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FROM THE DEPARTMENT OF DERMATOLOGY, HEAD: PROF. TAUNO PUTKONEN, M.D.
AND FROM THE DEPARTMENT OF PATHOLOGY, SECTION II,
HEAD: PROF. HARALD TEIR, M.D., UNIVERSITY OF HELSINKI

RETICULAR NETWORK AND KARYOMETRIC PROPERTIES OF LYMPHOMAS OF THE SKIN

BY

KATRI REHTIJÄRVI

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PREFACE

The present investigation was carried out during the period 1959 to 1962. The series consists of cases which I myself have had the opportunity to examine and follow for an even longer period, i.e. from 1952 on, that is to say ten years.

It was Professor Harald Teir who suggested that I should undertake this work and he also placed at my disposal the laboratory facilities of Section II of the Department of Pathology, Helsinki University.

I am greatly indebted to Professor Teir for his encouragement and support at all stages of this work. He it was who initiated me into the problems of cytology and karyometry, and his guidance was consistent and critical.

I am likewise greatly indebted to Professor Tauno Putkonen, who aided my work in many ways, both in his capacity as Chief of the Department of Dermatology, Helsinki University Central Hospital, and by tendering advice and criticism.

My sincere thanks are due to Mrs. Carmen Hopea and the entire laboratory staff of the Department of Pathology for the preparation and staining of the histologic specimens.

In particular I wish to thank Mr. Paavo Korhonen, of the Photographic Department of Helsinki University, for the expert assistance he gave me in photographing the histologic material, Mr. Risto Collan, M.B., Ch.B., for carrying out the tedious karyometric work and Mr. Pentti Kerola, M.A., for the statistical treatment of the results.

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Katri Rehtijärvi

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I. INTRODUCTION AND REVIEW OF THE LITERATURE

1. LYMPHOMAS

Lymphoma is the term applied in the U.S.A. to tumors and tumor-like conditions of the lymphoreticular tissue. Under this heading are included mycosis fungoides, Hodgkin's disease, lymphoreticular sarcomas and sarcomatosis, and leukemic infiltrations. Despite its benign nature, lymphadenosis cutis benigna, or follicular lymphoma of the skin, is also often referred to this group of diseases.

The earliest mention of a disease in the group of true malignant lymphomas relates to mycosis fungoides, whose classical features were described by Alibert as long ago as 1806. Hodgkin's disease has been known since 1832. Lymphosarcoma was described as a distinct entity by Kundrat in 1893. Its follicular form has been recognized since 1927, when Brill et al. and Symmers described it under the name of giant follicular hyperplasia. Leukemic skin infiltrations in patients suffering from lymphatic leukemia were first described by Biasiadecki in 1876, and Schilling and Reschad distinguished monocytic leukemia as a separate form in 1913.

Keim is credited with recocnizing that the disorders in question represented a group of diseases of the same system and, in 1929, called this group lymphoblastoma. A constant finding in these diseases, which vary greatly as to their clinical picture, was a cell type of the so-called lymphocytic series.

The etiology of the lymphomas is unknown. Whether they are tumors or due to infection is the question which has long led to contention concerning all the diseases included in this group. From time to time the dispute has been lively, mycosis fungoides especially being subject debate. Paltauf and Zumbusch (1913), Ormsby (1934) and Niethammer (1940), for instance, argued in favor of the infection theory, whilst Fraser (1925), Warthin (1931) and Winer (1947 a) and others supported the neoplasm theory. The modern American attitude is that lymphomas are malignant tumors. The German standpoint, represented by Gans and Steigleder (1957) and Gottron (1960), accepts as malignant tumors only sarcomas of the lymphatic tissue metastasizing to the lymph nodes. However, the tumor theory is evidently gaining ground all over the world.

The diseases of the lymphoma group are all rare. At the Department of Pathology of Michigan University their total frequency in patho-anatomic specimens was according to Warthin (1931), 506/100,000, or 0.5 per cent. In autopsy series the frequency of leukemia was 0.62—0.86 per cent, according to Custer (1948), a figure

that he considered more reliable than the incidence given for clinical series. Hodgkin's disease and lymphatic leukemia are the commonest. In Gall and Mallory's (1942) series of 680 lymphoma patients these two diseases together constituted about one half of all cases. Of the rates of incidence of the various types of leukemia, Winer's (1947 b) series of 455 leukemia patients should be mentioned, in which lymphatic leukemia occurred in 28 per cent, monocytic in 1.5 per cent and granulocytic leukemia in 70.5 per cent of cases. In Rosenthal and Harris' (1935) series of 600 leukemia patients 27 per cent had lymphatic, 1.9 per cent monocytic, and 71.1 per cent granulocytic leukemia.

Our clinical knowledge of the diseases of the lymphoma group is founded on an extensive medical literature, a large part of which consists of case reports. The continuous reporting of cases is partly due to the fact that these are rare and partly to the great variations in the clinical picture. Almost every individual case of lymphoma represents a type of its own, a fact commented upon by many authors. There are several thousands of cases reported. In his works »Cutaneous manifestations of malignant lymphomas» (1959) and »Leukemia cutis» (1960), Bluefarb surveyed this extensive literature.

Diseases of the lymphoma group have a greater predilection for men than for women. Of Gerwig's (1928) 602 patients with mycosis fungoides, 62 per cent were men. Of Heite's and Socha's (1951) own series of 15 patients and of 704 cases collected by them from the literature, 57 per cent were men. In Bluefarb's (1959) series, the preponderance of men with the d'emblee and erythroderma forms was more marked, 75 and 91 per cent respectively. For Hodgkin's disease the ratio of men to women was 1.4 : 1 in Sugerbaker and Craver's series (1940), and 2.5 : 1 in Harris's series. According to Winer (1947 b), leukemia is twice as common in men as in women. In lymphosarcoma and reticulum cell sarcoma the ratio of men to women is 7 : 3, according to Sugerbaker and Craver (1940). Harris, on the other hand, states that the reticulum cell type shows no predisposition for either sex.

The diseases belonging to the lymphoma group are primarily diseases of middle age.

According to the above authors, the average age of onset of mycosis fungoides is 45 years, the majority of the patients falling into the age groups 40 to 60 years. The disease is found in all adult age groups and only in exceptional cases has it been diagnosed in a child.

The average age of onset of lymphosarcoma and reticulum cell sarcoma is likewise 45 years. This disease is rarely found in young persons or after the age of 70.

The great majority of patients with leukemia are 40 years old at the onset of the disease. However, this disease may occur at any age.

In Hodgkin's disease the average age of onset is 30 years only. The disease has been observed in all age groups and often in children.

In all diseases belonging to the lymphoma group an acute form rapidly leading to death is known. An acute course of the disease is most frequently encountered among patients with granulocytic and monocytic leukemias, according to Winer (1947 b) in about one half of cases.

The duration of the disease from the point of view of life expectancy varies in mycosis fungoides. The premycotic stage may last for years. Patients at the tumor stage die, on average, within 5 to 10 years. There are cases on record, however, in which the patient lived longer, over 30 years even (Heite and Socha 1951). According to Bluefarb (1959), the duration of the disease in its d'emblee form may be some weeks or months only.

Hodgkin's disease occurs in three forms, each having a different prognosis. Paragranuloma is the most benign form of the disease (Jackson 1937, Lumb 1957). Its histologic picture shows lymphoid hyperplasia and Sternberg-Reed cells. This form has sometimes remained unchanged for as long as 20 years. However, in the 6 cases of paragranuloma reported by Harrison (1952), the duration of the disease was only 7 to 8 years. A paragranuloma may progress to Hodgkin's granuloma, which is the commonest form of the disease. The average duration of the disease in this form is, according to Jackson, 2.5 years. The histologic picture shows, besides Sternberg-Reed cells, eosinophilia, necrosis and fibrosis. The third variety is the highly malignant Hodgkin's sarcoma, in which the cell infiltration is composed of large tumor cells.

In leukemias the average time of survival is, according to Custer (1948), half a year or more in the acute varieties and in the chronic varieties one year or more. In lymphatic leukemia, however, more chronic and more benign varieties have been observed in old persons, and in these the duration of the disease may be several years (Engelbreth—Holm 1954, among others). The time of survival of patients with aleukemic leukemia of the skin is also often longer and moreover these varieties often remain undiagnosed for long periods.

All diseases belonging to the lymphoma group are malignant and lead to death sooner or later. The conditions gradually become more malignant, a sign of this progress being the formation of ever less mature cells. At re-examination Gall and Mallory's (1942) series showed a change towards poorer differentiation in 23 per cent of cases.

As the disease progresses, the cell picture in mycosis fungoides becomes more monomorphic, resembling sarcoma. In Herzberg and Überscher's (1951) opinion, this represents a change in the degree of malignancy. Peiser and Brandenburg (1959) also observed that in far-advanced mycosis fungoides different stages of development occur simultaneously, »Stufen der Malignität».

The most benign variety of Hodgkin's disease, paragranuloma, may progress to Hodgkin's granuloma, which may further develop into Hodgkin's sarcoma (Evans 1956, Jackson and Parker).

In the course of time follicular lymphoma loses its follicular character. A change towards better differentation never occurs (Symmers 1942, Rappaport et al. 1956).

Cutaneous symptoms may be observed in all forms of lymphoma, sometimes regularly, sometimes more rarely. Each type of lymphoma may begin with cutaneous symptoms and occasionally these constitute the only manifestation of the disease. This brings these diseases within the realm of dermatology.

The cutaneous manifestations, which have a specific histologic picture, comprise

papular lesions, infiltrations or plaques, nodules or tumors, ulcerative lesions or extensive ulcerations. Erythroderma, which exhibits a specific histology, has been observed in all forms of lymphoma and non-specific exfoliative dermatitis also occurs in connection with various types of lymphoma. The skin lesions are cutaneous and subcutaneous.

In the skin lesions the histopathologic changes consist of proliferation of reticular tissue which is immature and varies as to its degree of differentiation. This proliferation originates around the arterioles and adnexa of the skin and between the fat cells of the subcutaneous tissue. In different varieties of the disease the cell infiltrations have characteristics of their own. In different areas of the same tumor, tissue in different stages of differentiation may occasionally be found. In mycosis fungoides and in Hodgkin's disease these infiltrations are polymorphic, containing inflammatory cells also. The leukemic infiltrations are monomorphic, containing one type of cell.

Lesions of the mucous membrane are rare but, according to Bluefarb (1959), such lesions have been reported in most types of lymphomas. Lesions of the internal organs are of frequent occurrence. They are autochthonous. In sarcoma, metastases to the lymph glands and internal organs are not infrequent.

In lymphoma patients the formation of antibodies is often reduced, which results in an increased susceptibility to infection.

Reed (1904) was the first to observe a negative tuberculin reaction in patients with Hodgkin's disease. Many other authors have subsequently made similar observations.

Increased attention has recently been paid to the various changes in the serum albumin fractions sometimes observed even at an early stage of lymphoma (Amorati et al. 1951, Knoth 1958, among others).

All these observations indicate involvement of the reticuloendothelial system.

Lymphadenosis cutis benigna or follicular lymphoma of the skin constitutes an exception to the lymphomas described in the foregoing. It is benign and does not result in death, as do the other lymphomas. In contrast to what has been established with regard to the other lymphomas, it is two to three times more frequent in women than in men and no particular age disposition is known. The disease presents with skin manifestations which are localized or disseminated. Spontaneous involution is not infrequent. Trauma, pruritus, insect bite, and eruption caused by sunshine have been reported as causative factors (Bäfverstedt 1943, Bluefarb 1960). Follicular lymphoma of the skin may also be associated with traumatic scars, with the cutaneous changes of acrodermatitis atrophicans, etc. The heterogenous external factors are, according to Bluefarb (1960), factors contributing to the occurrence of the disease but they do not explain its disseminated nature.

2. CLASSIFICATION OF LYMPHOMAS

The great diversity of the tumors and tumor-like conditions originating in the lymphatic tissue have given rise to a multitude of classifications and synonyms.

The German literature treats mycosis fungoides, Hodgkin's disease, sarcomas of the lymphoid tissue and skin leukemias as separate diseases. They are not classed together under any common heading. A disease called reticulosis is likewise considered to be a separate entity. This term is chiefly used for progressive proliferation of the reticular tissue, for which Gottron (1960) uses the name »Retikulosen in engerem Sinne». The corresponding term of Gans and Steigleder (1957) is reticulosarcomatosis, while the synonym used in the Anglo-Saxon literature is reticuloendotheliosis.

Gottron (1960) defined his term »Retikulosen in engerem Sinne» as follows: »independent, cellular and irreversible proliferations in the reticular system. In the developing cell series there is polymorphism which is due to poor differentiation of the cells and which cannot be considered a sign of malignancy. The foci arise autochthonically and! not as true metastases». In Gottron's opinion, the first case described in the literature is Schilling and Reschad's case reported in 1913, in which, besides the cutaneous manifestations which are to be interpreted as reticulosis, monocytic leukemia was described for the first time.

Robb-Smith's (1938) classification, adopted for use in the Anglo-Saxon literature, distinguishes between 12 diseases of the reticular tissue, among them such more benign disorders as sarcoidosis and storage reticulum cell reticuloses.

Bluefarb (1960) suggested a classification of the diseases of the reticuloendothelial tissue into five groups:

1. inflammatory and infectious hyperplasia,
2. granulomatous reticulosis,
3. cutaneous leukemia,
4. malignant lymphomas and
5. Kaposi's sarcoma.

He referred mycosis fungoides, Hodgkin's disease and lymphosarcoma to the malignant lymphomas.

Lever (1949) adopted a classification based on Gall and Mallory's suggestion. According to the latter authors, lymphomas are malignant tumors originating in the lymphoid tissue as multiple foci. The group comprises the following seven diseases:

1. stem cell lymphoma
2. reticulum cell lymphoma
3. lymphoblastic lymphoma
4. lymphocytic lymphoma
5. follicular lymphoma
6. Hodgkin's disease
7. mycosis fungoides

In this classification attention has mainly been paid to the predominant cell type. This grouping, as Gall and Mallory (1942) pointed out, is also justified from the clinical angle, since the prognosis with regard to longevity is different in the different conditions.

Steigleder and Hunscha (1958) criticized a classification based on the predominant cell type. They pointed out that the infiltrating tissue is not always monomorphic,

neither is the cell picture constant. To define the cells is sometimes difficult and the many denominations used by different authors for the same cells are confusing.

In his investigation »Reticular tissue in laboratory mice», Dunn (1954) encountered the same difficulties in classifying tumors of the reticular tissue of experimental animals. There are border cases and intermediate forms. The only possible starting point in the classification of tumors is the normal cells in which the tumors originate. Tumors of the reticular tissue of mice may originate from the following cells: stem cell, granulocyte, reticulocyte, lymphocyte and plasma cell.

There is the same consistency in Rappaport's (1956) correction of the lymphoma classification. He distinguished between two types of lymphocytic lymphoma, one well differentiated and the other poorly differentiated. The reticulum cell lymphoma is likewise classified into two groups, well differentiated and poorly differentiated. Rappaport does not consider follicular lymphoma to be a separate form and according to him the word follicularis or nodularis should, when necessary, be added to the terms lymphocytic lymphoma and reticulocytic lymphoma. A lymphoma exhibiting both lymphocytic and reticulocytic cell infiltration is said to be of mixed type.

In the present investigation I have adopted a classification of lymphomas based on the predominant cell type. Lymphocytic and reticulocytic lymphomas are divided, in accordance with Rappaport's classification, into well differentiated and poorly differentiated types. For subdivision, the terms localized, generalized and systemic have been used.

At the initial stage of the disease a localized lesion may be observed in all types of lymphoma, since the tendency towards autochthonous multiple disease foci may remain latent for a long period. Skin lesions may likewise constitute the only manifestation of the disease in such conditions as leukemia cutis or specific erythrodermas. Cases in which changes occurred in the peripheral blood and in the blood-forming organs were placed in the systemic group.

Hodgkin's disease and mycosis fungoides form a polymorphic type group of their own.

Stem cell lymphoma is rare in man. Both granulocytic and monocytic and lymphocytic leukemia, however, may begin as leukemia cutis, in which stem cells occur. In such cases the infiltrating cells are of the same nondifferentiated type. The predominant cell is an undifferentiated »blast» cell that cannot be more exactly characterized. In the course of time differentiation takes place (Friedman and Leithold 1960).

In the literature, stem cell lymphoma and reticulosarcomatosis are used as synonyms as well. In such instances these terms refer to tumors in which the stage of differentiation of the reticulum cell varies in different parts of the tumor and in which there occur poorly differentiated areas, i.e. areas containing stem cells. In the present investigation such a lymphoma is referred to the group »reticulum cell lymphoma, poorly differentiated». Stem cell lymphoma is placed in a group on its own and by this term leukemia cutis with stem cells is understood.

Lymphadenosis cutis benigna (follicular lymphoma of the skin, lymphocytoma) has been considered a form of benign reticular hyperplasia and is not included in the group of lymphomas.

The classification of lymphomas adopted in the present investigation and the commonest synonyms are given below:

I *Lymphoma lymphocyticum*

1. Well differentiated
   generalized (leukemia cutis, lymphocytic type);
   systemic (lymphocytic leukemia)
2. Poorly differentiated
   localized (lymphosarcoma, round cell sarcoma);
   generalized (lymphosarcomatosis, aleukemic reticulosis, lymphoblastic lymphoma).

II *Lymphoma reticulocyticum*

1. Well differentiated
   generalized (leukemia cutis, monocytic type);
   systemic (monocytic leukemia)
2. Poorly differentiated
   localized (reticulum cell sarcoma, polymorphic cell sarcoma, retothelial sarcoma);
   generalized (reticulosarcomatosis, reticuloendotheliosis, stem cell lymphoma).

III *Lymphoma polymorphicum*

1. Hodgkin's disease (lymphogranulomatosis maligna)
2. Mycosis fungoides.

IV *Lymphoma nondifferentum*

Stem cell type
   generalized (leukemia cutis, stem cell type).

3. RETICULAR TISSUE OF THE SKIN

Marshall (1956) defined reticular tissue as follows: »a tissue composed of fixed cells (primitive reticular cells) supported on a framework of fibrils and including all cells in the body derived from this tissue». Reticular tissue occurs in the lymph nodes, the thymus, the bone marrow and the spleen, which are permanent centers of this tissue, and as tissue elements scattered throughout the body; the latter include the primitive reticulum cells in the adventitia of the blood vessels, the histiocytes of the connective tissue and the cells of the peripheral blood.

The functions of the reticular tissue have been stated to include the blood formation, phagocytosis, the formation of antibodies and, in the process of wound healing, the formation of reticulin fibers and fibrotic tissue.

The connective tissue of the embryo is at first composed of spindle-shaped primitive reticulum cells. The first fibers to develop in this tissue are reticulin fibers. The formation of fibers begins in the embryo at about three months. The collagenous and elastic fibers of the skin develop later (Montagna 1956).

The reticulin fiber system is a normal component of connective tissue throughout the body. The parenchymal cells of the lungs, the liver and the kidneys are situated in the network formed by these reticulin fibers. The meshes of the net can be seen in the openings between the lobuli and around these organs. Reticulin fibers form part of the glandular connective tissue and in adipose tissue they surround the fatty cells. In the hematopoietic organs the new cells develop in the meshes of the reticular network (Maximov and Bloom 1950).

Mall and Siegfried studied the chemical properties of the fiber substance, to which they applied the term reticulin. Reticulin is a fibrillary substance which is chemically closely related to collagen but differs from it in certain respects, e.g. in its staining with silver salts. The physical and chemical properties of reticulin and collagen are very similar and many researchers consider reticulin to be a precollagen (Mallory and Parker 1927, Dublin 1946 and Fresen 1953, among others).

In wound healing reticulin fibers first appear and subsequently develop into collagenous fibers. Reticulin fibers often unite and continue directly as collagenous fibers.

In their electron microscope investigations, Herrath and Dettmer (1953) found that the reticulin fibers exhibited the same periodicity as the collagenous fibers. When the fibers stain with silver salts, the silver granules lie close to the outer fiber surface. The fibers vary in thickness, the thickest being composed of a bundle of several fibrils. The individual fibrils never branch but the bundles divide and become fibers of the network.

According to Maximov (1927), the reticulin fibers are intimately related to the reticulum cells. The elongations of the reticulum cells are thin cytoplasmic processes which, veil-like, stretch to the fibers of the reticulin network, and fibers are also seen within the cytoplasm. Herrath and Dettmer (1953) also observed a plasmatic bridge between the reticulum cells and the reticular fibers and believed that these cells gave rise to the fibers.

In normal skin the reticular tissue occurs as small islets perivascularly and surrounding the hair follicles, sweat glands and sebaceous glands. It is composed of a sparse cell infiltration in which there are primitive reticulum cells, histiocytes, fibroblasts and mast cells. These are situated in the delicate supporting network of reticulin fibers described by Homma (1922). In the uppermost layer of the dermis there is furthermore a dense network of reticulin fibers, a component of the basal membrane. The junction between the corium and the epidermis is strengthened by the short fibers demonstrated by Szodorey (1931), which extend between the basal cells.

In response to various stimuli in pathologic conditions the primitive reticulum cell in the vascular adventitia may begin to proliferate, whereupon the reticular tissue in the skin increases. Since Maximov's (1932) investigation, this opinion has gained universal acceptance. From the primitive reticulum cell, to use Hadfield and Harrison's (1953) expression, those reactive and fertile »blast» cells which proliferate and differentiate, develop to form in the skin a tissue which corresponds, both genetically and functionally, to the reticuloendothelial tissue.

Inflammatory cell infiltrations are part of the histopathologic picture of all infections and inflammations. The changes in the reticular network in these conditions have been little studied. However, Zurhelle (1922) observed that in syphilitic lesions of various stages and in some other chronic infections the reticulin fiber network developed but that in acute suppurative inflammations and in keloids the fibers were absent.

Way and Klovekorn (1926) also found that the fiber network increased in various infections and inflammations. The network was proportional to the cellular infiltration. In the tricophytin reaction they found that the network was already present after 48 hours. Way (1947) demonstrated that a reticulin fiber network does not occur in primary degenerative lesions, amyloid degeneration, myxedema or scleroderma.

Knoth (1957, 1958) investigated a large number of different inflammatory dermatoses and found that the reticulin fibers always increased concurrently with the reticulohistiocytic cell proliferation. In his view, moreover, a small amount of reticulohistiocytic cells, which are necessary for the formation of the network, is always present in a lymphocytic infiltration.

Frenk (1961) investigated the reticulin fiber network in histiocytomas and fibromas. In histiocytomas, which are rich in cells and contain a multitude of phagocytic cells, the connective tissue network was well developed, while in fibromas, which are poorer in cells, collagenous fibers were found.

The supporting network of lymphomas is composed of reticulin fibers alone, collagenous and elastic fibers being entirely absent. Foot and Day (1925) demonstrated that the network was present in tumors of the lymph nodes and in Hodgkin's disease and that it penetrated with the tumor cells through the glandular capsule. Zurhelle (1922), Way and Klovekorn (1926) were the first to report the presence of the supporting network in mycosis fungoides.

In the numerous case reports on diseases belonging to the lymphoma group the presence of argyrophil fibers between the tumor cells has often been adduced in support of the diagnosis. Gottron (1960) stressed the importance of Knoth's investigation in this respect, Knoth (1957) having demonstrated that the network occurs in all reticulohistiocytic proliferations and not in lymphomas alone.

