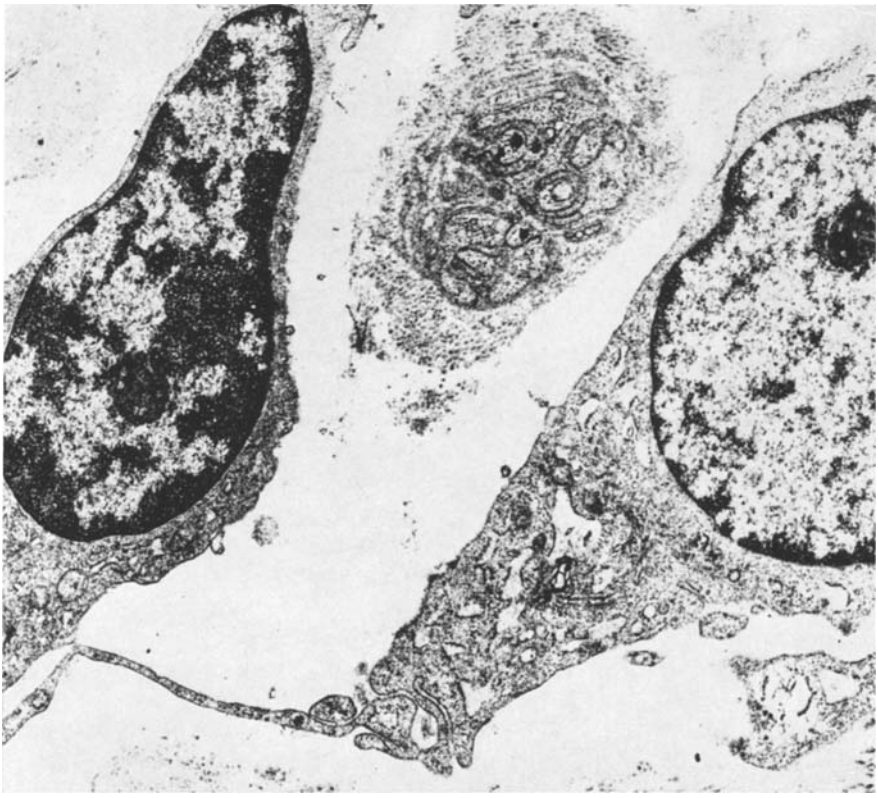

Fig. 11. Lymphocyte and histiocyte in subcutaneous infiltrate of patient N.C. of regular appearance (uranyl acetate, 18400 ×)

tron dense material (Figs. 1, 11). Nuclei usually were round with a loose marginated chromatin and round prominent nucleoli.

Besides these cells, long branching, non-phagocytic reticulum cells were noted. Cells interpreted by light microscopy as lymphoblasts or atypical lymphoid reticulum cells showed a structure intermediate between lymphocyte and histiocytic reticulum cell (phagocytic reticulum cell) differing from the latter by less active phagocytosis, increased cytoplasmic ribosomes and more densely clumped nuclear chromatin.

No lymphoma cells meeting the morphological criteria described by Mori and Lennert (1969) were noted.

Discussion

As already indicated, alterations in the architecture of lymphoreticular tissues in Steinbrinck-Chediak-Higashi syndrome were mentioned previously by several authors (Bedoya *et al.*, 1969; Page *et al.*, 1962). There is a tendency to classify these lesions as lymphoproliferative disorders or neoplasias and to treat the patients as if they had lymphomas (see our case S.E.P.). Our study did indeed

reveal an extensive generalized hyperplasia of organized and diffuse lymphoreticular tissues. Cells participating in this proliferative process belonged to several series such as reticulum cells, histiocytes, lymphocytes and sinus endothelial cells, showing varying degrees of differentiation. Also, the bone marrow appeared hyperplastic with maturation arrest leading to peripheral leukopenia in some cases. Despite lymphoid cells tending to invade tissues surrounding organized lymphoreticular structures, the general pattern of lymphoreticular tissues was well preserved, showing the typical reticular network, differentiation into cortex and medulla of lymph nodes, postcapillary venules and paracortical lymphocyte aggregates, and red and white pulp of spleen. This pattern did not change except after advanced chemotherapy. From an interpretation of these morphological changes, lymphoreticular hyperplasia appeared rather to be reactive in nature than neoplastic. Similar lesions in humans and in experimental animals were described following cancer chemotherapy (Krüger, 1970; Krüger *et al.*, 1971; Gross 1964; Krüger *et al.*, 1971a) and in some cases the term "polyblastic reticulosis" was used to describe their indefinite nature. Some features of hyperplastic lymph nodes in SCH are similar in some aspects to changes observed in human rheumatoid disease except that follicular hyperplasia is not prominent in SCH. Also, hyperplasia of lymphoreticular tissues which eventually leads to lymphoma is described in Sjögren's syndrome (Talal *et al.*, 1967). Besides lesions representing probable SCH in animals like the Gray Collie Syndrome (Windhorst *et al.*, 1968), the Aleutian Mink Disease (Helmboldt *et al.*, 1965), or similar disease in cattle (Padgett *et al.*, 1964), or in mice (Bennett *et al.*, 1969), atypical reactive lymphoreticular hyperplasias were seen in humans and different experimental models (Krüger, 1970; Gillman and Gillman, 1949; Uher, 1961; Gerhartz, 1963; Krüger 1971b). Common in all of these lesions, as in our cases of untreated SCH, is that a variety of different cell lines are participating in the proliferation; this contrasts to the finding in lymphomas where, with the exception of Hodgkin's disease, proliferating cells represent a more uniform cell population.

It has been theorized at other places that impaired antigen processing (lysosomal deficit) or impaired antigen neutralization and resulting prolonged antigen stimulation may support cell proliferation in lymphoreticular tissues (Krüger, 1970). Experimental evidence (Krüger, 1970a; Krüger *et al.*, 1971), as well as lymphoreticular hyperplasia and lymphomas observed in human immunodeficiency syndromes (Ten Bensel *et al.*, 1966; Peterson *et al.*, 1964) support this assumption. Defectiveness of the immune response in patients with SCH has not yet been demonstrated (Padgett *et al.*, 1970). Treatment with chemotherapeutic agents, many of which are immunosuppressants, alters the lymphoreticular hyperplasia by depletion of well differentiated cells (Aisenberg, 1971; Krüger, 1971c), except for sinus endothelial cells and histiocytes. The appearance of lymphoreticular tissues becomes more uniform and similar therefore to neoplasia: the similarity is even more pronounced by appearance of chemotherapeutically induced atypical cells.

Furthermore, it has been claimed that cancer chemotherapeutic agents perhaps also may act as carcinogens (Schmähl, 1970). It is the impression from our morphologic study, therefore, that in SCH syndrome, lympho-reticular changes at the beginning are reactive in nature rather than neoplastic. This reaction may

be caused by a lysosomal deficit leading to accumulation of materials including antigens in tissues and cells. The extensive compensatory participation of actively phagocytizing histiocytes may support this idea. Lymphoid cells, stimulated to proliferate by the persistent phagocytized but not adequately broken down antigenic material, may add to the pool of potential phagocytic cells (Pearsall and Weiser, 1970; Noltenius *et al.*, 1969), which, however, due to a genetic defect remain inefficient. This may explain a progressive cell proliferation of non-neoplastic nature.

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