In a biopsy series of 305 glandular tumors chiefly comprising Hodgkin's disease, lymphosarcoma and reticulum cell sarcoma, Mackenzie (1959) found that the quantity of reticulin fibers varied in different parts of the same tumor, an increase or decrease of the reticulin being readily visible. In these cases demonstration of the fibers was of definite but limited value in the diagnoses.

In all these investigations greater attention has been paid to the presence and quantity of reticulin fibers than to the structure of the network they form. The behavior of the reticular network in various types of lymphoma and inflammations of the skin has not been studied closely. Textbooks and manuals contain only scattered short references to the subject. Illustrations depicting the supporting network of normal skin, inflammations and lymphomas are likewise omitted from the textbooks on histology.

4. KARYOMETRIC PROPERTIES AS A CRITERION OF MALIGNANT GROWTH

Heidenhain (1907) and Jacobj (1925) defined the laws governing the growth of tissues. When a cell divides mitotically, two daughter cells arise. The smallest vital particle which has the power of division was called by Heidenhain the protomere. Of these protomeres each cell contains a constant quantity which is redoubled when the cell divides. Jacobj investigated normal tissues, measuring a large number of nuclei (1000 cells) and dividing them into nuclear classes. He called the smallest nuclear size the »Grundklasse», the most frequent nuclear size being the »Regelkernklasse». The ratio of the sizes of the different nuclear classes was 1 : 2 : 4 : 8. Hertwig (1932) found that the relation between the nucleus and the plasma remained constant. Accordingly, the increase in volume during growth is determined beforehand. Such growth according to definite laws is called rhythmic growth.

Classes of nuclei temporarily larger than normal have sometimes been found in the organism. Clara (1930) and Arndt (1935), for instance, observed an increase in nuclear size in cirrhosis of the liver. Teir (1944) pointed out that in the outer orbital gland of the white rat, under the membrane, and possibly as the result of pressure, larger nuclear classes are to be found. By cutting the outer orbital gland and its surroundings with scissors Järvi and Teir (1951) attempted to change the nuclear classes experimentally. The scar tissue, however, had little influence on the nuclear classes. In his investigation on cases of localized ostitis fibrosa, Mustakallio (1935) found the size of the nuclei and nucleoli to be larger than normal in the growth centers.

Heiberg (1908) was the first to observe that the nuclei of cancer cells are almost always larger than normal nuclei. Consequently there are larger nuclear classes in cancerous tissue. This is not invariably the case, however, and Heiberg himself stressed that the nuclei may occasionally be smaller than normal. Nomicos (1910), Borst (1910) and Haudemer (1934) made the same observation. The latter also measured the size of the nucleoli and observed an increase in their size as well, a circumstance which was particularly striking when the carcinoma nuclei were smaller than normal. Other authors who also observed enlarged nuclei in carcinomas are Stenius (1925), Saxén (1926) Brofelt (1928), Klossner (1931), and Thesleff (1933).

Arndt (1935) and Schairer (1936) called attention to the rhythmic growth of adenoma cells. Arndt (1935) also established that the polymorphy of cancer cells is

not irregular but that larger nuclear classes are present. Ehrich (1936) likewise pointed out that double and quadruple nuclear sizes occur but that the nuclei may also increase in size simply by swelling.

Heiberg (1908) considered nuclei 15 μ in diameter or larger as cancer-suspect, since the nuclei observed in epithelial proliferations are generally smaller.

Rentzov (1935), Vorbeck and Repsilber (1936) carried out karyometric measurements on lymphoid tissue. Vorbeck found that with regard to size medium-sized lymphocytes in lymphoid germinal centers formed a group of their own. According to Repsilber (1936), the commonest nuclear size in lymphosarcoma is twice the nuclear size of a small lymphocyte. Rentzov (1935) found the commonest nuclear size in lymphogranulomatosis maligna to be that of a small lymphocyte and he therefore considered lymphogranulomatosis to be a specific inflammation rather than a tumor.

Heiberg (1930) and Engelbreth-Holm (1932) measured the nuclear sizes in leukemias and in all cases examined they found nuclei larger than normal. The difference in diameter was not large but the nuclear volume of a leukemic cell was twice the normal.

When the cell becomes a tumor cell, considerable morphologic and physiologic changes take place in the nucleus. Young and immature cells proliferate and when the cell matures proliferation ceases. Damashek and Gunz (1960) described a leukemic leukocyte as an immature cell in which, for instance, the nuclear chromatin pattern is fine and uniform, as is common in an immature cell, and the nucleus is enlarged. The mitotic activity is also higher and the mitoses are often abnormal. Fluctuations in the number of chromosomes may be observed and the mitotic figures may be pathologic, tripolar and multipolar.

It should be understood that in immature proliferating tissue the average nuclear size is larger than under normal conditions and that, exceptionally, smaller nuclei may also be encountered.

II. PROBLEMS

Owing to the diversity and abundance of types, clinical diagnosis of diseases belonging to the lymphoma group is often difficult. Histopathologic and morphologic criteria therefore constitute important diagnostic aids. The aim of the present investigation was to study the structure of lymphomas by means of special histologic methods.

The work resolves itself into two parts, in which an answer is sought to the following questions:

What is the structure of the supporting reticular network in lymphomas of different types and how does it differ from normal skin and from benign proliferation of reticular tissue in the skin?

When inflammatory conditions of the skin are compared with lymphomas, are there karyometrically demonstrable diagnostic differences in the infiltrating cells?

III. MATERIAL AND METHODS

The material consists of a series of 22 cases of lymphoma of various types with skin manifestations seen at the Department of Dermatology of Helsinki University Central Hospital. The majority of these (21) form part of a series of patients followed up for the 10-year period 1952 to 1961, one case alone belonging to an earlier series from 1947.

The total number of patients with lymphoma seen during this 10-year period was 63. The total number of new patients during the same period was 40045. Compared with other skin diseases the incidence of lymphomas was thus 1 : 635.

The distribution of these 63 cases on the different types of lymphoma can be seen from the following table. The table also shows the distribution of the skin manifestations and the number of cases chosen for the present study.

Diagnosis	Total no. of lymphomas	No. of cases with skin manifestations	No. of cases included in present series
Lymphocytic lymphoma, well differentiated	9	2	2
» » poorly »	8	7	4
Reticulum cell lymphoma, well differentiated	2	1	1
» » » poorly »	4	4	3
Hodgkin's disease	20	3	3
Mycosis fungoides	19	19	7
Stem cell lymphoma	1	1	1
Total	63	37	21

It will be seen from the table that with the exception of mycosis fungoides the majority of the lymphomas with skin manifestations were included in the present series.

Control series

The control series is divided into two groups, one comprising specimens of normal skin and the other specimens of benign proliferations of the reticular tissue.

To obtain a sufficient number of normal specimens from living patients would have presented difficulties and these specimens have therefore been taken from

cadavers. This group comprises three persons only but the histologic structure of the network in all samples (36 biopsies) was so homogeneous that these specimens were considered sufficient.

The group of benign reticular proliferations comprises specimens of different inflammatory diseases of the skin. In all inflammations an inflammatory cell infiltration occurs in the skin and there are changes in the reticular supporting network. Some premalignant stages of lymphoma either resemble or are identical with chronic inflammatory dermatoses, differing from these only in that the process is progressive. A differential diagnosis must then be made between inflammatory hyperplasia and lymphoma. In this connection benign tumors of the reticular tissue require less consideration.

Normal skin

The specimens of normal skin were taken from three cadavers aged 13, 20 and 70 years. These were autopsied at the Department of Pathology of Helsinki University. The specimens were taken at the latest one day after death. From each cadaver a specimen of the skin was taken from 12 different points of the body: breast, abdomen, back and extremities.

Benign reticular hyperplasias of the skin

This group comprises dermatoses judged on the basis of their clinical course to be benign. The specimens were taken from 12 patients suffering from the following diseases:

Secondary syphilis
Edema and eczema in association with hypoproteinemia
Lichen ruber planus, 2 patients
Dermatitis herpetiformis, 2 patients
Acrodermatitis atrophicans
Poikiloderma congenitale
Poikiloderma atrophicans vasculare, 2 patients
Lymphadenosis cutis, 2 patients

The syphilis case was included as an example of proliferation of the reticular tissue brought about by infection. The edematous dermis of the hypoproteinemia patient illustrates the changes induced by anasarca. Lichen ruber planus, dermatitis herpetiformis and dermatitis atrophicans are benign inflammatory dermatoses of unknown etiology. Poikiloderma congenitale is a nevoid benign form of poikiloderma. Poikiloderma atrophicans vasculare is known as an essentially benign dermatosis from which a lymphoma may occasionally develop. In 1936, Oliver for the first time demonstrated that this dermatosis occasionally was a prodromal stage of mycosis fungoides. Bluefarb (1959) mentioned that this skin disorder has occurred in association with all the various types of lymphoma.

Dostrovsky and Sagher (1945) observed malignant changes as much as 14 years after the onset of the skin disorder. It should be mentioned that acrodermatitis atrophicans as well may occasionally precede or be associated with lymphoma (Herzberg 1952, Bäfverstedt 1953, Knoth 1958). Lymphadenosis cutis is a benign proliferation of lymphoreticular tissue but has sometimes been observed to occur in association with malignant growths (Bäfverstedt 1943).

The selection of these disorders as a control series aims at demonstrating the nature of the nonspecific changes in the reticular tissue.

Lymphomas of the skin

The study is based on 85 biopsy specimens taken from 22 patients. The material is distributed as follows:

Diagnosis	No. of cases	No. of biopsies
Lymphocytic lymphoma, well differentiated	2	4
» » poorly »	4	23
Reticulum cell lymphoma, well differentiated	1	2
» » » poorly »	3	8
Hodgkin's disease	4	22
Mycosis fungoides	7	24
Stem cell lymphoma	1	2
Total	22	85

The group of patients with mycosis fungoides is the largest. Specimens were taken at different stages of the disease. One patient had the premycotic stage of the disease, three the classic tumor form, one mycosis fungoides d'emblee, and one erythroderma with polymorphous cell infiltration. Sixteen of the lymphoma patients belonging to the present series have died and on nine of these autopsy was carried out at the Department of Pathology, Helsinki University, and this autopsy material has been at my disposal.

Some of the present cases are very rare and this is one reason for the presentation of the case reports. The majority of the cases have been discussed at the histological demonstrations at the Department of Dermatology under the guidance of Professor Teir. Case 22 was published by Sonck (1956) under the heading reticulosarcomatosis primaria of the skin. The patient with skin nodules of monocytic leukemia, case 19, was demonstrated by Professor Putkonen before the Finnish Dermatological Society in 1959. Some of the patients of the present series were treated with radioactive phosphorus. The results of this treatment were reported by Holsti and Voutilainen (1960).

The case reports include condensed case records and the relevant photographs.

Methods

Histologic and cytologic examinations were made of 190 biopsy specimens taken from 37 patients. The specimens are distributed on the different diagnostic groups as follows:

Specimens from lymphomas	85
Specimens from inflammatory dermatoses	29
Autopsy specimens from lymphomas	40
Postmortem specimens from normal skin	36

The majority of the specimens from living patients were taken with a punch under local anesthesia. The diameter of the punch was 5 to 8 mm. The older material includes some cases in which the specimen was taken with a scalpel. The specimens of normal skin were likewise punched. The autopsy specimens were taken with a knife. The specimens were fixed in formalin and paraffin. Of all specimens, numerous sections, including serial sections, were prepared. The specimens were stained with hemalaum-eosin, hematoxylin-van Gieson and Foot. Some specimens were also stained with Koneff's azan and, to demonstrate elastic tissue, with orcein.

Examination of the argyrophil connective tissue

The argyrophil connective tissue was examined in all cases. Silver impregnation was carried out according to Foot's method. A detailed analysis and a comparison of the changes were made from photographs.

Karyometric examination

Karyometric examination was carried out in 16 cases. The specimens selected for this examination were from the following disorders:

1. Secondary syphilis
2. Hypoproteinemic edema and eczema
3. Poikiloderma congenitale
4. Lymphadenosis cutis
5. Lymphoma reticulocyticum, well differentiated
6—7. Lymphoma reticulocyticum, poorly differentiated
8. Hodgkin's disease
9. Mycosis fungoides, premycotic stage
10—12. Mycosis fungoides, tumor stage
13. Acrodermatitis atrophicans
14—16. Poikiloderma atrophicans vasculare.

Thus, some cases were benign inflammatory proliferations of the reticular tissue, some were lymphomas, and some were cases of chronic dermatoses such as occasionally occur in association with malignant lymphomas.

The specimens of normal skin were postmortem specimens. Feyrter (1960) demonstrated that in cadaver tissue changes take place which result in considerable polymorphism of the nuclei. Neither would cell infiltration in normal skin have offered any material for comparison of cell types with those of lymphomas, and they were thus excluded from the karyometric examination.

For this examination paraffin sections of blocks fixed in formalin were used. During the course of fixation changes take place in the tissue cells and characteristic features disappear. The cells shrink and exact determination is rendered more difficult. Exact determination of cell types in bone marrow and blood specimens may also be difficult, even though these preparations consist of fresh smears.

The cells to be measured were divided into three groups. All cells with light nuclei were placed in the first of these. This group thus consisted of endothelial cells, reticulum cells, lymphoblasts and stem cells.

The second group comprised cells whose nuclei were hyperchromatic and had nucleoli, whilst mature lymphocytes were referred to the third group.

The composition of the groups is seen from the following table:

Group of endothelial cells	Group of hyperchromatic cells with nucleoli	Group of lymphocytes
Endothelial cells lining blood vessels	Histiocytes	Mature lymphocytes
Isolated cells with light nuclei		
a) in connection with blood vessels		
b) unconnected with blood vessels		
Stem cells		
Reticulum cells		
Lymphoblasts		

Excluded from karyometric examination were neutrophil and eosinophil granulocytes, plasma cells, mast cells and red cells. Fibroblasts and fibrocytes were likewise not included.

Against this division it can be argued that different developmental stages of the same cell are referred to different groups. These developmental stages could not at any rate be exactly determined histologically. On the other hand, the cells of whole cell series develop from one another. By measuring a large number of nuclei in each of these clearly defined groups of cells, comparable quantitative figures are obtained.

The nuclei were drawn on paper with an Abbé camera lucida, the linear magnification being 1 : 2500. The surface area of the nuclei was measured by planimetry twice in succession and the average of these measurements was used.

The number of cells measured varied between 140 and 380 except in the case of the lymphocytes, which were absent or scarce in many lymphoma cases.

The average volume of the nuclei in the different groups of cells was determined as follows:

Planimetry of the cross section of measured cells gave a certain value P. The nucleus was assumed to have a spherical shape, and thus the volume V, expressed in μ^3, was obtained from the formula:

$$V = \frac{32}{46{,}855} \cdot P^{3/2}.$$

The accuracy of the planimeter only enabled the areas to be measured to the nearest integer. According to the above formula the V value was calculated for each P value.

Statistical method

In the statistical treatment of the karyometric observations nonparametric testing methods were employed, in which the observations are not assumed to be normally distributed. In calculations of the test values, ranks corresponding to the magnitude of the observations were used, and not the actual observations themselves. The testing of the significance of the standard deviation of several independent samples was carried out by Kruskall—Wallis' one-way analysis of variance by the method described on pp. 184—194 in Siegel's book, and for the testing of the standard deviation of two samples the method described on pp. 152—154.

The degree of statistical significance of the differences can be expressed either by P values (probability to make a wrong decision) or by confidence levels as follows:

The difference is almost significant, the confidence level is

$$95\text{—}99\ \%, \text{ or } 0.01 < P \leqq 0.05.$$

The difference is significant, the confidence level is

$$99\text{—}99.9\ \%, \text{ or } 0.001 < P \leqq 0.01.$$

The difference is highly significant, the confidence level is

$$99.9\ \%, \text{ or } P \leqq 0.001.$$

IV. RESULTS

A. RETICULAR FRAMEWORK

The structure of the reticular supporting network proved to be very similar in different specimens from a single case. Silver impregnation brought out the argyrophil network characteristic of the disease or of the stage of the disease, just as the histopathological picture revealed by other staining methods was typical, although not always pathognomonic. When the results are presented, the structure of the reticular network and the general histopathology of the case are described from the same field of vision. A general histopathological survey is given in connection with the case reports.

1. NORMAL SKIN

No difference in the structure of the reticular network could be observed in specimens taken from different parts of the body. A delicate network of reticulin fibers was seen surrounding the arterioles, sweat glands, sebaceous glands and hair follicles (fig. 1).

The collagenous fibers in the papillary layer were often particularly fine. Argyrophil substance was seen in greater quantities at the border of the corium and the epidermis. The fibers demonstrated by Szodorey extended in fringe-like formations between the basal cells (fig. 2).

2. BENIGN RETICULAR HYPERPLASIAS OF THE SKIN

Case 1 in the case reports is an example of infectious inflammation of the skin. The maculopapular eruption of secondary syphilis contained a cell infiltration in which the inflammatory cells were chiefly lymphocytes and plasma cells situated in the area of the upper third of the corium. In this area the argyrophil network was considerably changed. The collagenous fibers had disappeared. The argyrophil fibers surrounded the enlarged capillaries and lined the interstitial spaces forming a continuous latticework (fig. 3).

Case 2 is an example of swollen and inflamed skin caused by hypoproteinemia. The specimen was taken from a static eczema in the leg of a patient suffering from

kidney disease. The changes in the reticular framework comprised the whole edematous corium. In this case, too, the cell infiltrations chiefly contained lymphocytes and plasma cells. The collagenous fibers had disappeared. Interstitial spaces and lacunae were lined with argyrophil fibers. Where there were dense aggregations of cells, however, the network was absent (fig. 4).

Cases 3 and 4 are examples of changes in the reticular framework in lichen ruber planus. In the former the specimen is from a young newly-developed lichen papule in the skin of the thigh. The lymphocytic infiltration was situated in the network of argyrophil fibers, which were missing, however, at the sites of dense cell aggregations. In the right border of fig. 5, in the upper part of the corium, there is a zone of fine collagen which, at the site of the lesion, divides into thinner argyrophil fibers around the cell aggregations. The argyrophil fibers in the upper part of the corium are long and continuous. In the aggregation of lymphoid cells only some slender filaments are seen between the cells.

In the latter case the specimen was taken from an older hyperkeratotic lichen lesion from the skin of the leg. Besides lymphoid cells, histiocytes and fibrocytes were demonstrable. The cells lay in a network of regular structure. The dense cell accumulations characteristic of acute inflammation were missing. Some of the fibers of the network were long and gradual transformation into collagenous fibers was seen (fig. 6).

Cases 5 and 6 are examples of changes in the reticular tissue in dermatitis herpetiformis. The specimen was taken from a vesicle. In both cases the cell infiltration was characteristic of dermatitis herpetiformis and among the cells there was an abundance of eosinophil granulocytes. In the former case an unbroken argyrophil network formed the floor of the vesicle (fig. 7). In the latter case the infectious granulocyte infiltration destroyed the network, as shown in fig. 8.

The changes occurring in acrodermatitis atrophicans are illustrated by case 7. Specimens were taken from infiltrated skin of the buttocks and again three months later, after penicillin treatment, from the same area, the skin at this time having already become atrophic.

The skin contained a cell infiltration with numerous histiocytic cells. These cell aggregations were situated in a sparse network of argyrophil fibers among the split collagenous fibers. In the upper corium more continuous argyrophil fibers lay parallel to and densely packed against the epidermis.

There were no cell infiltrations in the specimen taken from atrophic skin. In the upper corium long argyrophil fibers were parallel to the surface. Deeper in the corium, sparse cell infiltrations and a delicate argyrophil network were seen around the dilated veins (fig. 10).

Case 8 is an example of changes in the reticular tissue in poikiloderma congenitale. The cell infiltrations were lymphocytic and occurred at regular intervals in the upper corium as perivascular aggregations. A regular delicate network of reticulin fibers was seen (fig. 10).

Cases 9 and 10 constitute examples of changes encountered in the reticular tissue in poikiloderma atrophicans vasculare. Specimens were taken from an infiltrated

and an atrophic lesion. Besides lymphocytes, the cell infiltration in the former exhibited an abundance of histiocytes. In the area of the pars papillaris, well developed argyrophil fibers surrounded capillaries, and lined interstitial spaces and lacunae. Deeper in the corium where the cell infiltrations were denser, there were fewer fibers which could be separately distinguished between the cells (fig. 12).

In the atrophic lesions of poikiloderma atrophicans vasculare the changes in the reticular tissue were very similar to those in the atrophic lesions of acrodermatitis atrophicans. The cell infiltrations had disappeared, and the argyrophil network in the upper corium had shrunk forming, continuous linear fibers running parallel to the surface among which some enlarged interstitial spaces were still seen (fig. 13).

Cases 11 and 12 are examples of changes in the reticular tissue in lymphadenosis cutis benigna. In the former case, the nodular cell aggregations were composed of lymphocytes. The reticulin network in the area of the nodule was poorly developed or lacking. The argyrophil fibers surrounded the nodule. In the latter case the connective tissue trabeculae surrounded the nodular aggregations of reticulum cells like a septum. In the area of the nodule a regular network was lacking. Isolated argyrophil filaments occurred sparsely and irregularly between the cells (fig. 14).

Conclusions:

In all specimens of normal skin the reticular network proved to be homogeneous and in accordance with earlier investigations. The sparse cell infiltrations around the arterioles and adnexa of the normal skin were situated in the narrow delicate network of argyrophil fibers described by Homma (1922).

In the inflamed skin the reticulohistiocytic proliferations were situated in an argyrophil network which grew in size with the cell infiltrations, an observation that agrees with that of Knoth (1957). This network was lacking in foci in the abundant lymphocyte, plasma cell and histiocyte aggregations showing an acute stage of inflammation.

In the upper part of the corium cell infiltrates divided the fine collagen into thinner fibers which stained argyrophilically and formed a network around the cell aggregations. Deeper in the corium, cell infiltrations were situated in a delicate network between the fragmented collagenous fibers.

When in healing inflammatory conditions the cell infiltrations regressed, the argyrophil network shrank, the fibers parallel with the surface became long and continuous and lay packed against the basal membrane. In some cases an atrophic dermis thus developed. When the lymphatic cell infiltrations changed to contain histiocytes and fibrocytes, the argyrophil fibers developed into collagenous fibers and the inflammation healed, leaving no trace.

In lymphadenosis cutis benigna a regular framework was lacking in the area of both the lymphocytic and reticulocytic nodules. Structures resembling the lobules of the lymph nodes were surrounded by argyrophil connective tissue trabeculae.

Cases 13 and 14 are examples of well differentiated lymphoma lymphocyticum. The lymphoid cell infiltrations around the enlarged capillaries were situated in a regular network of argyrophil fibers. In large cell accumulations indicating an acute process such a framework was lacking, however, in foci (fig. 15) or in the large areas where the collagenous fibers were fragmented (fig. 16). In more chronic forms of the disease, even large cell accumulations deep in the corium were situated in a delicate network of regular structure (fig. 17).

Cases 15, 16, 17 and 18 were cases of poorly differentiated lymphoma lymphocyticum. There was no regular network in the area of the tumor. Between the tumor cells, however, there were isolated short fragments of argyrophil fibers varying in thickness, and short, thick fragments of collagenous fibers. Here and there argyrophil fibers were seen surrounding capillaries and lining interstitial spaces (fig. 18). When the lymphosarcoma was generalized into erythroderma in case 16, the reticular network was otherwise the same but vertical bundles of argyrophil fibers, remnants of the hair follicles, were seen at regular intervals (fig. 19). When the tumor tissue did not reach the epidermis, the presence of long continuous argyrophil fibers in the upper corium constituted a sign of inflammatory reaction of the papillary layer. When the tumor tissue reached the epidermis, Pautrier's abscesses were observed here and there in the epidermis as, in mycosis fungoides (case 18).

Case 19 is a case of well differentiated lymphoma reticulocyticum. In this cutaneous leukemia the infiltrating cells were monomorphic. Argyrophil fibers surrounded the capillaries and lined the spaces in the edematous dermis. The fibers were delicate and did not form a continuous network and they often occurred as separate fibrils. At the site of the dense cell accumulations all fibers were missing (fig. 20). The changes were similar to those in the lymphedema case of the control series.

Cases 20, 21 and 22 were examples of poorly differentiated lymphoma reticulocyticum. The cell picture of these lymphomas varied greatly. In case 20 there was a single primary lesion of the skin and the cells were comparatively monomorphic immature cells of the reticular system. A regular network was lacking. Argyrophil fibers occurred as delicate and irregularly situated fragments between the cells (fig. 21). In case 21 the lesion was also primary. The tumor was situated in a lymph node under the chin reaching to the skin of the throat. The cells were phagocytic reticulohistiocytes. There was no regular network. There were argyrophil fibers varying in length and thickness running in all directions through the tumor tissue and occurring as slender separate filaments between the cells (fig. 22). In the upper corium there were often long, continuous argyrophil fibers, a sign of inflammatory reaction. Case 22 was one of highly malignant lymphoma localized to the skin. In this lymphoma the degree of maturity of the reticulum cells varied in different parts of the tumor. At those sites of the tumor where the cells were very immature, the network was missing (fig. 23). In places it was irregular (fig. 24). At the sites where the differentiation in a histiocytic direction was farthest advanced, the network surrounded the tumor cells like a densely woven basket (fig. 25).

Skin manifestations of Hodgkin's disease with their specific histology occurred in cases 23, 24, 25 and 26. In case 23 the lesions consisted of separate cutaneous nodules, while in the remaining cases they were large infiltrative tumors and nodules. The cell infiltrations were in all cases polymorphic and characteristic of Hodgkin's disease. In case 24, however, there were foci in which the cell picture was one of a more monomorphic tumor tissue. Throughout the area of the polymorphic infiltration a strong reticular network was seen which was sometimes regular and fine-meshed (fig. 26), or of irregular density (fig. 27). The reticular network was missing from the monomorphic tumor cell islets.

Cases 27, 28, 29 and 30 were examples of initial lesions of mycosis fungoides. Case 27 was one of erythroderma with polymorphic cell infiltration. The patient was treated with radioactive phosphorus which was observed to settle in the skin in the immature cells. After the treatment the skin became paler, pigmented and slightly atrophic. Case 28 represented the premycotic stage of Alibert's classic mycosis fungoides which two years later progressed to the tumor stage. In case 29 the specimen was taken from the apparently healthy skin of a patient in the tumor stage. Histologic examination, however, revealed changes characteristic of mycosis fungoides, including Pautrier's abscesses. In the two latter cases the cell infiltrations chiefly contained histiocytic cells, the endothelial cell type being in the minority. In all these cases both the histiocytic and the polymorphic cell infiltration was contained in a well developed strong reticulin fiber network. However, in the abundant cell aggregations indicative of an acute condition the network was lacking (fig. 28).

The mycosis fungoides cases 29, 30, 31 and 32 represented the tumor stage of Alibert's disease. The reticular network surrounded the blood vessels as a tumor-like new growth (figs. 29 and 30). Case 33 was the d'emblee form of mycosis fungoides. The infiltrative cellular tissue was polymorphic and characteristic of mycosis fungoides, also found in autopsy specimens both from the skin and from the internal organs. The reticular network was correspondingly of a regular structure.

In the late tumor stage of Alibert's disease the picture of the reticular network changed, however. In the tumors, areas were observed in which a regular network was wanting. In these areas the cell infiltrations had also changed, becoming more monomorphic and resembling sarcoma. The fibers of the network varied in thickness and the network was irregular (figs. 31 and 32).

No. 34 was a case of stem cell lymphoma. This was cutaneous leukemia in which the infiltrating cells were monomorphic and nondifferentiated. A reticular network was lacking. In the border areas of the infiltration some argyrophil fibers were seen which encompassed the cell aggregations (fig. 33).

Conclusions:

In lymphomas of the skin the reticular network exhibited features characteristic of the respective type of lymphoma, i.e. of the type of cell infiltration.

In lymphoma of the well differentiated lymphocytic type the reticulin fibers formed a delicate network in which, in places, the meshes of the net often remained somewhat open.

In lymphoma of the poorly differentiated lymphocytic type a regular network was missing. Irregularly situated among the cells were seen short filaments of argyrophil fibers.

In lymphoma of the well differentiated reticulocytic type the reticulin fibers lined the capillaries and tissue spaces without forming a continuous network. Between the cells, fibers were seen as separate thin fibrils.

In lymphoma of the poorly differentiated reticulocytic type, no regular network was present. However, comparatively abundant argyrophil fibers were usually seen running in all directions between the tumor cells both as delicate fibrils and as fiber bundles varying in length and thickness. When there were areas in the tumor in which the stage of maturity of the cells varied, a different kind of network was correspondingly observed in the different areas. If the cells were very immature, the argyrophil fibers were entirely lacking. When the cells differentiated in a histiocytic direction, the network was abnormally dense, surrounding the tumor cells as an irregular basketwork.

In Hodgkin's disease and in mycosis fungoides the polymorphic cell infiltration occurred in a well developed and regular network of reticulin fibers. In late tumor lesions when the cells became monomorphic and resembled sarcoma, the network became irregular or was missing.

In stem cell lymphoma occurring as a leukemic skin infiltration, no argyrophil network was formed.

In the abundant cell aggregations indicative of an acute condition, the reticulin network was missing in foci even in the initial lesions of all malignant lymphomas.

B. KARYOMETRY

The results of the karyometric investigation are given in table I. The first group comprises four patients with benign proliferation of the reticular tissue, i.e. syphilis, edema resulting from hypoproteinemia, congenital poikiloderma and lymphadenosis cutis benigna. These conditions, different as regards etiology but benign as regards prognosis, constitute control material with regard to the nuclear size. The second and third groups in the table comprise lymphomas, the former three cases of reticulum cell lymphoma and Hodgkin's disease and the latter four cases of mycosis fungoides in different stages. The fourth group consists of chronic dermatoses, acrodermatitis atrophicans and poikiloderma atrophicans vasulacre, conditions which, as has been mentioned in the foregoing, sometimes precede lymphoma.

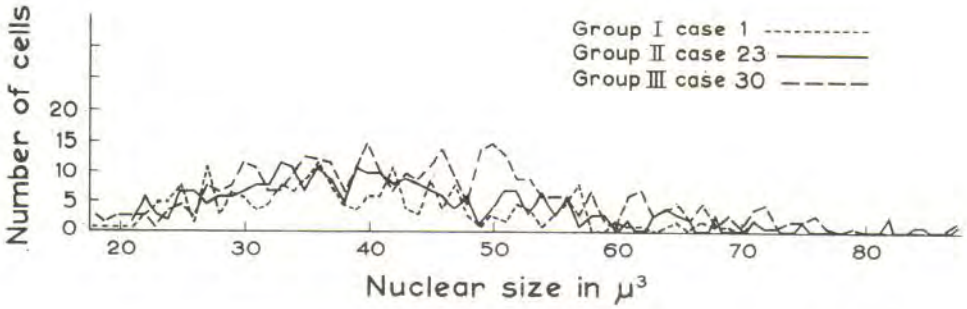
Graphic examples of the distribution of the nuclear sizes of the endothelial cells and of the histiocytes are presented on page 32. It will be seen from the graphs that in the cases belonging to the different groups the distribution is skewed and the dispersion

TABLE I

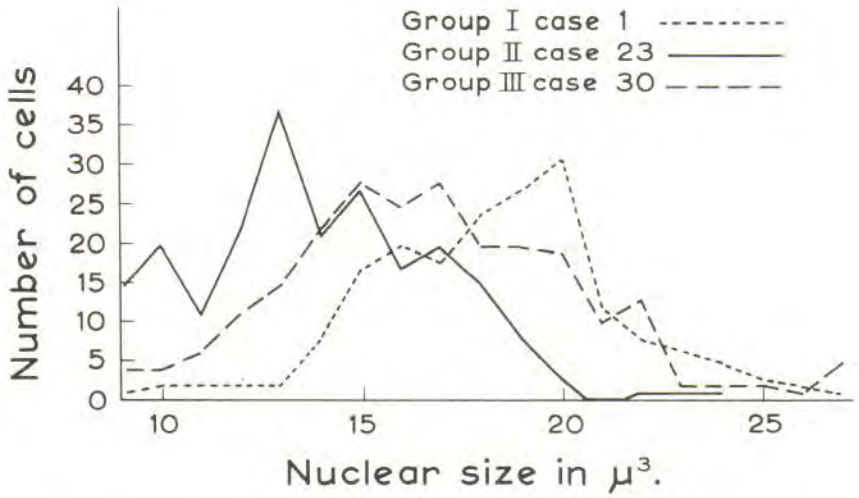
The results of the karyometry

Diagnoses	Endothelial cells				Histiocytic cells				Lymphocytic cells			
	n	$\bar{x}$	$s_{\bar{x}}$	s	n	x	$s_{\bar{x}}$	s	n	$\bar{x}$	$s_{\bar{x}}$	s
Group 1												
Syphilis sec (Case 1)	216	99.8	3.2	46.4	191	30.6	0.6	7.9	114	17.8	0.5	5.1
Hypoproteinemic edema (Case 2)	286	88.6	2.6	43.5	199	29.4	0.6	8.5	40	23.4	1.1	6.9
Poikiloderma congenitale (Case 8)	256	110.4	3.3	53.4	205	28.1	0.5	7.0	—	—	—	—
Lymphoma follicularis (Case 12)	244	93.4	2.7	41.7	173	31.5	0.6	7.4	190	26.2	0.5	6.7
Group 2												
Lymphoma retic. well diff. (Case 19)	366	112.7	2.3	44.6	—	—	—	—	186	22.6	0.4	6.0
Lymphoma retic. poorly diff. (Case 20)	286	140.1	3.6	61.2	190	31.7	0.7	10.2	50	19.0	0.6	3.9
Lymphoma retic. poorly diff. (Case 22)	247	139.5	4.8	75.6	160	21.0	0.7	8.5	—	—	—	—
Hodgkin's disease (Case 23)	278	111.6	3.5	58.2	219	20.4	0.5	6.7	74	16.8	0.5	4.3
Group 3												
Mycosis fungoides stadium premycot. (Case 28)	236	123.7	2.6	39.2	197	29.4	0.4	6.1	—	—	—	—
Mycosis fungoides stadium tumorosum, initial erythema (Case 29)	391	120.3	2.9	57.8	236	27.2	0.6	9.4	26	18.6	1.1	5.4
Mycosis fungoides, tumor (Case 30)	328	125.1	3.5	63.4	206	31.4	0.7	10.2	151	22.6	0.5	6.7
Mycosis fungoides, tumor (Case 32)	370	245.3	4.4	84.5	463	35.4	0.5	11.2	262	25.5	0.4	6.4
Group 4												
Acrodermatitis atrophicans (Case 7)	327	98.1	3.1	56.8	228	25.1	0.5	7.8	99	18.5	0.5	5.3
Poikiloderma atrophicans vasculare (Case 9)	311	85.0	2.4	42.5	178	21.7	0.4	5.9	53	18.9	0.6	4.6
Poikiloderma atrophicans vasculare (Case 10)	264	129.4	3.0	48.4	186	23.8	0.4	5.1	—	—	—	—
Poikiloderma atrophicans vasculare (Case 25)	228	154.3	4.1	61.2	165	26.1	0.5	6.9	—	—	—	—

n = number of cells
$\bar{x}$ = mean volume of nucleus in μ^3
s = standard deviation
$s_{\bar{x}}$ = standard error of mean



Graphic examples of the distribution of nuclear sizes in the group of endothelial cells.



Graphic examples of the distribution of nuclear sizes in the group of histiocytes.

very marked. For the statistical analysis of the results of the karyometry we therefore adopted the nonparametric testing methods presented on page 24.

The results of testing of the homogeneity of the different groups are given in table II. The table presents test values (χ^2) and corresponding P values. In all groups the dispersion in nuclear size between the individual patients is significantly greater than the dispersion in the size of the cells of the same patient. In the further statistical treatment, therefore, the mean values of nuclear size calculated for each patient are employed.

TABLE II

The results of testing of the homogeneity in the groups I—IV
χ^2 = test value

Cell type	I		II		III		IV	
	χ^2	P	χ^2	P	χ^2	P	χ^2	P
Endothelial cells	10.8	$0.01 < P < 0.02$	21.0	< 0.001	340.0	< 0.001	94.4	< 0.001
Histiocytes	9.0	$0.02 < P < 0.05$	106.0	< 0.001	41.4	< 0.001	14.7	$0.001 < P < 0.01$
Lymphocytes	65.6	$P < 0.001$	32.8	< 0.001	20.3	< 0.001	0.1	< 0.5

1. BENIGN RETICULAR HYPERPLASIAS OF THE SKIN

In benign reticular hyperplasias (group I), the nuclear sizes in the group of endothelial cells varied between 88.6 and 110.4 μ^3. There was thus a considerable size range within the group. The dispersion was likewise marked and the distribution was skewed. Within the groups of histiocytes and lymphocytes these differences in size were smaller and the distribution was closer to normal.

The group of endothelial cells in these cases comprised principally endothelial and reticulum cells.

2. RETICULUM CELL LYMPHOMAS AND HODGKIN'S DISEASE

In this disease group (group II) the nuclear sizes in the endothelial cells varied between 112.7 and 140.1 μ^3. The nuclei were thus in all cases larger than in the control series. The variation in size within the group was also larger. The dispersion was wider and the distribution more skewed than in the control series. There was less variation in the nuclear sizes of the histiocytes in this group, however, and the distribution was closer to normal.

The result of testing groups II and I showed that the average nuclear volume of the endothelial cells was almost significantly larger than in the control series ($0.01 < P < 0.05$, i.e. the confidence level was 95 per cent).

Comparison between groups II and I did not reveal statistically significant differences ($P > 0.05$) between the nuclear sizes of histiocytes and lymphocytes.

In the three reticulum cell lymphomas of group II the cell infiltration both in the well-differentiated and in the two poorly differentiated types was monomorphic, chiefly consisting of cells of the same type. The group of endothelial cells in which the enlarged nuclear sizes were observed consisted chiefly of reticulum cells, the endothelial cells connected with the blood vessels being in the minority. The group of cells measured from the skin infiltrations in Hodgkin's disease was less homogeneous, however.

3. MYCOSIS FUNGOIDES

The results of measurements in this disease group (group III) show that the nuclear sizes of the endothelial cells vary between 120.3 and 245.3 μ^3. Thus the average nuclear size in all cases of this group was larger than in the control series. Within this disease group the nuclear sizes were also larger, the largest nucleus being twice as large as the smallest. The dispersion was larger and the distribution more skewed than in the control series. In the group of histiocytes and lymphocytes, however, the nuclear sizes were of equal magnitude and the distribution close to normal.

The result of the testing between groups III and I was that the average nuclear volume of the endothelial cells of group III was almost significantly larger than in the control series ($0.01 < P < 0.05$, or with 95 per cent confidence level). Neither were significant differences between the nuclear sizes of histiocytes and lymphocytes to be observed in a comparison of groups III and I ($P > 0.05$).

The group of endothelial cells in mycosis fungoides infiltrations comprised several different cell types: lymphoblasts, reticulum cells, endothelial cells and atypical immature cells with delicate cytoplasm, round, oval or irregular nucleus, distinct chromatin network and one or two nucleoli. In a mycosis fungoides infiltration the latter cells contain the largest nuclei. In the karyometrically examined material it was they that were responsible for the skewed distribution and for the wide dispersion of the nuclear sizes within the group. Owing to the limits of the present method of investigation, it could not be said whether there is a similar change towards enlarged nuclear size in the other cells with pale nuclei present in mycosis fungoides.

4. ACRODERMATITIS ATROPHICANS AND POIKILODERMA ATROPHICANS VASCULARE

The nuclear sizes of the endothelial cells in this disease group (group IV) varied between 85.0 and 154.5 μ^3. In two cases of poikiloderma atrophicans vasculare the nuclei were larger than in the control series. In these cases the dispersion was wide and the distribution skewed. The nuclear sizes of the histiocytes and lymphocytes were again of the same magnitude as that of the control series and the distribution was normal.

Statistical comparison of group IV with group I shows that there are no statistically significant differences between the groups of endothelial cells, histiocytes and lymphocytes ($P > 0.05$), although two values in the group of endothelial cells were considerably higher than in the control series.

Conclusions:

The average nuclear size was larger in the group of cells, which chiefly contained endothelial and reticulum cells when, lymphomas were compared with inflammatory proliferations of reticular tissue. In two cases of poikiloderma atrophicans vasculare the nuclear size in the same cell group was also considerably larger than in the controls.

V. GENERAL DISCUSSION

Reticular network

In broad outline, the nature of the reticular network in different types of lymphoma has been known. There are references in the literature to the structure of the network in different types of lymphoma. Thus Gottron (1937) mentioned that in leukemic tumors of the skin the network is sparse and resembles that of the lymph node. Lever (1949), in his textbook on histopathology, mentioned that the capacity of very immature reticulin fibers of lymphomas to form reticulin fibers is very poor, whereas when the tumors contain histiocytic cells the network becomes well developed. When studying specimens of glandular tumors Mackenzie (1959) found a reduced quantity of fibers in some tumors and an increased quantity in others, and he considered this fact to be of some diagnostic significance. On the other hand, recent investigations (Knoth 1958) have shown that the network develops in all proliferations of reticular tissue and not only in lymphomas.

The experience gained during the present work has confirmed earlier observations insofar as the reticular network was observed to characterize both lymphomas and inflammatory hyperplasias, and to be better developed in both of these when associated with histiocytic proliferation.

From a comparison of the variations in the network in the control series and in the different types of lymphomas we may observe the following points:

The well differentiated cells of leukemias of the skin were situated in a network which did not differ to any significant degree from the network observed in the lymphoid and plasma cell proliferations of inflammatory conditions. The poorly differentiated cellular tissue in lymphosarcoma and lymphosarcomatosis, however, showed a characteristic absence of a regular network, thus differing in structure both from inflammatory proliferations and from other lymphomas. The poorly differentiated cells of reticulum cell sarcomas and sarcomatoses were likewise observed in a network which differed from that observed in benign proliferations, being irregular or abnormally dense or entirely lacking, depending on the different stages of differentiation of the reticulum cells. In the initial lesions of polymorphic lymphomas the structure of the network in the area of the papillary layer was quite similar to that in benign proliferations containing histiocytes. There was a characteristic difference between the network of these tumors and that of inflammations. In the cutaneous tumors of Hodgkin's disease the network was occasionally exceedingly dense, as in reticulum cell sarcomas, thus differing in structure from the network of the mycosis fungoides tumors.

The variations in the reticular network were thus found to afford a useful clue to the diagnosis of cutaneous lymphomas. The value of the network as a diagnostic aid is illustrated by the following examples from the case records of the present investigation:

The records included cases 16 and 27, which were both cases of 'homme rouge', or erythroderma, a clinical picture found in all types of lymphoma. These types cannot be distinguished on the basis of their clinical picture.

In case 16 the patient was a woman in whom, at the age of 72, an eczema broke out all over her body. The eczema consisted of smooth glistening papules which followed the skin wrinkles, or of continuous infiltrations. Histologic examination revealed a cell infiltration immediately under the epidermis which had destroyed the normal structure of the skin. Lymphocytes, histiocytes, immature cells of endothelial cell type and with light nuclei, tumor cells with darker nuclei, eosinophilic cells and some plasma cells were observed among the cells. Silver staining demonstrated that a regular network was lacking in the way characteristic of lymphosarcoma and this observation confirmed the histological diagnosis.

In case 27 the patient was a man in whom, at the age of 61, intense erythema of the skin of the entire body had occurred. Histologic examination showed infiltrated zone in the papillary layer, the infiltration comprising lymphocytes, histiocytes and cells of endothelial cell type with light nuclei. Among the histiocytes were nuclei which stained deeply. Silver staining demonstrated a highly developed and regular reticular network. The patient was treated with radioactive phosphorus which, after treatment, was found to have accumulated in the patient's skin, confirming the presence of immature cells. After the treatment the eczema healed, the skin became paler and pigmented and slight atrophy developed.

With regard to the reticular network this case differed sharply from case 16. The disorder was diagnosed as mycosis fungoides. A more exact diagnosis might at this stage have been poikiloderma atrophicans vasculare.

In cases 18 and 34, on the other hand, the skin trouble appeared as separate nodular tumors.

In case 18 the patient was a man in whom, at the age of 73, red, cushion-like infiltrations appeared in the skin of the chest and back, these infiltrations becoming generalized during the course of the next half year. Histologic examination revealed that the cell infiltration reached the epidermis, forming cell aggregations similar to those in Pautrier's abscess between the cells of the epidermis. The cell infiltration contained deformed tumor cells with large nuclei and a coarse chromatin pattern, cells of the endothelial cell type and lymphocytes at various stages of development. There was an abundance of mitoses. Some of these were pathologic, forming circular or tripolar figures. Silver staining demonstrated the absence of the regular network characteristic of lymphosarcoma.

In case 33, however, the patient was a woman in whom, at the age of 53, tumors occurred which on the basis of their histologic picture were diagnosed as mycosis fungoides d'emblee. The patient died four years after the onset of the disease. At autopsy, tumors were found not only in the skin, but also in the heart, lungs, kidneys,

uterus and extradurally in the brain. The cell infiltration in all specimens was polymorphic and characteristic of mycosis fungoides. In all specimens silver staining also demonstrated a regular network typical of the tumor stage of mycosis fungoides.

Mycosis fungoides d'emblee was first described by Vidal and Brocq in 1885. The disease presented as one or several, never generalized, tumors. However, many authors dispute the existence of such a form of the disease, considering it to be a lymphosarcoma (Fraser 1925, Montgomery 1936). Bluefarb (1959) is also of the opinion that all the cases of mycosis fungoides d'emblee which he has observed subsequently turned out to be lymphosarcomas. In the case described above, the diagnosis mycosis fungoides d'emblee seems justified, however. The clinical picture, histologic examination and course of the disease constitute evidence in favor of this. Until the end the tumors preserved the same structure, which was typical of the tumor stage of mycosis fungoides. At all stages the reticular network distinguished the case from the lymphosarcoma cases described above.

Karyometric properties

The karyometric examination revealed an enlarged nuclear size in all cases of malignant lymphoma of the endothelial cell group.

The largest nuclei and the largest variations in their sizes were observed in mycosis fungoides. These large cells, which occur in mycosis fungoides infiltrations and stain lightly, were observed by Tzanck (1938) in the sternal punctate of a patient suffering from this disease. They are large pale cells with a delicate cytoplasm, round, oval or irregular nuclei and a distinct chromatin net. In Tzanck's (1938) opinion, these cells are true tumor cells of mycosis fungoides. According to Jaffe', they develop from periadventitial histiocytes. Weidman (1932), however, believed that they originate in the endothelium of the small blood vessels and that in mycosis fungoides it is a question of 'Endothelzell Wucherungen'.

Increase in the size of the nuclei in the group of endothelial cells was also observed in the two cases of poikiloderma atrophicans vasculare. Dostrovsky and Sagher (1945) described a case in which, in the lesions of poikiloderma atrophicans vasculare, mycosis fungoides tumors occurred as much as fifteen years after the onset of the eczema. Poikiloderma atrophicans vasculare may occasionally be found in association with other lymphomas as well (Bluefarb 1959). In the poikiloderma cases with large nuclei of the present series, the duration of the cutaneous lesion was twelve years in one case (case 10), while in the other case (case 25) malignant lymphoma developed two years after the onset of the eczema, the lymphoma being interpreted as an ulcerative lesion of Hodgkin's disease.

Like poikiloderma atrophicans vasculare, the dermatoses lymphadenosis cutis benigna (lymphocytoma) and acrodermatitis atrophicans occasionally occur in association with lymphoma. Herzberg (1952) described a case in which both lymphocytoma and reticulosarcoma developed in a patient with acrodermatitis atrophicans. Lymphocytoma has been observed to develop in granulomas occurring after a bite by *Ixodes ricinus* and in erythema chronicum migrans. Paschoud (1958) transferred it

by transplants in several passages from patients with erythema chronicum migrans to other persons.

It is interesting to note that the geographical distribution of *Ixodes ricinus* and acrodermatitis atrophicans is the same. Hauser (1955) showed that both are confined to Europe and North America.

In the lymphoid germinal centers larger nuclear classes are found. In the material examined karyometrically it was observed that in lymphadenosis of the skin the average size of the nuclei of lymphocytes was larger than in other cases. Within the scope of the method employed, however, karyometric examination of the acrodermatitis atrophicans cases did not reveal changes in the nuclear size. Yet Götz (1954) transferred this dermatosis by a transplant into the region of the elbow from one person to another.

As a summary, it is tempting to assume that simultaneous occurrence of the dermatoses poikiloderma atrophicans vasculare, lymphadenosis cutis benigna and acrodermatitis atrophicans and of lymphoma is not accidental but that the pathoanatomic basis of these dermatoses is likewise injury to and a change in the nucleus.

The hope cherished at the beginning of the present work that karyometry would prove a diagnostic aid in distinguishing between poikiloderma atrophicans vasculare and the premycotic stages of mycosis fungoides proved vain.

VI. SUMMARY

The aim of the investigation was to study the reticular framework in lymphomas of the skin and the nuclear sizes of the cells of the lymphomatous tissue.

The material comprised 22 cases of lymphoma of different types, the control series consisting of specimens from normal skin and from inflammatory dermatoses. The number of biopsy specimens was 190. The reticular framework was examined using Foot's method for staining the connective tissue. Karyometric examination was carried out in 16 cases. Before measurement, the nuclei were drawn on paper with the aid of an Abbé camera lucida, the linear magnification being 1 : 1200.

The results of the investigation on the reticular framework are presented and illustrated with plates of a series of 33 microphotographs.

Using a classification based on the predominating cell type, the lymphomas were divided into the following main groups:

lymphocytic type, well differentiated
lymphocytic type, poorly differentiated
reticulocytic type, well differentiated
reticulocytic type, poorly differentiated
polymorphic type
stem cell type

The reticular network exhibited features characteristic of each group.

In lymphomas of the well differentiated lymphocytic type a delicate framework was observed which formed a clear network. The network most nearly resembled the supporting network of the lymph nodes.

A reticular network was lacking in lymphomas of the poorly differentiated lymphocytic type. Among the tumor cells isolated and mostly short fragments of argyrophil fibers varying in thickness were seen.

In lymphomas of the well differentiated reticulocytic type, reticulin fibers surrounded capillaries and lined tissue spaces without forming a continuous network. The picture resembled that seen in lymphedema.

In lymphomas of the poorly differentiated reticulocytic type a regular network was generally lacking. In the tumor tissue a comparatively large number of reticulin fibers could be seen running in all directions and varying in length and thickness; they also occurred as isolated delicate fibrils between the cells. If there were areas in the tumor in which the stage of cell differentiation varied, then a different kind of network was also observed in the different areas. When the cells were very im-

mature the network was missing and if differentiation in a histiocytic direction had taken place, then the network formed a dense basket around the cells.

In Hodgkin's disease and mycosis fungoides the polymorphic cell infiltration occurred in a well-developed reticulin fiber network. In late tumor lesions in which the cell picture had changed to a monomorphic one, the network was irregular.

When stem cell lymphoma occurred in the form of cutaneous leukemia, it did not form reticulin fibers.

In cases with active cell proliferation, there were foci where the reticular network was lacking even in the initial lesions of lymphomas.

The reticular framework proved to be useful in the diagnosis of cutaneous lymphomas. By studying this network it was possible, for instance, to distinguish between some lymphoma erythrodermas and to confirm the diagnosis of mycosis fungoides d'emblee.

When cases belonging to the malignant lymphomas were compared with inflammatory proliferations of reticular tissue in the control series, karyometry demonstrated that the average nuclear size was larger in the group of cells which chiefly comprised endothelial and reticulum cells. A corresponding change was not observed in the histiocytic and lymphocytic cell groups. In two cases of poikiloderma atrophicans vasculare the nuclear size in the endothelial and reticulum cell groups was also considerably larger than in the controls.

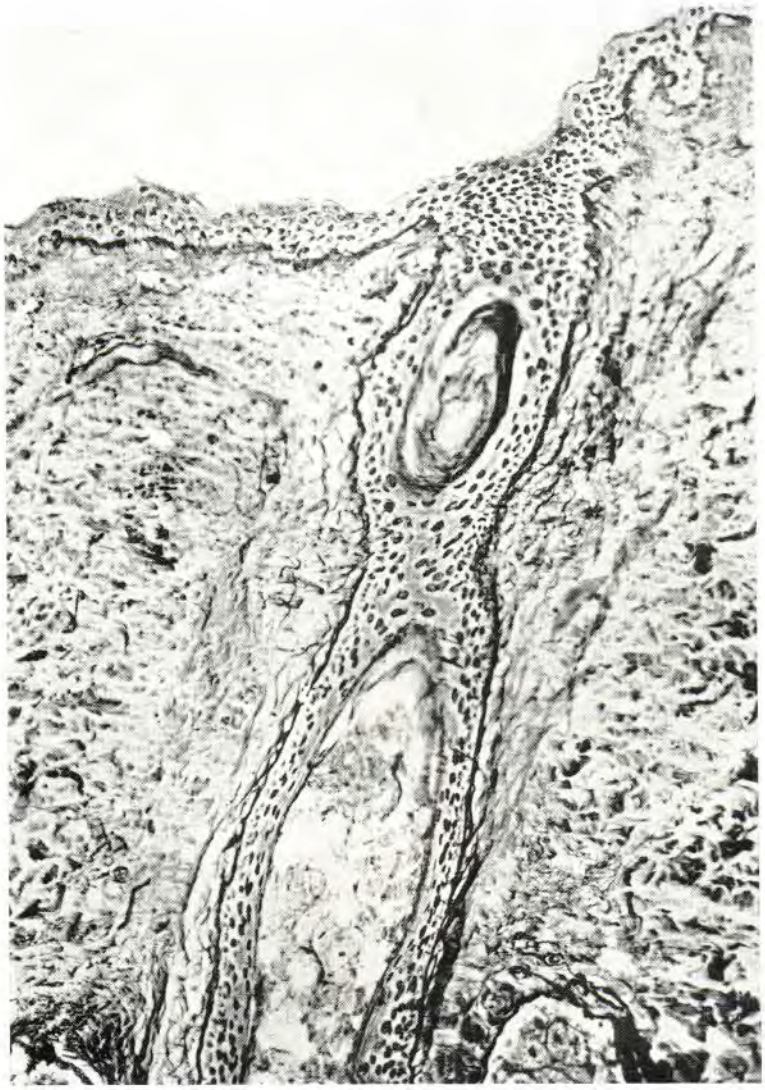


Fig. 1. Normal skin.
A narrow zone of reticular network surrounding a hair follicle. (Foot × 300)

Fig. 2. Normal skin.

Fringe-like short argyrophil fibers extend between the basal cells. Delicate reticulin fibers in the surroundings of the arterioles. (Foot × 300)

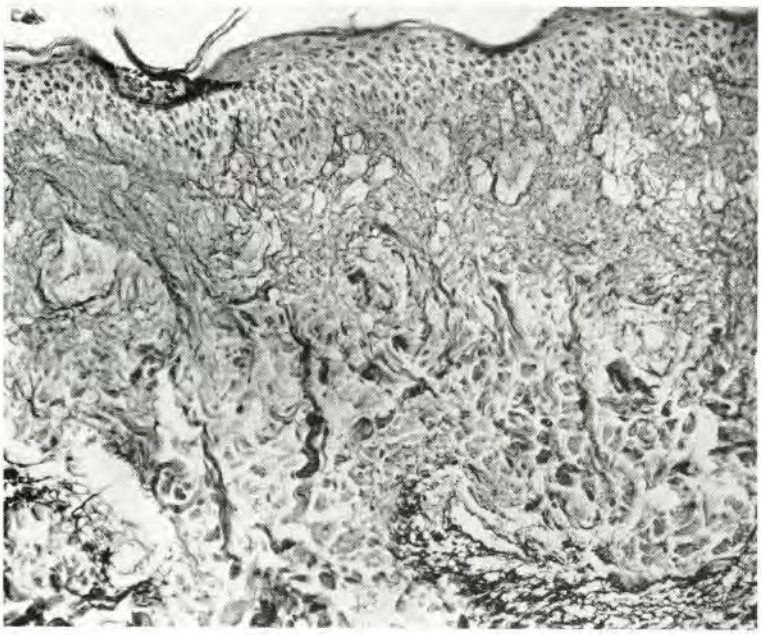


Fig. 3. Syphilitic papule. Case 1.

In the upper third of the corium reticulin fibers surround the enlarged capillaries and line the interstitial spaces, forming a continuous lattice-work. (Foot × 300)

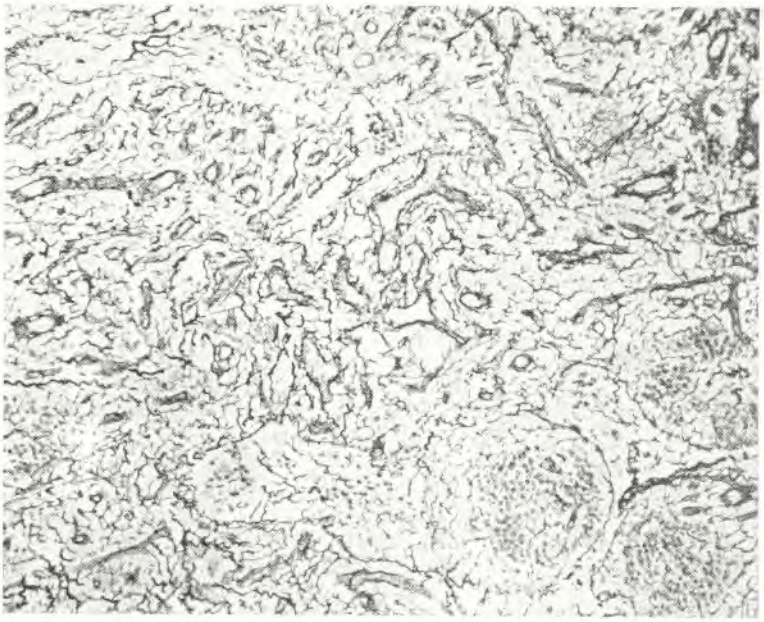


Fig. 4. Hypoproteinemic edema and eczema. Case 2.

In the edematous corium reticulin fibers and line the interstitial spaces. At the site of dense plasmocytic cell aggregations in the right corner the fibers are missing. (Foot × 300)

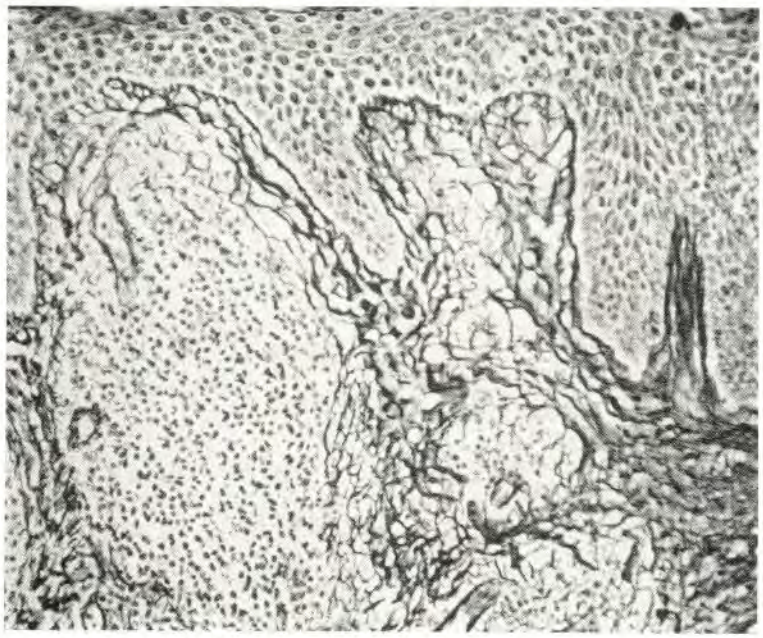


Fig. 5. Lichen ruber planus. Case 3.

In the right border of the figure a zone of fine collagen is seen. It divides into thinner argyrophil fibers around the cell infiltrations. The network is missing at the site of dense lympho cytic cell aggrge ations. (Foot × 300)

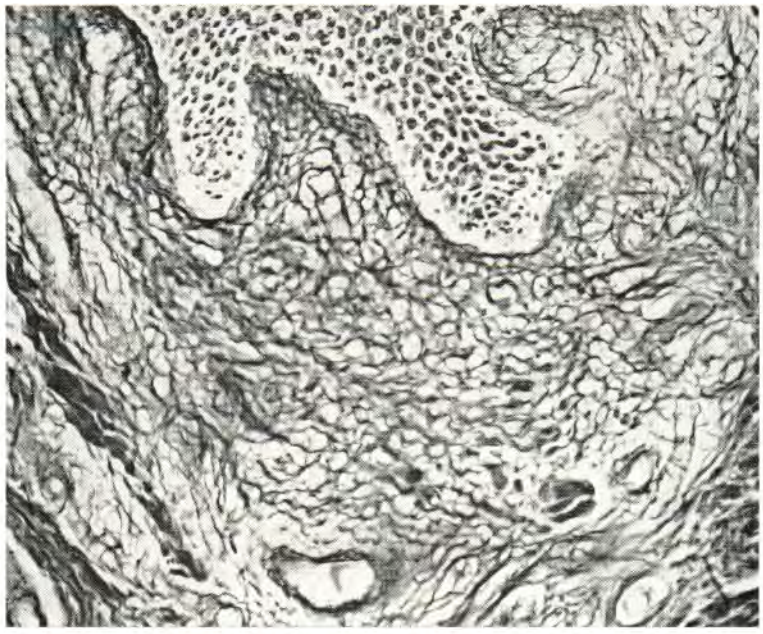


Fig. 6. Lichen ruber planus, a hyperkeratotic lesion. Case 4.

The reticular network is well developed. The fibers are long and in places a gradual transformation into collagenous fibers is seen. (Foot × 300)

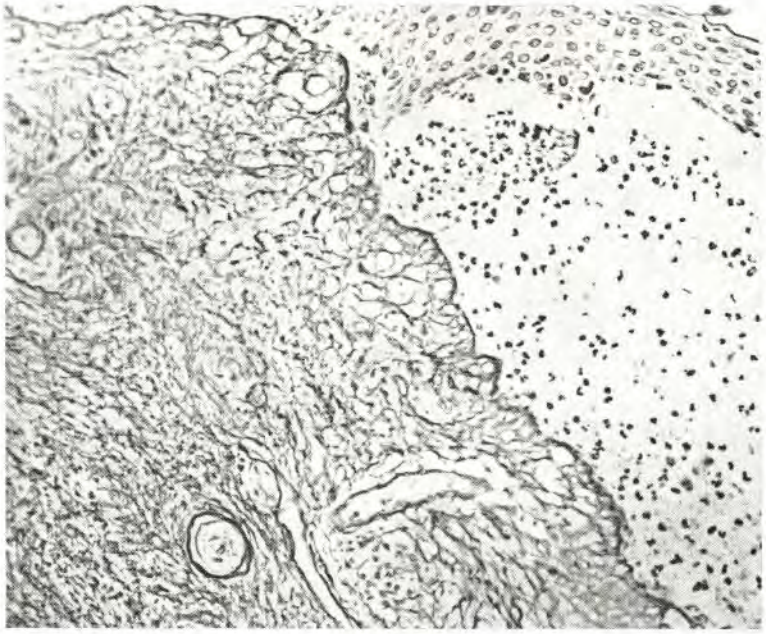


Fig. 7. Dermatitis herpetiformis. Case 5.

In the upper part of the corium the reticulin fibers surround the capillaries and line the interstitial spaces forming the floor of the vesicle. (Foot × 300)

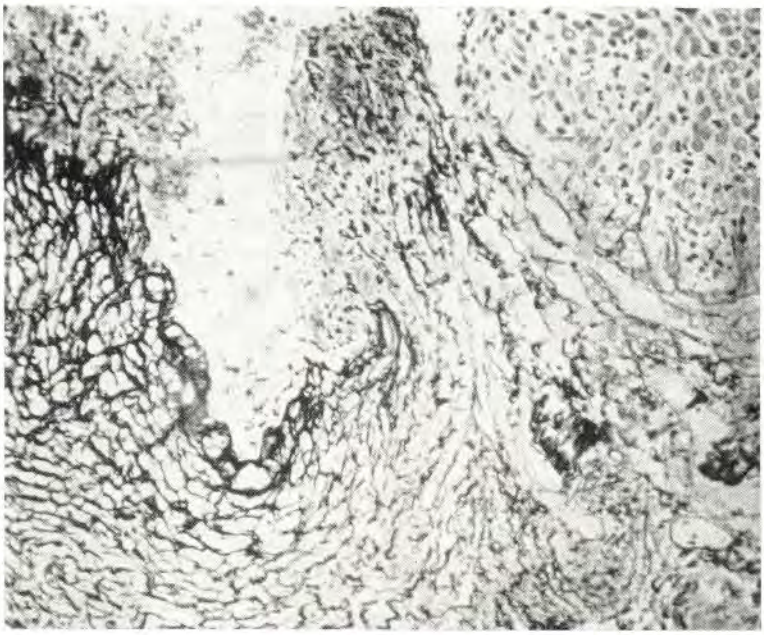


Fig. 8. Dermatitis herpetiformis, an infected vesicle. Case 6.

The infectious exudate has torn the supporting network and penetrates through the epidermis. (Foot × 300)

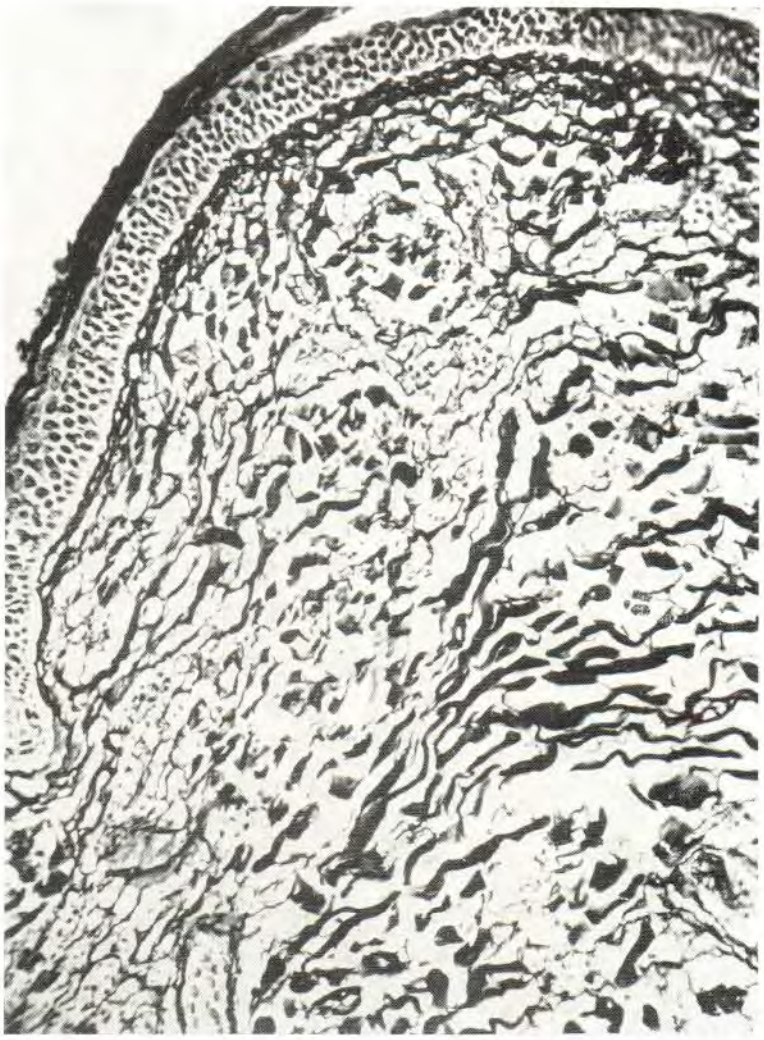


Fig. 9. Acrodermatitis atrophicans. Case 7.

There are dense argyrophil fibers just beneath the epidermis. The collagenous fibers are fragmented. A sparse reticular network is seen in areas of cell infiltrates. (Foot × 300)

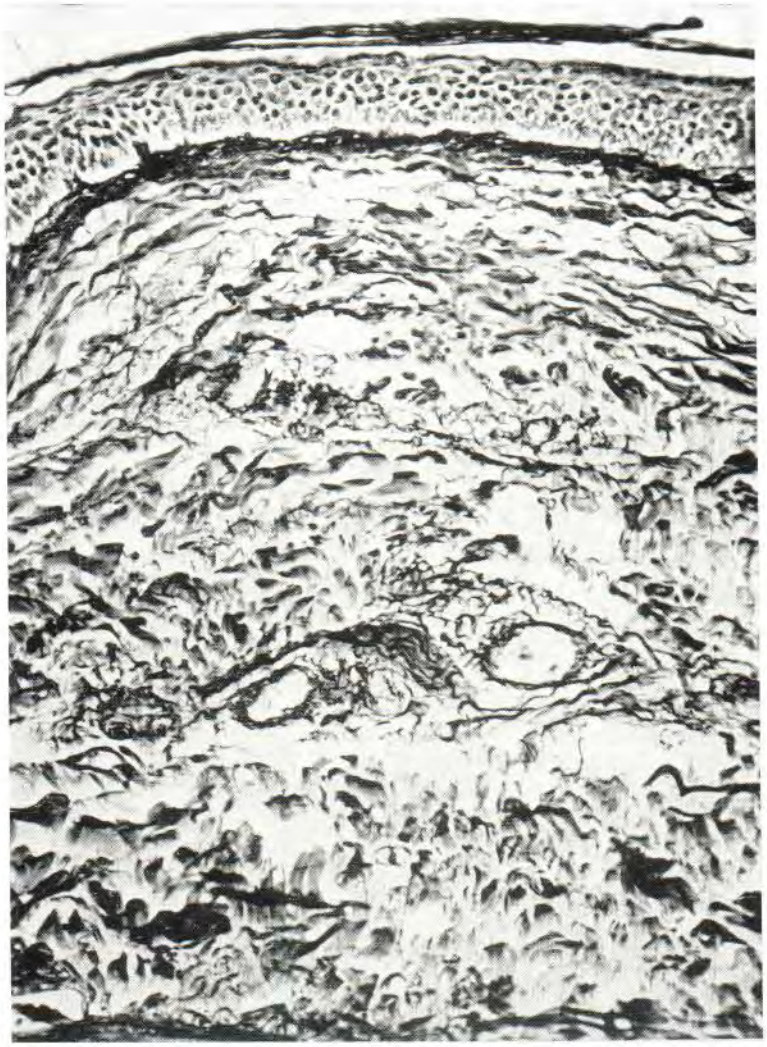


Fig. 10. Acrodermatitis atrophicans, atrophic stage. Case 7.

Beneath the atrophic epidermis a dense zone of parallel argyrophil fibers. Deeper in the corium reticulin fibers in the surroundings of the enlarged vessels. (Foot × 300)

Fig. 11. Poikiloderma congenitale. Case 8.
In the upper corium a delicate reticular network. (Foot × 300)

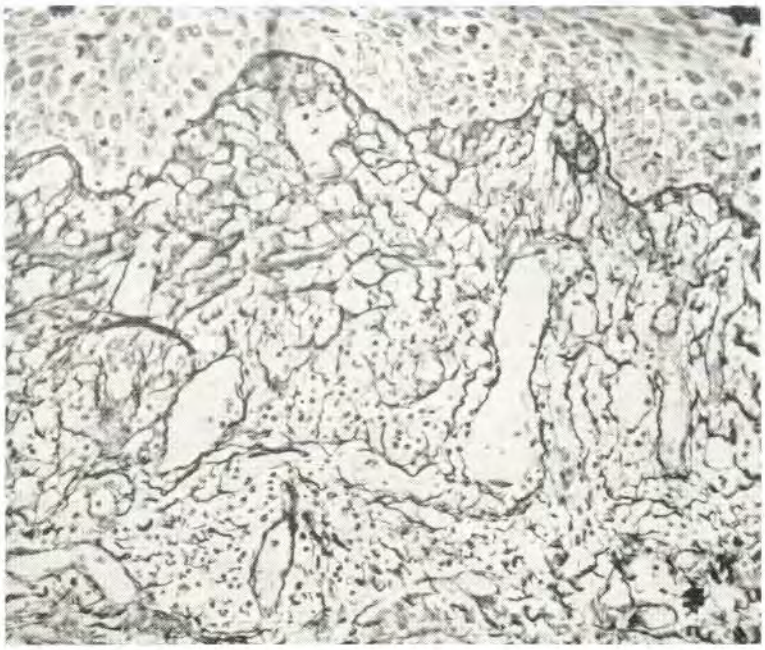


Fig. 12. Poikiloderma atrophicans vasculare. Case 9.
In the upper corium a well developed reticular network. Deeper, cell aggregations with only isolated fibers. (Foot × 300)

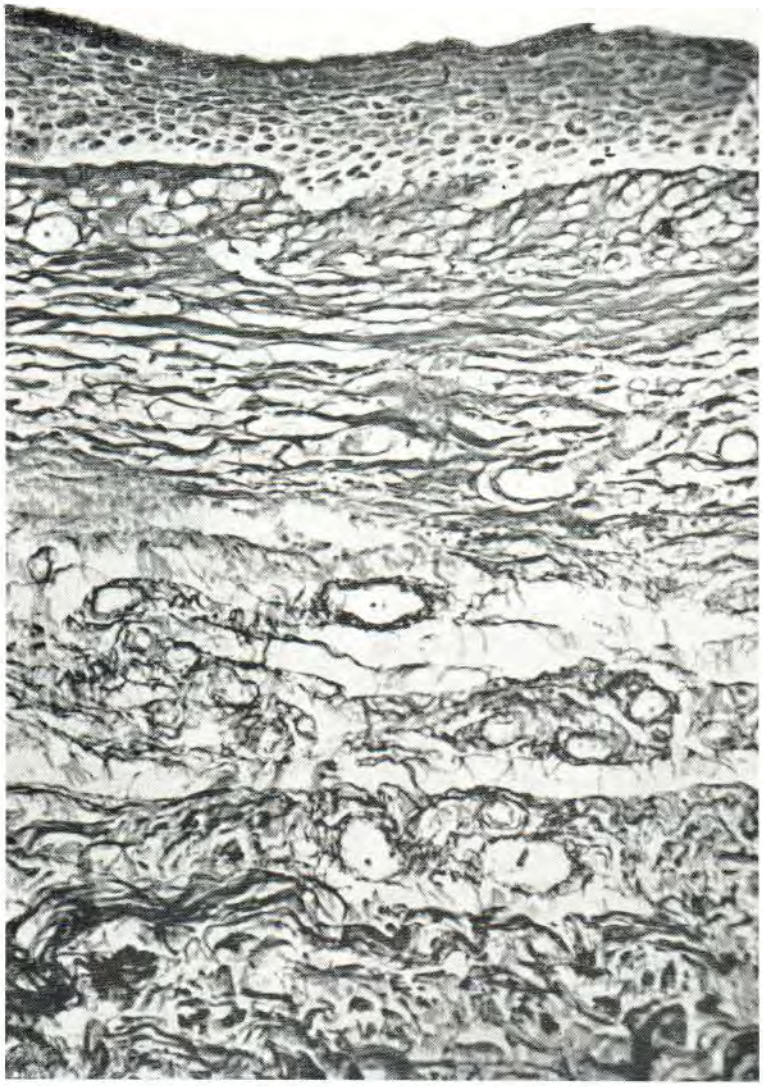


Fig. 13. Poikiloderma atrophicans vasculare, atrophic stage. Case 9.
In the upper corium a dense zone of parallel argyrophil fibers. (Foot × 300)

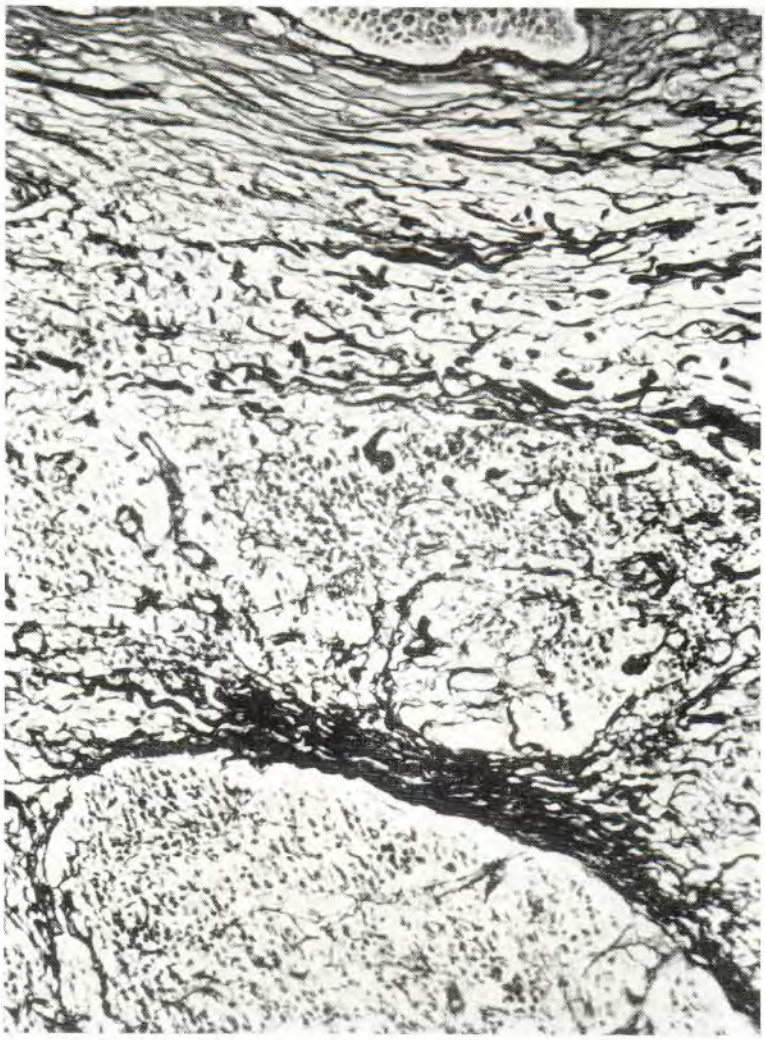


Fig. 14. Lymphadenosis cutis benigna. Case 12.

Deep in the corium structures resembling lobules of the lymph nodes surrounded by connective tissue trabeculae. Cell aggregations without fibers. (Foot × 300)

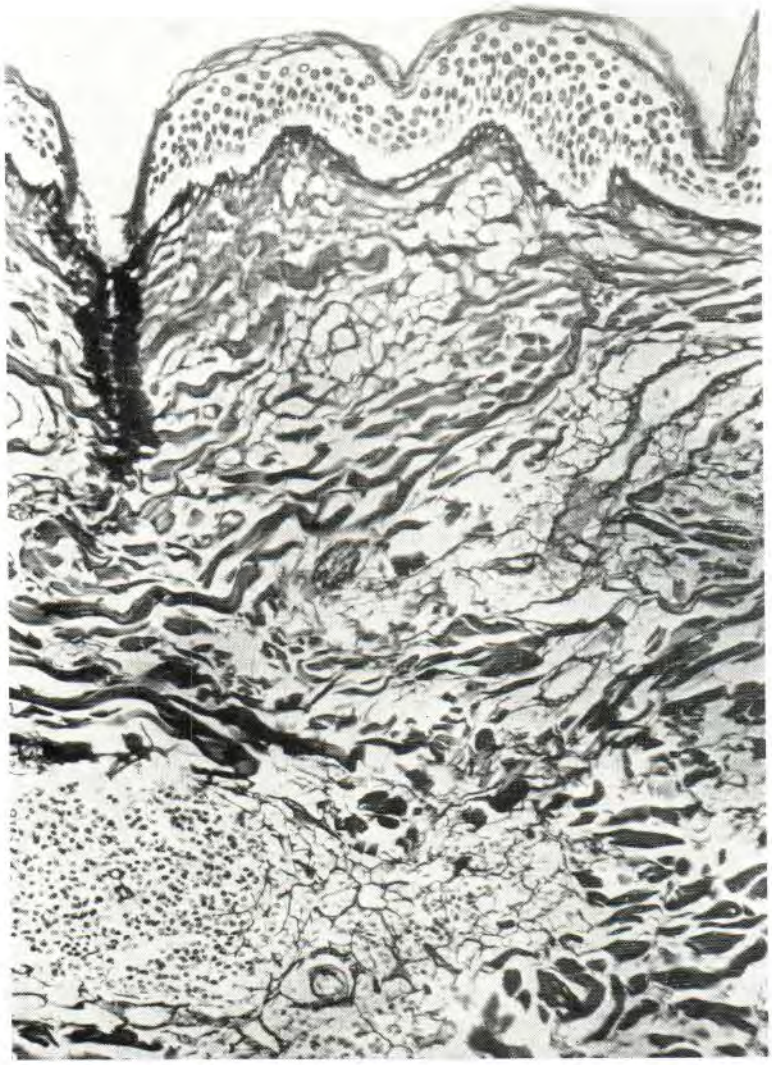


Fig. 15. Lymphoma lymphocyticum, well differentiated. Case 13.

At the site of the dense cell aggregations reticulin fibers are missing. Islets of reticular network are seen in the surroundings of the enlarged capillaries. (Foot × 300)

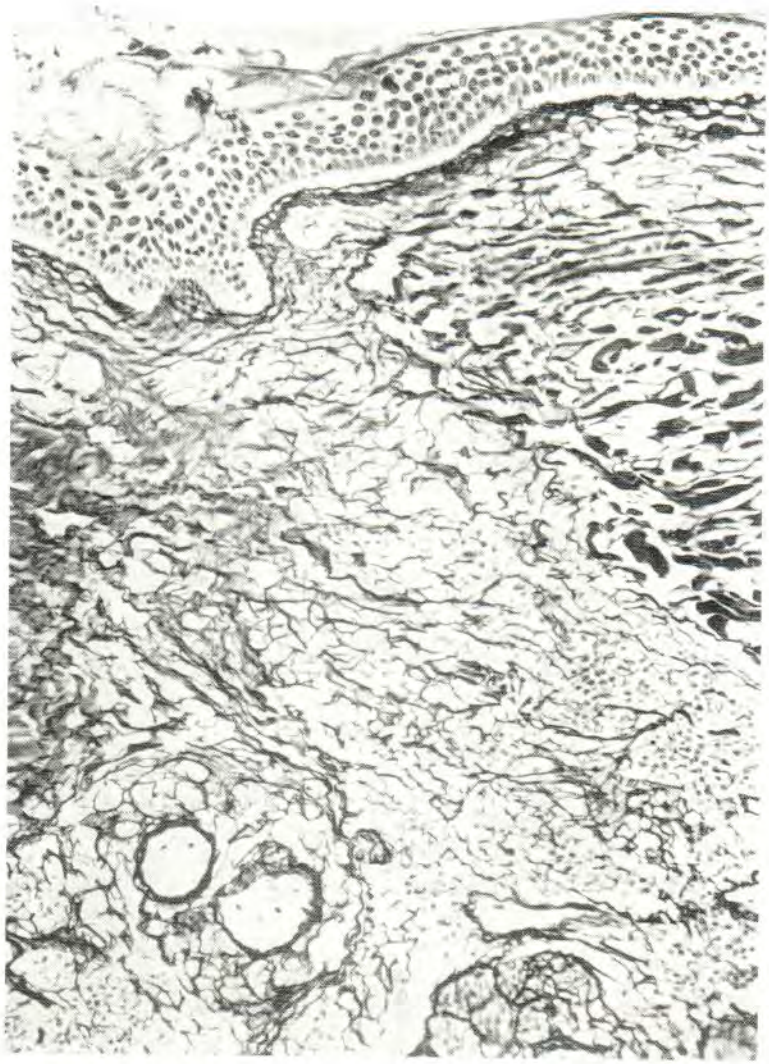


Fig. 16. Lymphoma lymphocyticum, well differentiated. Case 13.

In large areas of the corium the collagenous fibers are fragmented. These fragments are seen between the infiltrative cells. A well developed reticular network is missing. (Foot × 300)

Fig. 17. Lymphoma lymphocyticum, well differentiated. Case 14.
Deep in the corium large cell aggregations located in a delicate reticular network. (Foot × 300)

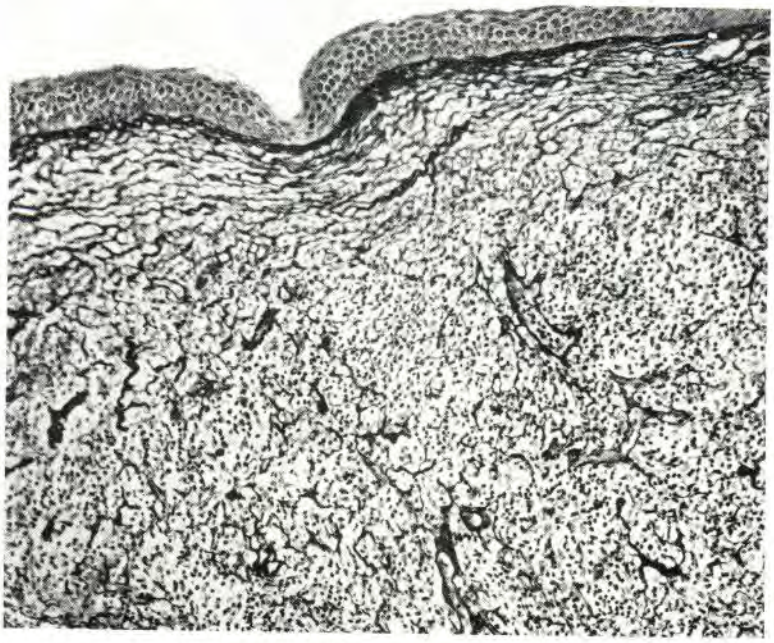


Fig. 18. Lymphoma lymphocyticum, poorly differentiated in a patient with acrodermatitis atrophicans. Case 15.
Beneath the epidermis an atrophic zone with parallel argyrophil fibers. Deeper in the tumor tissue the reticular network is missing. Fibers occur irregularly here and there surrounding capillaries or lining interstitial spaces. (Foot × 300)

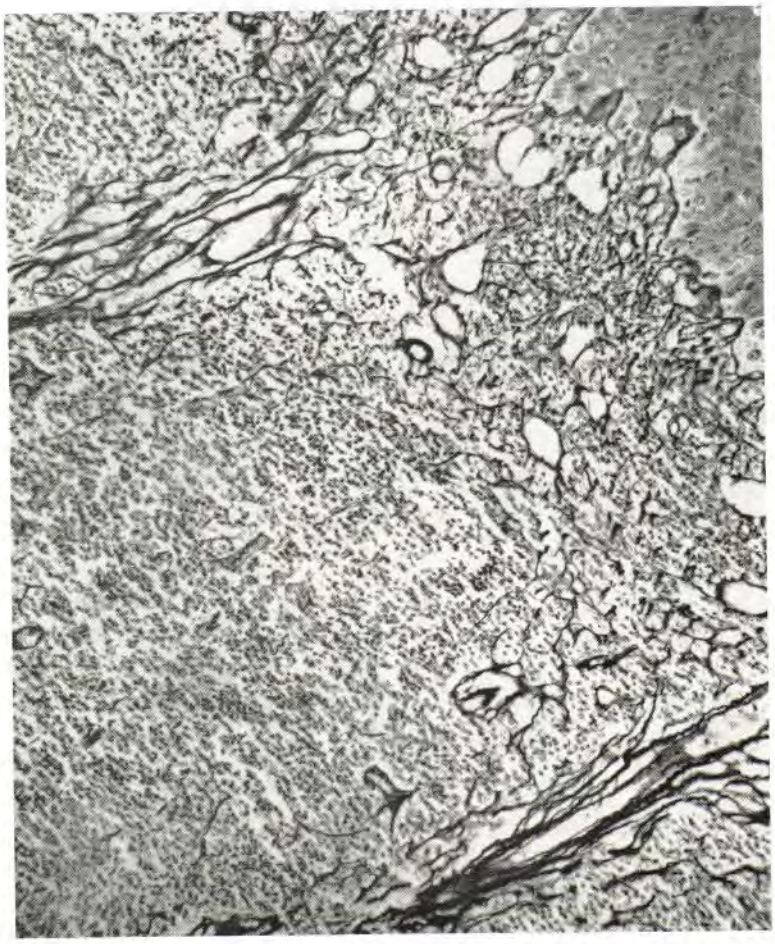


Fig. 19. Lymphoma lymphocyticum, poorly differentiated. Case 16.

The tumor tissue reaches to the epidermis. The supporting network of reticulin fibers is missing. Fibers occur here and there lining interstitial spaces or as separate fibrils between the cells. Vertical bundles of argyrophil fibers are remnants of hair follicles. (Foot × 300)

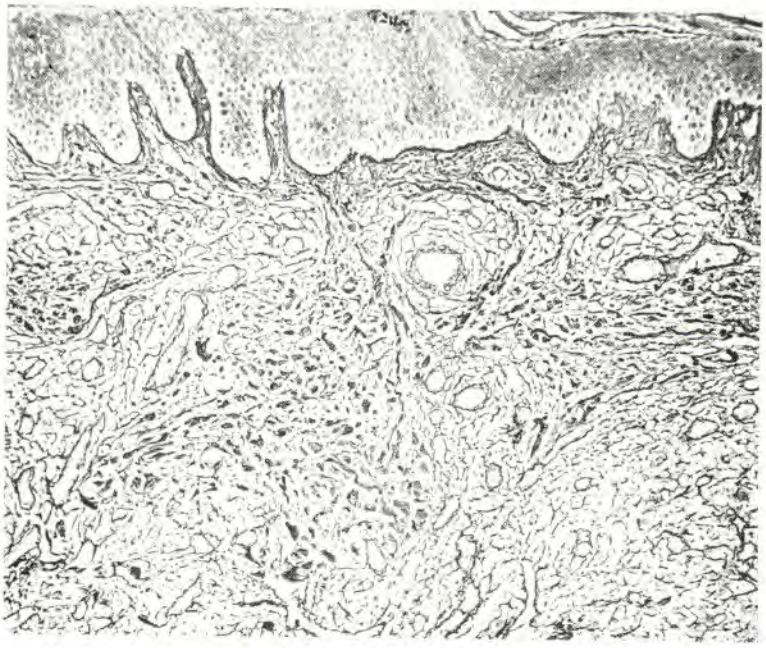


Fig. 20. Lymphoma reticulocyticum, well differentiated. Case 19.

In the upper part of the corium around the capillaries is a well developed reticular network. Deeper between the reticulum cells the fibers line the interstitial spaces without forming a continuous network. (Foot × 300)

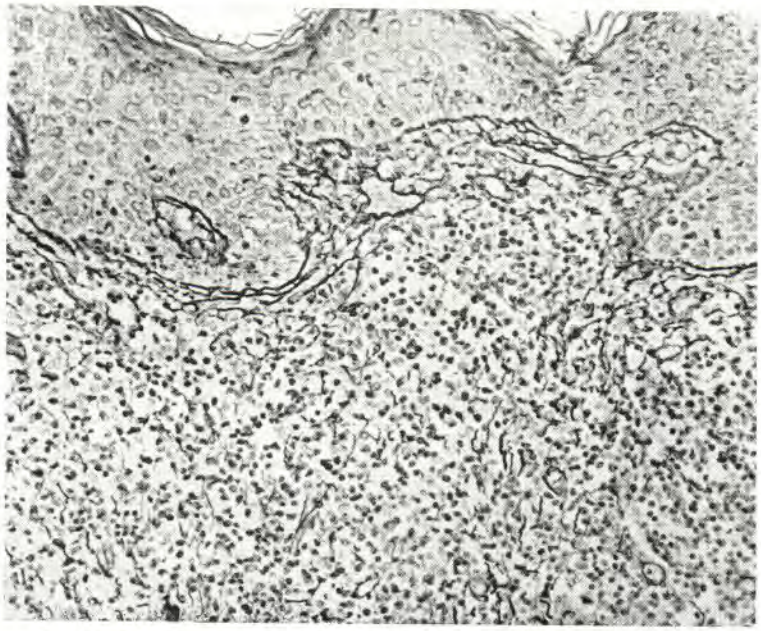


Fig. 21. Lymphoma reticulocyticum, poorly differentiated. Case 20.

A supporting network of reticulin fibers is missing. Isolated fibrils occur between the cells. (Foot × 300)

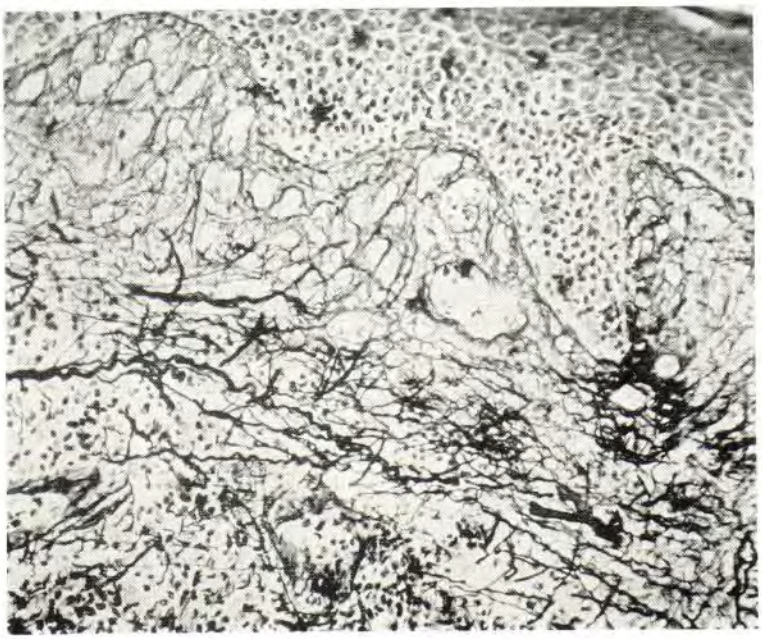


Fig. 22. Lymphoma reticulocyticum, poorly differentiated. Case 21.

In the tumor tissue are collagenous fiber fragments of varying length and thickness running in all directions. Reticulin fibers are seen only as separate fibrils between the cells. (Foot × 300)

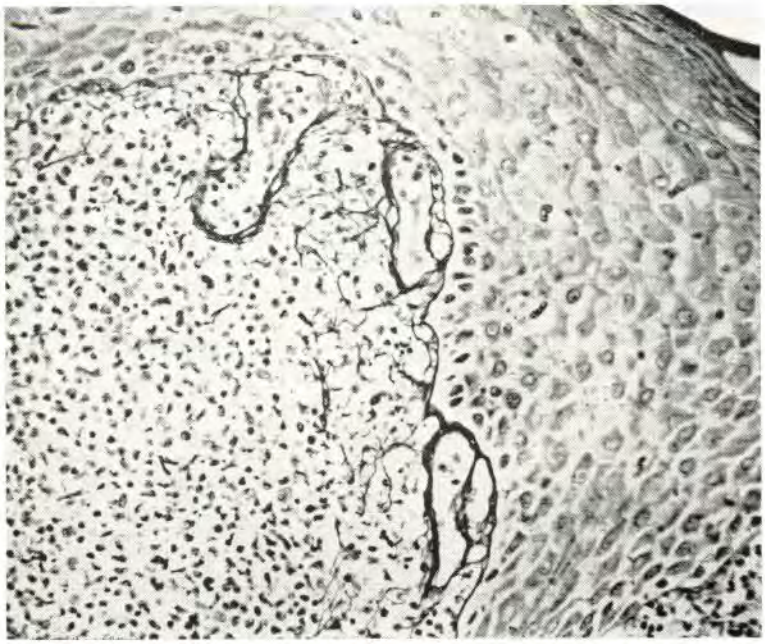


Fig. 23. Lymphoma reticulocyticum, poorly differentiated. Case 22.

The supporting reticular network is missing. At the dermo-epidermal junction irregular bundles of argyrophilic fibers are seen. (Foot × 300)

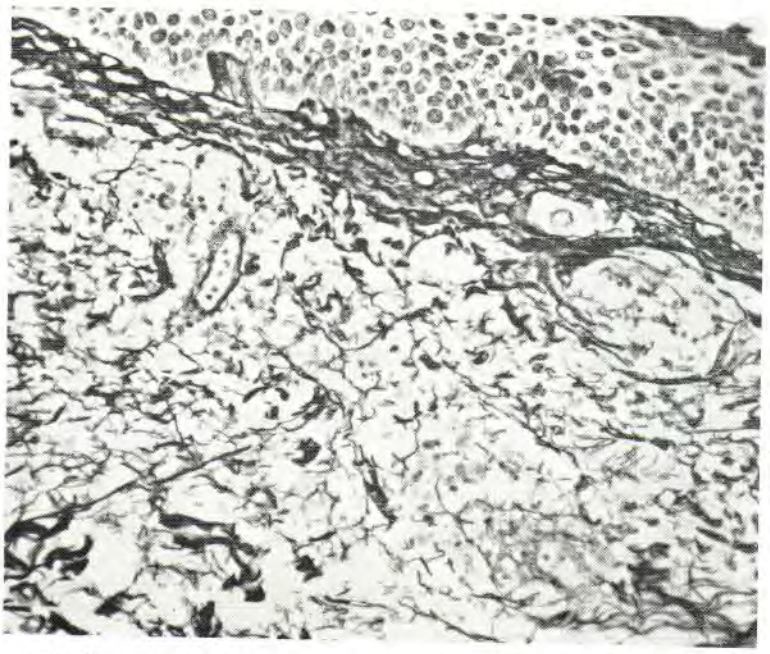


Fig. 24. Lymphoma reticulocyticum, poorly differentiated. Case 22.

The supporting network is missing. There are fragments of collagenous fibers varying in length and thickness. Reticulin fibers are seen only as separate filaments. (Foot × 300)

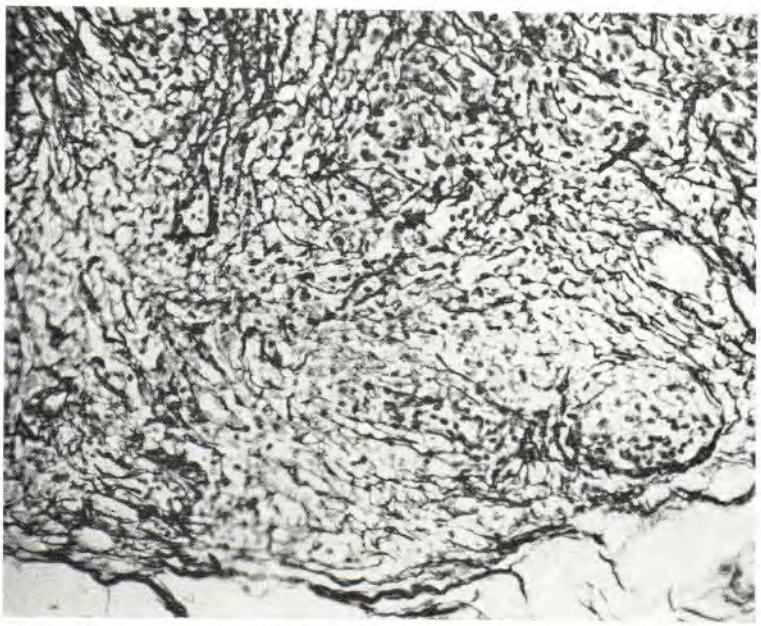


Fig. 25. Lymphoma reticulocyticum, poorly differentiated. Case 22.

The reticular network is well developed forming a dense basketwork around the cells. (Foot × 300)

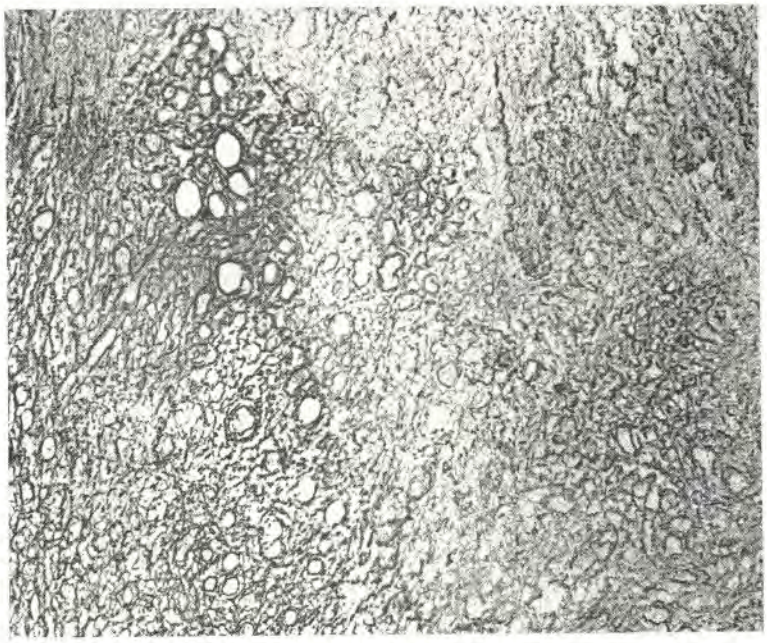


Fig. 26. Hodgkin's disease. Case 23.
A well developed reticular network is present. (Foot × 300)

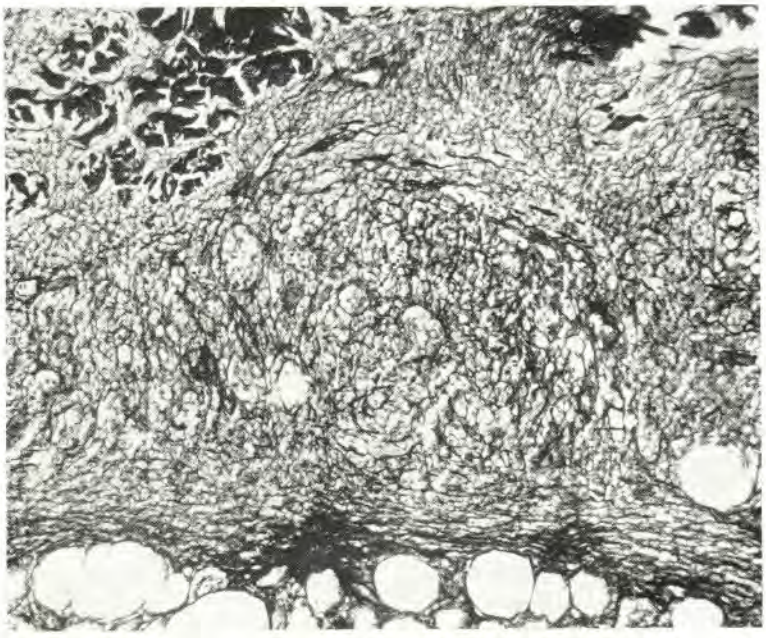


Fig. 27. Hodgkin's disease. Case 26.
A highly developed reticular network, dense, irregular and with fine meshes. (Foot × 300)

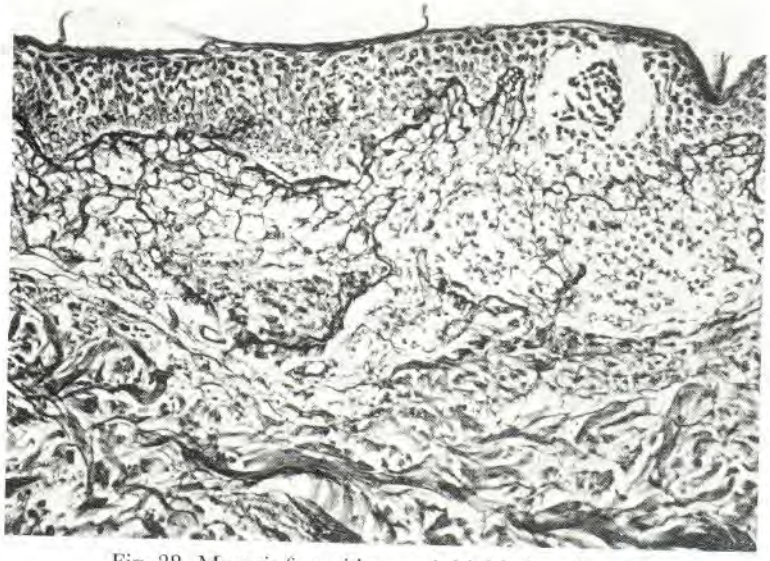


Fig. 28. Mycosis fungoides, an initial lesion. Case 29.

A zone of well developed reticular network is present in the papillary layer. Under Pautrier's abscess at the site of a dense aggregation of cells the network is missing. (Foot × 300)

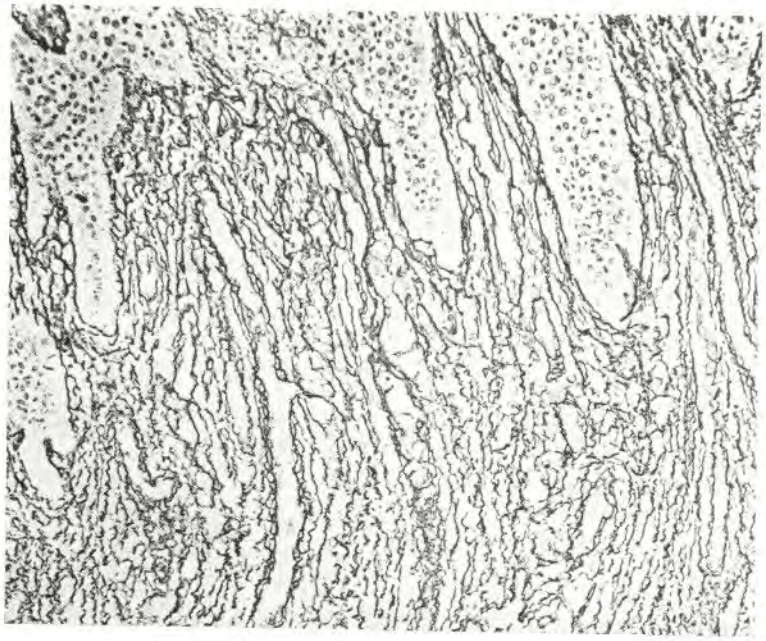


Fig. 29. Mycosis fungoides, tumor. Case 30.

There is a well developed supporting network of reticulin fibers. (Foot × 300)

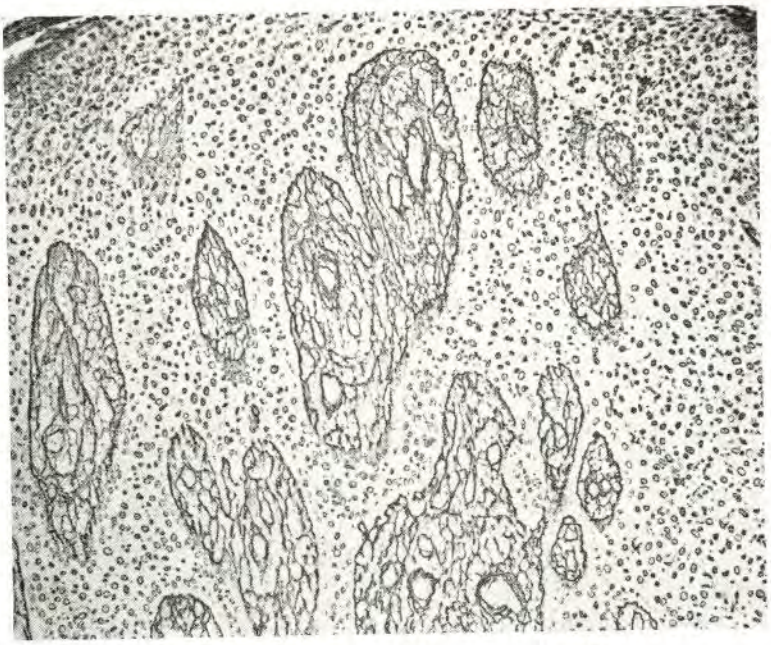


Fig. 30. Mycosis fungoides, tumor. Case 31.
The well developed reticular network is seen in an oblique section of the surroundings of blood vessels between the epidermal processes. (Foot × 300)

Fig. 31. Mycosis fungoides, autopsy specimen of tumor. Case 29.
The reticular network is poorly developed or lacking. (Foot × 300)

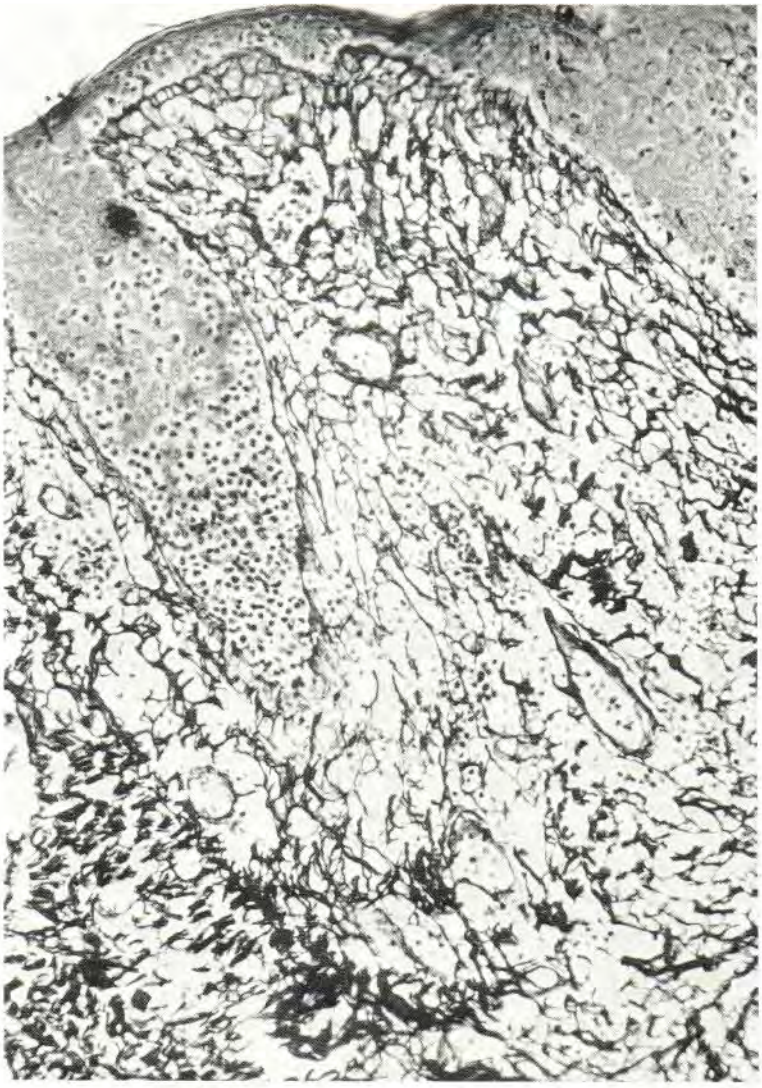
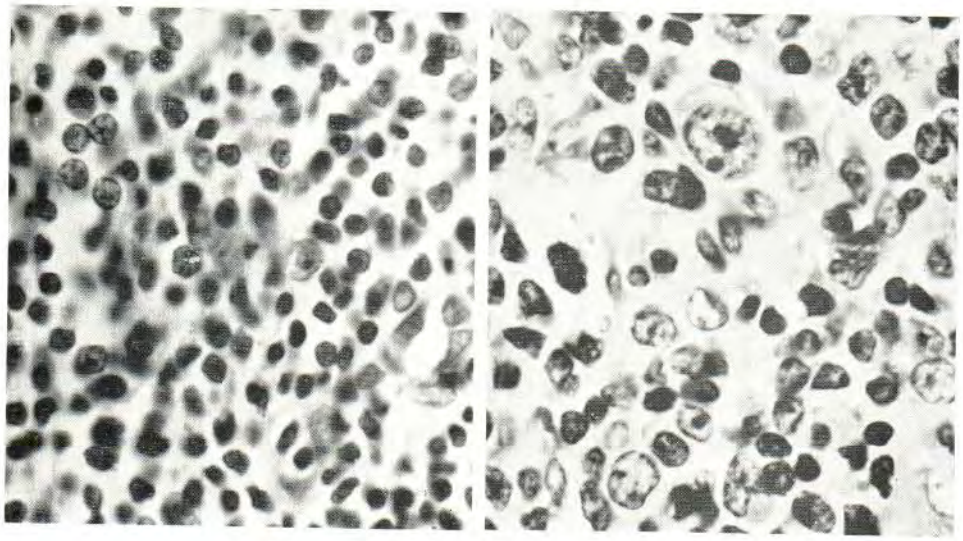
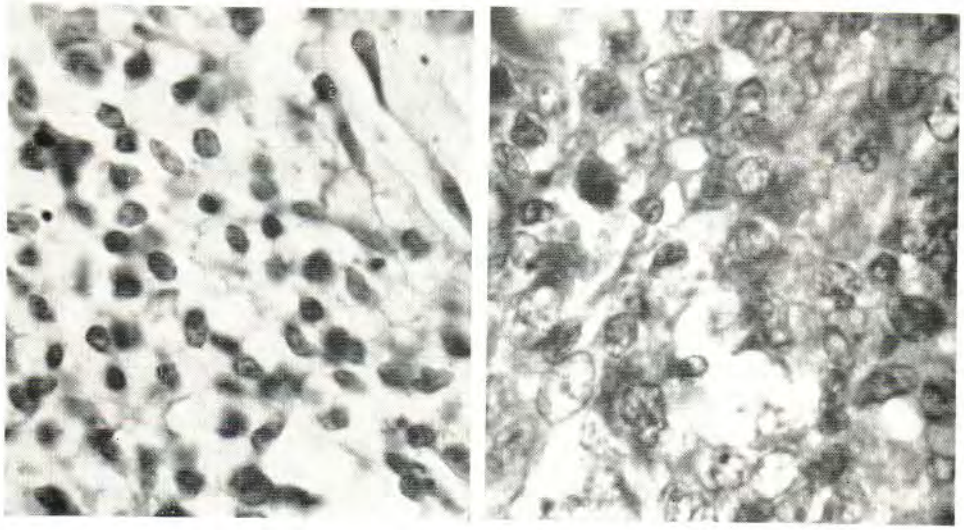


Fig. 32. Mycosis fungoides, autopsy specimen of tumor. Case 29.
The collagenous fibers are fragmented. The reticular network is irregular and poorly developed. (Foot × 300)

Fig. 33. Stem cell lymphoma. Case 34.
The supporting network of reticulin fibers is missing. (Foot × 300)



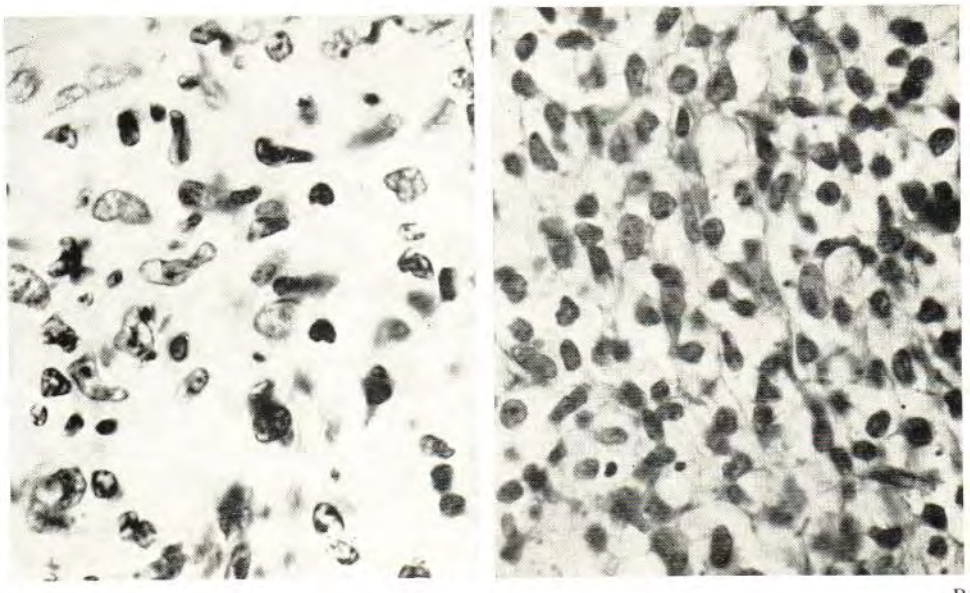
A B



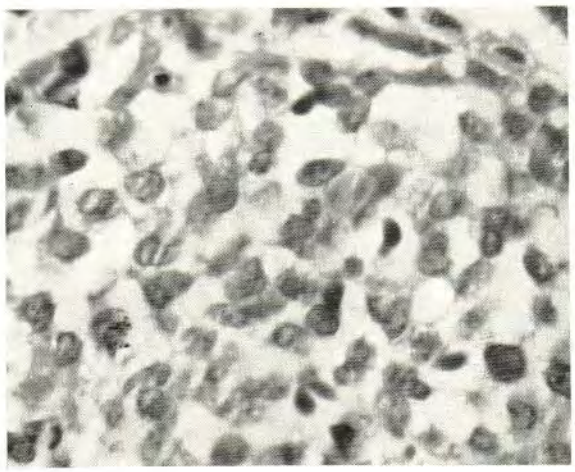
C D

A. Lymphocytic lymphoma, well differentiated, case 14.
B. Lymphocytic lymphoma, poorly differentiated, case 16.
C. Reticulum cell lymphoma, well differentiated, case 19.
D. Reticulum cell lymphoma, poorly differentiated, case 22.

Fig. 34
(Hemalaum-eosin × 800)



A B



C

A. Hodgkin's disease, case 27.
B. Mycosis fungoides, tumor, case 30.
C. Stem cell lymphoma, case 34.

Fig. 35
(Hemalaum-eosin × 800)

VII. CLINICAL CASE REPORTS

CASE 1.

Diagnosis: Lues secundaria. Syphilides maculopapulares. Condylomata lata reg. ani. Rec.no. 363/59.

A man aged 49. In February 1959, reddish eruption appeared, first on the skin of the trunk and later over the entire body. Examination in March revealed the following changes: Everywhere, including the scalp and the skin of the palms and soles, reddish and in places slightly scaling maculopapules 3 to 10 mm in diameter. In the anal region condylomata lata formations 1.5 to 3 cm wide. Tufts of hair loosened on pulling. Bean-sized inguinal and pea-sized cubital lymph nodes were palpated.

Treponema pallidum was found in the condylomas. Serological tests for syphilis: Wr., chol.Wr., Kahn and sitolipin positive.

Histology: A slightly acanthotic epidermis. In the papillary layer the blood vessels are dilated and their endothelial cells swollen. Perivascular lymphocytic and plasma cell infiltrations.

Silver impregnation: In the papillae of the corium and in their immediate neighborhood in the upper dermis, delicate argyrophil fibers surround the capillaries and line the interstitial spaces, forming a uniform reticular structure. The deeper layers of the dermis are fairly normal (fig. 3).

CASE 2.

Diagnosis: Oedema et exzema staticum crurum amborum. Nephrosonephritis. Hypoproteineamia. Rec.no. 280/59.

A woman aged 48. Since 1956, she had suffered from nephropathy. The amount of albumin in the urine has varied between 0.5 and 0.9 per cent. Since April 1958, she has had edema of the legs. Examination in February 1959 showed marked edema of the legs and feet. The skin of the legs was erythematous and nodular. Normal blood count. Blood pressure 150/100 mmHg.

Electrophoresis: albumin and alpha$_1$globulin 25.9, alpha$_2$- and betaglobulin 61.2, gammaglobulin 12.9 per cent.

Urine albumin 0.9 per cent.

Total plasma proteins 4.3 per cent. ESR 102 mm in one hour.

Histology: The whole corium is edematous and enlarged, with many dilated veins and capillaries. Perivascular lymphocyte and plasma cell aggregations, which in places coalesce to form large infiltrations.

Silver impregnation: Surrounding the capillaries and lining the interstitial spaces is a delicate argyrophil reticulum. In the dense cell aggregations fibrils are lacking or are seen as separate filaments between the cells (fig. 4).

CASE 3.

Diagnosis: Lichen ruber planus. Rec.no. 2937/59.

A woman aged 23. Since 1954, she has suffered from exacerbations of lichen ruber planus. Two weeks prior to presentation purplish papules again appeared on a palm-sized area of the skin of the left thigh.

Histology: The horny layer of the epidermis is thickened. The granular layer is accentuated and the rete ridges elongated. The basal cell layer is well preserved. In the papillary part of the dermis there is a dense lymphocytic infiltration.

Silver impregnation: In the dense lymphocytic infiltration argyrophil fibers are lacking. In the margins of the infiltration, where the cells are not so abundant and where histiocytes are seen, the argyrophil reticulum is well developed (fig. 5).

CASE 4.

Diagnosis: Lichen ruber planus, hypertrophicus. Rec.no. 563/59.

A woman aged 57. Has suffered for several months from pruritic hyperkeratotic lichen ruber planus on the anterior surface of both legs. At times purplish papules have appeared on the volar surface of the wrists and on the thighs.

Histology: The epidermis is hyperkeratotic, the stratum granulosum being thickened. There is uneven acanthosis. The dermis is infiltrated, often as far as the epidermis, where the basal layer is lacking. There are histiocytes and fibrocytes among the lymphocytes.

Silver impregnation: In the upper dermis there is a well developed argyrophil network. The fibers are long and in places a gradual transformation into collagenous fibers is seen (fig. 6).

CASE 5.

Diagnosis: Dermatitis herpetiformis. Rec.no. 1088/59.

A woman aged 70. She had experienced attacks of itching for 4 years. In August, 1959, a bullous eruption appeared in symmetrical areas on the forearms, shoulders and legs.

Histology: A subepidermal vesicle, which mostly contains eosinophils. Edema and cell infiltration in the upper corium, the cells being lymphocytes, eosinophils and neutrophils.

Silver impregnation: In the upper corium the argyrophil fibers line the interstitial spaces forming the floor of the vesicle (fig. 7).

CASE 6.

Diagnosis: Dermatitis herpetiformis. Infectio secundaria. Rec.no. 852/59.

A woman aged 42. Six weeks prior to presentation itching and blisters had appeared on the skin of the trunk and extremities. The skin was excoriated by scratching and the lesions purulent.

Histology: A large infectious infiltrate is seen in the upper corium. It contains many neutrophils, and only a few eosinophils. The center of the infiltrate is necrotic. In other parts of the corium there is a cell infiltration typical of dermatitis herpetiformis.

Silver impregnation: A well developed argyrophil network in the upper corium. The infectious exudate has torn the supporting network and penetrates through the epidermis (fig. 8).

CASE 7.

Diagnosis: Acrodermatitis atrophicans Herxheimer. Rec.no. 643/57.

A woman aged 42. Since 1940, the skin of the lower extremities and the gluteal region had gradually become purplish, wrinkled and thin, the blood vessels beginning to show through the skin. Redness and infiltration in the upper gluteal region. Biopsy of the infiltration.

Histology: The epidermis is thin and atrophic. The whole corium is edematous. Between the collagenous fibers and perivascularly there are cell infiltrations containing lymphocytes and histiocytes.

Silver impregnation: At the boundary between the corium and epidermis is a thick layer of argyrophilic fibers lying parallel with the surface. A delicate reticular network is seen between the fragmented collagenous fibers (fig. 9).

The patient was treated with 9 million I.U. of penicillin. Three months later a new biopsy was taken from the same area. The redness and infiltration had disappeared and the skin was pale and atrophic.

Histology: The epidermis is thin and band-like. The collagenous bundles are straight and rigid. Between them dilated capillaries and small perivascular lymphocytic infiltrations are seen.

Silver impregnation: In the upper corium argyrophil fibers run parallel with the surface. Deeper in the corium there is a reticular network in the surroundings of the dilated blood vessels (fig. 10).

CASE 8.

Diagnosis: Poikiloderma congenitale. Rec.no. 848/59.

A woman aged 30. She had suffered since birth from a striate eruption, which first appeared as a 5 cm broad zone on the skin of the lower abdomen above the inguinal folds. During the past two years this zone had broadened and an eruption

had appeared on the upper part of the thighs, below the breasts, on the neck, and in the sacral and popliteal regions. Three years previously epileptic attacks began, which were controlled by treatment with barbiphenyl and hydantin.

The skin disorder consisted of small papules arranged in lines following the wrinkling of the skin. The bilateral lesions were situated symmetrically on the skin of the abdomen (fig. 36), as narrow zones below the breasts, in the popliteal regions and on the skin of the upper thighs, and as islets on the neck and in the sacral region. The surface of the papules was even, and the yellowish red color disappeared on pressure. The bones of the cranium and the long bones were roentgenologically normal. Ophthalmoscopic examination of the eyes revealed no changes.

Histology: The epidermis is thin and atrophic. The rete pegs are shortened. The upper third of the dermis is fibrotic; in the papillary portion the blood vessels are dilated, and there are many enlarged interstitial spaces. In the upper dermis corresponding to the follicular structure of the skin, there are regularly spaced perivascular lymphocytic infiltrations.

Silver impregnation: There is a delicate argyrophil network in the papillary portion of the dermis corresponding to the sites of the perivascular lymphocytic infiltrations (fig. 11).

CASE 9.

Diagnosis: Poikiloderma atrophicans vasculare. Rec.no. 468/57.

A woman aged 63. Had suffered from the actual eruption for about 9 years. The first patch appeared on the inner side of the left upper arm, and later patches appeared on the trunk and lower extremities. The patches were mostly dry and scaling. Some of them healed, leaving the skin thin and wrinkled. Some patches were temporarily reddish and sometimes even oozing.

In 1948, the patient was treated with x-rays for metrorrhagia. For two years she had suffered from high blood pressure and attacks of palpitation.

Examination in June 1957: On the skin of the trunk and extremities, roundish slightly scaling patches of varied size were seen. On both upper arms and the posterior surface of the right thigh were large, atrophic, pigmented areas.

The pulse was irregular and uneven. Blood pressure 200/105 mm Hg. No palpable lymph nodes. Spleen and liver not enlarged. Normal blood count. ESR 19 mm in one hour.

Histology: An infiltrated patch: In the upper dermis a dense inflammatory cell infiltration is seen. The cells are lymphocytes and histiocytes. The capillaries and interstitial spaces are enlarged.

Silver impregnation: In the upper corium a well developed, reticular network. In the deeper layers there are cell aggregations with only isolated fibers (fig. 12).

Histology: An atrophic patch: The epidermis is atrophic and its basal layer degenerated. There is homogenization and sclerosis of collagen with little inflammatory infiltrate. The capillaries are dilated.

Silver impregnation: In the upper corium there is a dense zone of parallel argyrophil fibers. The lower corium shows dilated capillaries and in their surroundings a delicate reticulum (fig. 13).

CASE 10.

Diagnosis: Poikiloderma atrophicans vasculare. Rec.no. 1589/59.

A woman aged 55. She had suffered from the actual skin disease for over 10 years. The first patches appeared on the skin of the abdomen, and similar patches later appeared on the thighs and legs. The patches remained unchanged for years. They did not itch or cause any other discomfort.

Appendicectomy at the age of 25, operation for hernia at the age of 53. Menopause at 40. Diabetes mellitus was diagnosed in 1959.

Examination in December 1959: On the skin of the trunk and the lower extremities there were brownish red, slightly scaling patches, varying in diameter from 5 to 10 cm. Most of the patches were slightly infiltrated, some of them showing little atrophy. No enlarged lymph nodes. The liver and spleen were not palpable.

Blood count: Hgbn 13.1, erythrocytes 4940, index 0.94, leukocytes 6200, segmented cells 47, eosinophils 1.0, basophils 0.5, monocytes 14.5, lymphocytes 37. Total plasma proteins 7.5 per cent.

Positive Nylander test. Blood sugar 127 mg per cent.

Electrophoresis: albumin 93, alfa$_1$globulin 6, alfa$_2$globulin 11, betaglobulin 15, gammaglobulin 25.

Histology: The epidermis is atrophic. In the upper dermis an inflammatory cell infiltration is visible as a uniform zone, the cells being lymphocytes and histiocytes. In places the inflammatory cells are migrating through the epidermis.

Silver impregnation: In the upper dermis there is a well developed argyrophil reticulum surrounding the capillaries and lining the interstitial spaces.

CASE 11.

Diagnosis: Lymphadenosis cutis benigna. Outpatient. Rec.no. 6187/60.

A schoolgirl aged 14. Since 1958, there had been two firm reddish nodules on the skin of the right knee. They had remained almost unchanged and had not caused any discomfort.

Examination in November 1960: Two purplish intradermal nodules measuring about 2.5 × 1 and 6.5 × 2 cm on the skin of the right knee. In the larger of the nodules there were follicular, reddish, pinpoint-sized papules. No swollen lymph nodes. Liver and spleen not enlarged.

Blood count: Hgbn 14.2, erythrocytes 4,480, index 1.01, leukocytes 7,200, eosinophils 2.5, ESR 20 mm in one hour.

Electrophoresis: albumin 56.6, alfa$_1$globulin 5.7, alfa$_2$globulin 10.3, betaglobulin 16.1, gammaglobulin 11.3.

Total plasma proteins: 9.0 per cent.

Histology: Some lymphocytes are migrating to the epidermis, which shows no other abnormalities. There are cell infiltrations around the arteries branching at the boundary between the papillary and reticular layers. They form round nodules and press slightly on the surrounding connective tissue. The infiltrating cells are lymphocytes, whose nuclei are larger than normal. There are some histiocytes among the cells. Small areas infiltrated by normal lymphocytes are seen around the capillaries.

Silver impregnation: There are argyrophil fibers surrounding the lymphocytic nodules of the papillary layer. The reticular network in the nodules is lacking. There are some isolated thin argyrophil fibrils between the cells.

CASE 12.

Diagnosis: Lymphadenosis cutis benigna. Rec.no. 901/59.

A woman aged 52. During 1958, some firm nodules appeared on the skin of the trunk (fig. 37) and thighs. Some of them disappeared and were manifested again after two weeks. There were altogether 10 nodules. The nodules at first itched, but later they caused no inconvenience. Typhoid fever at the age of 35.

Examination in June 1959: Firm, reddish, intradermal papules the size of small peas on the skin of both thighs, the neck and left flank.

General condition good. Lungs and heart normal. No enlarged lymph nodes. Liver and spleen not enlarged.

Blood count: Hgbn 12.1, erythrocytes 4170, index 1.01, leukocytes 6,100, ESR 13 mm in one hour.

Electrophoresis: albumin 70.8, alfa$_1$globulin 3.5, alfa$_2$globulin 7.1, betaglobulin 8.8, gammaglobulin 30.0 per cent.

Total plasma proteins: 7.0 per cent.

Sternal puncture: normal finding.

Histology: Normal epidermis. In the upper dermis there are some perivascular lymphocyte aggregates. The endothelial cells of the blood vessels are swollen, and in places almost spherical. Deeper in the corium there are structures resembling lobules of the lymph nodes divided by connective tissue septa. The cells are mainly well differentiated reticulocytes. Among them there are some separate cells with pale nuclei.

Silver impregnation: In the upper corium there is a zone of long argyrophil fibers lying parallel with the surface. The nodular cell aggregates are surrounded by argyrophil connective tissue trabeculae. The supporting network is lacking in the nodules. There are only sparse and isolated argyrophil fibrils (fig. 14).

Clinical course: According to an inquiry at the end of 1960, the general condition was good and the patient symptom-free. No further nodules had appeared at the site of the surgically removed or spontaneously healed ones.

CASE 13.

Diagnosis: Lymphoma lymphocyticum, well differentiated, generalized. Rec.no. 904/59.

A woman aged 52. Since 1957 she had suffered from attacks of itching, first on the arms and later on the whole trunk. One year prior to presentation two purplish patches, approximately 2 cm in diameter, appeared on the skin of the chest. One month before the examination similar patches appeared on the back, flanks, abdomen and chest. The eruption did not cause any discomfort.

For two years the blood pressure has been elevated to 200—300 mmHg.

Examination in July 1959: On the skin of the trunk, especially on the upper part of the back and on the chest, slightly purplish patches, 1 to 3 cm in diameter, were seen, which on palpation felt firmer than the surrounding skin. A roentgenogram of the lungs revealed no parenchymatous changes. No swollen lymph nodes. Liver and spleen not enlarged.

Blood count: Hgbn 13.3, erythrocytes 4,530, index 1.04, leukocytes 4,800, segmented cells 49.0, eosinophils 2.5, basophils —, monocytes 4.5, lymphocytes 44.0, ESR 12 mm in one hour.

Electrophoresis: albumin 73.5, alfa$_1$globulin 3.4, alfa$_2$globulin 5.0, betaglobulin 8.6, gammaglobulin 9.5 per cent.

Total plasma proteins: 7.1 per cent.

Sternal puncture: the lymphoid and reticular cells are somewhat increased in number.

Histology: The epidermis is atrophic. The rete pegs are shortened. In the thickened dermis there are islets of cell infiltrations. The cells seem to be mature lymphocytes. In places there are also reticulum cells, these places resembling a poorly developed lymphatic primary nodule. Some eosinophils are seen; otherwise the cell picture is uniform. There are infiltration islets in the subcutaneous tissue also.

Silver impregnation: Below the ribbon-like epidermis there is a narrow zone of long, argyrophil fibers lying parallel to the surface. Beneath this zone is another composed of dilated capillaries and interstitial spaces with a well developed reticulum. The collagen fibers in the whole corium are fragmented, the capillaries being dilated. In large cell infiltrations the supporting reticulum is poor developed or lacking. Between the cells separate fibers are visible as short irregularly distributed filaments. In addition, areas of corium are seen, where between the cell infiltrations there are long, irregular, black-staining fibers, seeming to be remnants of collagenous bundles (figs. 15 and 16).

Clinical course: At the end of 1962, the blood count was still normal.

CASE 14.

Diagnosis: Lymphoma lymphocyticum, well differentiated, systemic. Rec.no. 410/54.

A man aged 64. Since 1946 he had suffered from lymphatic leukemia, and was treated with arsenic and x-rays. In 1951, a generalized eczema first made its appearance, but healed on treatment with baths and ointments. Thereafter the patient often suffered from more localized eczema in varying sites. In February 1954, an ulcer appeared on the right gluteal region and erythema over the whole body.

At the age of 10 he had suffered from osteomyelitis of the femur. Peritonitis in 1919. Several attacks of pneumonia in recent years. Cough and dyspnea continuously.

Examination in March 1954: In the right gluteal region there was an approximately palm-sized flat ulceration with irregular edges and a purulent base. On the skin of the trunk and extremities large reddish and slightly scaling areas and small reddish papules were present side by side. The palms were scaling.

Roentgenogram of the lungs revealed hilar adenopathy with perihilar »streakings» and with adhesive pleurisy on the left side.

The lymph nodes of the chin, neck, axillary and inguinal regions were swollen, from fingertip to walnut-sized, forming conglomerates. In the right inguinal fold there was an egg-sized lymph node. The spleen was enlarged, extending down to the level of the umbilicus and to the midline. The liver dullness could be percussed 2 ½ fingers' breadth below the costal margin.

Blood count: Hgbn 71/84, erythrocytes 4.12, index 1.02, leukocytes 23,800, staff cells 1.5, segmented cells 1.5, monocytes 0.5, lymphocytes 96.5. ESR 7 mm in one hour.

Histology: The ulceration in the gluteal region: Below the cutaneous ulceration a profuse round cell infiltration is seen. There are perivascular lymphocytic infiltrations in the corium and in the subcutaneous tissue, the cells seeming to be mature lymphocytes (fig. 34 A).

Silver impregnation: Deep in the corium in the lymphocytic infiltration there is a delicate supporting network of reticulin fibers (fig. 17).

Clinical course: Treatment with sanamycin resulted in a period of slight temporary improvement.

According to the relatives, the patient died in March 1959.

CASE 15.

Diagnosis: Lymphoma lymphocyticum, poorly differentiated and localized, in a patient with acrodermatitis atrophicans Herxheimer. Rec.no. 216/54.

A woman aged 66. Two years prior to presentation flat doughy elevations appeared on both metatarsi. The tumor on the left foot became continuously larger and one year later a chronic ulceration developed on it medially below the ankle. During the past five months a similar flat tumor had slowly developed on the skin of the left knee.

For at least 10 years the skin of both lower extremities had been thin, wrinkled and purplish.

Examination in February 1954: On the right metatarsus there was a firm, slightly reddish tumor measuring approximately 4 × 5 cm. On the left foot an infiltration

extending to the median aspect of the ankle was seen. On this infiltration below the malleolus there was an ulceration measuring about 1 × 2 cm with a purulent base. On the skin of the left knee there was a doughy, slightly elevated, skin-coloured, infiltrated area measuring about 8 × 10 cm. The skin of both lower extremities, of the gluteal regions and the lower abdomen was thin, atrophic and purplish, the blood vessels showing clearly through it. Similar atrophy was seen to a smaller extent on the skin of the forearms, too. In the left inguinal fold was a lymph node the size of a fingertip, no other lymph nodes being palpable. Liver and spleen not enlarged.

Blood count: Hgbn 75 per cent, erythrocytes 4.66, index 0.80, leukocytes 6,700, staff cells 1.0, segmented cells 62.0, eosinophils 0.5, basophils —, monocytes 4.5, lymphocytes 32.0. ESR 40 mm in one hour.

Histology: An infiltration: Below the atrophic epidermis a large, uniform area of tumor tissue is seen, containing poorly differentiated lymphocytes. Among the lymphocytes there are a few large pale reticular cells and some plasmacytes.

Silver impregnation: Below the ribbon-like epidermis a narrow zone is seen, where the long argyrophil fibers are lying parallel with the surface. Beneath this zone, in the area of the actual tumor, a regular supporting network is lacking. Argyrophil fibers are seen here and there surrounding the capillaries and lining larger interstitial spaces and lacunar formations. Between the tumor cells, irregular fragments of fibers are seen (fig. 18).

Clinical course: According to the patient's relatives, the patient died in December 1956 from »cancer of the stomach».

CASE 16.

Diagnosis: Lymphoma lymphocyticum, poorly differentiated and generalized. Rec.no. 458/55.

A woman aged 72. In spring 1954, itching and redness appeared on both arms, spreading in the summer to the palms and dorsa of the hands. Thereafter the redness and pruritus gradually became generalized (fig. 38).

Since 1930, the patient had almost continuously suffered from various eruptions on the elbows, inguinal folds, abdomen, below the breasts and on the legs. During the summers the patient had often been asymptomatic or at least better.

In 1950, she suffered from cholelithiasis accompanied by icterus. The blood pressure had been elevated for several years.

Examination in May 1955: The whole skin was affected by a reddish eruption consisting of smooth and shining pinhead-sized papules. The papules in the axillary and cubital regions were tetragonal and followed the wrinklings of the skin. On the arms and legs there was uniform red infiltration. Edema of the legs. Auscultation of the heart revealed a systolic murmur and extrasystoles. Blood pressure 180/90 mmHg. In the inguinal folds there were fingertip-sized lymph nodes. Liver and spleen not palpable.

Blood count: Hgbn 68/81, erythrocytes 4.08, index 0.99, leukocytes 6,400, segmented cells 41.5, eosinophils 8, basophils 2.5, monocytes 11, lymphocytes 37. ESR 14 mm in one hour.

Sternal puncture: Slight eosinophilia; normal findings in other respects.

Histology: The epidermis is thin and atrophic, the stratum spinosum consisting in places of only a few cell layers. Immediately below the epidermis there is a large monomorphic cell infiltration comprising the whole dermis, the normal structure having been destroyed. The cells are poorly differentiated lymphocytes. Among them there are dark staining cells with very large nuclei (fig. 34 B). Here and there single large cells and cell groups of the reticular system with pale nuclei are seen.

Silver impregnation: A regular reticular network is lacking. Argyrophil fibers are seen here and there between the cells. In the papillary portion they line the interstitial spaces, which are more numerous here than in other parts of the corium. In addition, regularly spaced vertical bundles of argyrophil fibers are seen as remnants of hair follicles (fig. 19).

Clinical course: The patient was treated with sanamycin without any noteworthy improvement of the state of the skin. On account of acute cystitis the patient was transferred to a medical ward in January 1959, where she died unexpectedly. At that time the blood count was still normal, the number of leukocytes being 4,500. Autopsy revealed arteriosclerotic and myodegenerative changes. The skin lesions were the only manifestations of lymphoma.

CASE 17.

Diagnosis: Lymphoma lymphocyticum, poorly differentiated, systemic, cum acrodermatitis atrophicans. Rec.no. 343/59.

A woman aged 63. In summer 1953, bluish, elevated, slightly pruritic patches appeared on the left upper arm. One year later similar patches appeared on the skin, back and extremities. During the past year the patches on the left leg had risen and become cushion-like, beginning to suppurate and forming evil-smelling ulcerations.

From the age of 15, the patient had suffered from rheumatoid arthritis and cardiopathy. She had had attacks of bronchial asthma.

Examination in March 1959: Sharply marginated, purplish, even or elevated, infiltrated patches and firm nodules on the chin, arms, abdomen and thighs. The tumors on the inner side of the left upper arm had the form of annular cushions. On the inner side of the left leg there was a uniform tumor area with approximately ten crater-like suppurating ulcerations, 2 to 6 cm in diameter. The skin of the backs of the hands was purplish, thin and wrinkled. The skin of both legs and knees was papyraceous and wrinkled.

The patient was pale, tired and emaciated. No palpable lymph nodes. Spleen not enlarged. The liver dullness extended a finger's breadth below the costal margin.

At the level of the right third costa x-ray examination revealed a suspect rounded

shadow. Follow-up examination after one month demonstrated enlargement of the shadow and, in addition, new dense infiltrations in both lungs.

Blood count: Hgbn 10.3, erythrocytes 3,780, index 0.95, leukocytes 10,100, staff cells 5.0, segmented cells 58.5, eosinophils 2.0, basophils 1.0, monocytes 9.5, lymphocytes 24.0. ESR 41 mm in one hour.

Electrophoresis: albumin + alfa$_1$globulin 59.4, alfa$_2$globulin 11.4, betaglobulin 10.4, gammaglobulin 18.8 per cent.

Total plasma proteins 5.1 per cent.

Histology: A nodule on the upper arm: Below the normal epidermis there is a narrow zone of relatively normal connective tissue. Under this is structureless granular tissue, comprising the whole dermis, with remarkably pleomorphic cells, among them split and degenerated nuclei. Most cells are of the lymphosarcoma type; among them there are some large, dark-staining nuclei.

Silver impregnation: In the upper corium there is a zone with some remaining collagenous fibers. Below it there are densely distributed long argyrophil fibers lying parallel with the surface. Deeper, in the area of the actual tumor, the supporting network is lacking. Between the tumor cells thin argyrophil reticular filaments and thicker fragments of collagenous fibers are seen (fig. 20).

Clinical course: The tumors of the left leg were treated with x-rays, involution resulting. At the same time radioactive phosphorus was given to the patient, all the skin lesions becoming temporarily less prominent. The patient was tired and feverish, and a blood count revealed slight anemia. She went home between treatments and died there in April 1959. Autopsy was not performed.

CASE 18.

Diagnosis: Lymphoma lymphocyticum, poorly differentiated, and generalized in the skin. Rec.no. 1319/61.

A man aged 74. Early in 1961, reddish lumps appeared on the skin of the chest and the back. The number of lumps gradually increased and they also appeared on the skin of the extremities (fig. 39). There was no subjective discomfort.

Lung tuberculosis had been diagnosed in 1959, and was treated with PAS and INH until June 1961.

Examination in July 1961: Purplish cushion-like nodules, the largest measuring a few cm in diameter, were present on the skin of the trunk, upper arms and thighs. The nodules were intradermal and indolent. Fingertip-sized lymph nodes in the inguinal folds. Liver and spleen not enlarged. Clinical examination revealed no changes in the lungs; the roentgenograph showed fine mottling due to calcification in the middle and upper lobe of the right lung and strong, dense calcification in the right hilar region. No enlarged lymph nodes.

Blood count: Hgbn 15.5, erythrocytes 5.03, leukocytes 7,600, staff cells 3.5, segmented cells 53.5, eosinophils 1.0, monocytes 3.0, lymphocytes 39.0. ESR 5 mm in one hour.

Sternal puncture: normal finding.

Electrophoresis: albumin 57.0, alfa$_1$globulin 0.9, alfa$_2$globulin 8.3, betaglobulin 13, gammaglobulin 21 per cent.

Total plasma proteins 7.7 per cent.

Histology: In the dermis there is a uniform structureless cell infiltration extending in places to the epidermis, where it forms microabscesses resembling Pautrier's abscesses. The cells are lymphoid cells, varying greatly in size, form and relation of nucleus to cytoplasm. Mitoses are seen in abundance; some of them are atypical.

Silver impregnation: A reticular supporting network is lacking. Here and there argyrophil fibers are seen surrounding the capillaries and lining the interstitial spaces and as irregular fragments between the tumor cells.

Clinical course: Despite treatment with x-rays and Sendoxan the disease made rapid progress and the nodules on the skin enlarged and increased in number. At the end of 1961, persistent fever set in. The patient died at home between treatments in February 1962. Autopsy was not performed.

CASE 19.

Diagnosis: Lymphoma cutis reticulocyticum, well differentiated and generalized. Rec.no. 585/59.

A woman aged 38. In 1955, nodules appeared on the elbows and on the lobe of the left ear. In 1957, similar nodules appeared on the forearms, buttocks, thighs and legs (fig. 40). At times the skin over the nodules itched. One year before examination the nodules disappeared during cortisone therapy, but recurred after the treatment was discontinued.

Examination in April 1959: Purplish, semi-firm, smooth-surfaced, roundish or oval nodules symmetrically on the skin of the sacral region, flanks, thighs, legs and forearms. The size of the nodules varied from two millimeters in diameter to thumb-tip size. The nodules of the elbow region were infected. Bean-sized lymph nodes in the axillae and inguinal folds. Liver and spleen not enlarged.

Blood count: Hgbn 13.5/95, erythrocytes 4,460, index 1.06 leucocytes 10,300, segmented cells 15, eosinophils 45.5, monocytes 2.5, lymphocytes 37, thrombocytes 357,870, ESR 11 in one hour.

Electrophoresis: albumin 59.6, alfa$_1$globulin 3.1, alfa$_2$globulin 5.3, betaglobulin 10.2, gammaglobulin 21.8 per cent.

Total plasma proteins 7.6 per cent.

Sternal puncture: Erythrocytopoiesis normoblastic, and leukocytopoiesis active and normal. The number of eosinophils increased, as well as that of reticulum cells and plasma cells of different ages.

Histology: The epidermis is normal. In the upper dermis the blood vessels are dilated and their endothelial cells swollen. There are perivascular round cell infiltrations. Deep in the dermis there are large, dense cell infiltrations. The cells are well differentiated reticulum cells (fig. 34C). Eosinophils are present in the margins of the infiltration.

Silver impregnation: In the upper third of the corium a well developed argyrophil supporting network is seen surrounding the dilated blood vessels and lining interstitial spaces. The collagenous fibers are fragmented. Deeper in the corium the collagenous fibers have totally disappeared. The interstitial spaces and lacunae are lined by argyrophil fibers. The supporting network, however, is not continuous. There are cell aggregations without fibers (fig. 20).

Clinical course: In response to an inquiry at the end of 1960, the patient reported that her condition was good and that she could perform the housework on a little farm. She lives in a remote region and because of the long journey refused to attend follow-up examination. The former treatment of the patient consisted of 10 mill. I.U. of penicillin and an experimental dose of grenz rays, on which occasion the nodules were found to be radiosensitive.

CASE 20.

Diagnosis: Lymphoma reticulocyticum, poorly differentiated and localized in the skin. Private patient.

A woman aged 24. 8 months before presentation a small patch on the skin of the right flank became reddish and scaling, forming an excoriation covered by a scab. Two months prior to examination the patch was treated with x-rays (doses of 100 r, with an interval of two weeks between treatments), which led to temporary improvement.

Examination in November 1959: On the anterior axillary line at the height of the breast there was a rough scabby area, measuring approximately 1.5 × 2 cm., surrounded by a reddish halo 2 mm. broad. In the upper corner of the lesion there was a small group of follicular pinpoint-sized papules. In the right axilla a soft bean-sized lymph node was palpable. The liver and spleen were not enlarged. Lungs roentgenologically normal.

Normal blood count.

Histology: Below the somewhat acanthotic and hyperkeratotic epidermis a large and structureless cell infiltration is seen, extending to the deep layers of the dermis. The cells are large cells of the reticular system with pale nuclei. There are no neutrophils among them. In the margins of the lesion some eosinophils and lymphocytes are seen. No mitoses.

Silver impregnation: A supporting network of reticulin fibers is missing. Isolated fibrils occur between the cells (fig. 21).

Clinical course: After excision and antibiotic therapy the lymph node in the right axilla disappeared. At the end of 1962, the patient was still symptom-free.

CASE 21.

Diagnosis: Lymphoma reticulocyticum, poorly differentiated and localized to the cervical lymph nodes, involving cutaneous and subcutaneous tissue. Rec.no. 1154/59.

A man aged 69. Six months prior to presentation a continually enlarging lump

appeared on the neck below the chin. Several biopsy specimens were taken and a granulomatous inflammation was diagnosed. The previously unbroken skin was transformed into a large ulceration with a purulent base. The patient was sent to the Dermatologic Clinic for further investigations.

The patient had formerly had pneumonia once and tonsillitis several times. He suffered from a continuous »smoker's cough».

Examination in September 1959: On the right side of the neck there was a tumor, 8 cm. in diameter, with a necrotic center and reddish, elevated margins. Under the lesion a group of lymph nodes was palpable.

X-ray examination of the thorax revealed pleural adhesions, fibrosis and emphysema in both lungs. In the right lower lobe there were accentuated trabecular markings and bronchiectases. There was no enlargement of the hilar lymph nodes. In the axillae and supraclavicular fossae and inguinal folds separate pea- to bean-sized lymph nodes were palpable. The liver and spleen were not enlarged.

Blood count: Hgbn 13.3, erythrocytes 4,530, leukocytes 10,700, segmented cells 58.5, eosinophils 2.0, basophils 1.5, monocytes 9.5, lymphocytes 28.5, thrombocytes 213,000. ESR 56 mm in one hour.

Total plasma proteins 7.2 per cent.

Histology: Below the normal epidermis and the relatively well preserved papillary layer there is a netlike tumor tissue, rich in cells, comprising almost the whole corium and also visible as islets between the fat cells. The tumor tissue consists of cells of variable size, rich in chromatin. Among them there are nuclei 2 to 4 times larger than the lymphocytes. Some of the cells are phagocytic.

Silver impregnation: In the papillary portion of the dermis a fairly regular network of argyrophilic fibrils surrounds the dilated capillaries and lines the interstitial spaces. Deeper in the corium in the area of the actual tumor black-staining remnants of collagenous fibers are seen running criss-cross. Between the tumor cells the argyrophil fibers are lacking or are seen only here and there as isolated fibrils (fig. 22).

Clinical course: The tumor proved to be very radiosensitive, rapid involution taking place during roentgenotherapy. At the end of 1962, the condition of the patient was still good and no evidence of recurrence could be found.

CASE 22.

Diagnosis: Lymphoma reticulocyticum, poorly differentiated and generalized. Rec.no. 1197/53.

A woman aged 69. Five weeks prior to presentation the patient observed small pea-sized nodules behind the left auricle and in the right external auditory meatus. During the following weeks similar nodules had appeared on the face, chest and back (fig. 41).

In 1926, the patient was operated on for myomata, the uterus and one ovary being removed. She had suffered from elevated blood pressure for several years.

Examination in December 1953: There were reddish brown pinhead- to small pea-sized nodules on the skin of the face, chest and back. The remarkably firm nodules rose from the skin as hemispheres and moved with the skin on palpation. The center of some of the nodules was necrotic. The patient was tired and feverish. The lungs were roentgenologically normal. No palpable lymph nodes. Liver and spleen not enlarged. Blood pressure 185/90 mmHg.

Blood count: Hgbn 83.0, erythrocytes 4.90, index 1.02, leukocytes 8,000, staff cells 1.0, segmented cells 48.0, basophils 0.5, eosinophils 5.5, monocytes 9.0, lymphocytes 36.0 per cent. ESR 24 mm in one hour.

Histology: The epidermis is atrophic and ribbonlike. There is a cell infiltration comprising the whole dermis and clearly demarcated from the fatty tissue. The cells are highly pleomorphic cells of the reticular system, varying in degree of maturation and with large nuclei (fig. 34, D). Among them there are stem cells with pale, irregular nuclei. Some of the tumor cells are rich in chromatin or even hyperchromatic. In places giant cells with conglomerates of several nuclei are seen in the tumor. The number of mitoses is large, in places 5 to 10 per field.

Silver impregnation: The structure of the argyrophil reticulum varies greatly in different parts of the tumor. In one part of the tumor the reticulum is wholly lacking, and remnants of fibers are seen at the boundary between the corium and epidermis (fig. 23). In places there are fragments of collagenous fibers and argyrophil fibrils in a criss-cross arrangement. In a part of the tumor the argyrophil fibrils are long and parallel (fig. 24). In addition, areas of the tumor are seen in which a dense argyrophil reticulum surrounds the tumor cells, resembling basketwork. The structure of the network is irregular even in these places. In some places the fibrils are very dense, whilst in others large cell groups are seen without any fibrils (fig. 25).

Clinical course: Exitus after 4 months of hospitalization. The patient suffered from a continuous high fever and the skin was covered with evil-smelling necrotic tumors, the largest reaching the size of a walnut. Autopsy revealed that the tumors were confined to the skin.

CASE 23.

Diagnosis: Morbus Hodgkin with specific papular skin lesions. Outpatient no. 4802/58.

A man aged 46. The patient had had swollen lymph nodes in the inguinal folds for six months. Biopsy diagnosis: Hodgkin's disease. Fever for one month. Two weeks prior to presentation the skin became dry and itching and the patient was sent to the Dermatologic Outpatient Department for consultation.

Examination in December 1958: The skin was dry and scaling. Erythema on the backs of the hands. In the right cubital fold and on the skin of the back a few small pea-sized intradermal nodules were present. Behind the left auricle was an almond-sized, indolent lymph node, and a similar swelling on the right side below the chin. Fingertip-sized lymph nodes formed clusters in both inguinal folds. Lungs roentgenographically normal. Liver and spleen not enlarged.

Blood count: Hgbn 74.0, erythrocytes 5.82, index 0.74, leukocytes 9,550, segmented cells 68.0, basophils 0.5, eosinophils 2.0, monocytes 5.0, lymphocytes 24.5. ESR 70 mm in one hour.

Histology: Deep in the dermis a structureless cell infiltration is seen. The cells are large darkly staining histiocytes, some of them containing 2 to 3 nuclei. In addition, eosinophils, lymphocytes, fibrocytes and some plasma cells are present in the specimen.

Silver impregnation: The cell infiltration is situated in a fine-meshed well developed argyrophilic reticulum (fig. 26).

Clinical course: The patient died in a rural hospital in March 1959.

CASE 24.

Diagnosis: Morbus Hodgkin with specific infiltrations and nodules of the skin. Rec.no. 205/61.

A man aged 60. In November 1960, a lumpy induration appeared on the right side of the neck. The hardened area enlarged and a similar induration appeared on the chest as well. At the same time the patient suffered from continuous pain in the neck, headache and fatigue. A biopsy specimen was taken by the local doctor. Biopsy diagnosis: Mycosis fungoides. The patient was sent to the Vaasa Provincial Hospital, where he was treated with x-rays (total dose 1600 r). The pain in the neck was relieved but the skin changes were unaffected. The induration of the skin continued.

Examination in January 1961: On the right side of the neck over a palm-sized area the skin was purplish brown, indurated, nodular and immovable. The changed skin extended over the clavicle to the subclavicular region. There were separate intracutaneous nodules moving with the skin on the outer border of the pectoralis muscle and in the skin of the neck. In addition, an area of intracutaneous infiltration, 10 cm in diameter, was present lower on the chest. The intracutaneous nodules felt remarkably firm and were indolent on palpation.

The patient was pale and weary-looking. On the right side below the chin there were enlarged lymph nodes, which could not be properly palpated because of the induration of the skin. In the right supraclavicular fossa, in the axillae and in the inguinal folds there were pea-sized lymph nodes. Liver and spleen not enlarged.

Roentgenologic examination of the thorax: Small calcium deposits in the apical parts of the upper lobes pointed to inveterate tuberculosis. No fresh parenchymatous changes. Normal heart. No enlarged lymph nodes in the mediastinum and hili.

Blood count: Hgbn 11.2/72, erythrocytes 3,650, index 0.97, leukocytes 16,000, staff cells 4.5, segmented cells 72.0, eosinophils 12, basophils 1.0, monocytes 4.0, lymphocytes 6.5. ESR 103 mm in one hour.

Sternal puncture: The relation between erythro- and leukopoiesis seemed to be normal. Leukopoiesis was slightly enhanced, the eosinophilic premature forms and

mature cells being especially increased. Some of the myelocytes and neutrophils were atypical. The megakaryocytes were augmented.

Serologic tests for syphilis: Wr. —, chol.Wr. —, Kolmer —, sitolipin —. *Treponema pallidum* immobilization test negative.

Electrophoresis: albumin 43.4, alfa$_1$globulin 6.3, alfa$_2$globulin 16.6, beta-globulin 17.1, gammaglobulin 16.6 per cent.

Total plasma proteins 8.1 per cent.

Histology: In the thickened dermis and in the subcutis between the fat cells nodular cell infiltrations are seen. The infiltrating cells are atypical reticular cells of variable size. In places there are very abundant eosinophils among them. In addition, there are histiocytes, fibroblasts and mast cells in the infiltration. Profuse fibrosis.

Silver impregnation: In the nodules of the middle and lower parts of the corium and in the subcutaneous tissue a well developed supporting reticulum is seen. At some places the network is lacking in the dense cell aggregations at the center of the nodules, consisting of atypical reticular cells. The nodules are surrounded by long argyrophil fibers. The collagen is split and sclerotic.

CASE 25.

Ulcerative Hodgkin's disease in a patient with poikiloderma atrophicans vasculare. Rec.no. 170/47.

A woman aged 52. The patient had had reddish patches on the skin of the trunk and extremities since 1944. In the summer of 1946, a dark and purplish area approximately the size of a palm, appeared on the inner side of the left thigh. The center of the area developed a gradually enlarging ulceration.

Examination in January 1947: The skin was everywhere dry and scaling. On the skin of the trunk and extremities there were extensive areas mottled with red, where fingernail-sized reddish patches and pale healthy places alternated, forming stripes and networks. On the inner side of the left thigh there was a raised infiltrated purplish area, measuring about 15 × 15 cm. At its center a granulating ulceration measuring 6 × 3 cm and with a purulent base was seen.

Histology : The epidermis is thin and atrophic. In the upper dermis a narrow, ribbon-like zone of infiltration is seen, the cells of which at places push in among the basal cells. There are many dilated blood vessels with swollen endothelial cells. The cells are lymphocytes, histiocytes, melanophores, eosinophils and plasma cells. No changes deeper in the dermis.

Silver impregnation: In the upper dermis a well-developed argyrophil reticulum is seen.

Histology: The ulceration: In the specimen granulation tissue is seen, the cells being mainly histiocytes with large, dark nuclei. Among them there are abundant

uni- or multinuclear giant cells. In addition lymphocytes, plasma cells, eosinophils and some enlarged endothelial cells with pale nuclei and a few broken nuclei are seen.

Silver impregnation: The argyrophil framework is well developed and regular.

Clinical course: After several months' continuous fever, during which time she lost almost all the hair of the scalp and body, the patient died in 1949.

In addition to the skin changes, autopsy revealed carcinoma of the pancreas with hepatic metastases.

CASE 26.

Diagnosis: Morbus Hodgkin. Rec.no. 1293/61.

A man aged 56. In December 1960, the patient observed an almond-sized induration on the skin of the back and a similar formation on the inner side of the left thigh. One year later nodules began to appear abundantly on different sites on the skin of the trunk and extremities. The patient visited several doctors and a specimen was taken for biopsy from a lump, but the nature of the disease was not established. He was treated with cortisone for one month and anti-tuberculous drugs for 3 months without result.

The patient had suffered from tuberculous pleurisy in 1936.

Examination in July 1961: On the skin of the trunk and extremities there were numerous hard nodules, approximately 1 to 5 cm. in diameter. Some of the nodules were intracutaneous and slightly raised, the skin on the nodules being purplish. Others were tumors that could be palpated in the subcutaneous tissue. On the left flank there was a uniform infiltration, 15 cm. broad, comprising skin and subcutaneous tissue. The lesions were indolent.

Roentgenographic examination of the lungs revealed calcium deposits in both upper lobes, pointing to inveterate tuberculosis. Adhesions in the right pleural sinus. No glandular enlargement. In the left supraclavicular fossa a prune-sized, freely moving lymph node. In the right axilla a fingertip-sized lymph node. Liver and spleen not palpable. The spleen shadow in the roentgenographs was somewhat enlarged.

Blood count: Hgbn 14.7, erythrocytes 4.62, leukocytes 4,600, staff cells 1.5, segmented cells 50.5, eosinophils 3.0, basophils —, monocytes 5, lymphocytes 40.0. ESR 12 mm in one hour.

Sternal puncture: normal finding.

Electrophoresis: albumin 65, alfa$_1$globulin 2.6, alfa$_2$globulin 6.0, betaglobulin 14, gammaglobulin 13 per cent.

Total plasma proteins 7.2 per cent.

Histology: In the dermis and subcutis a large and solid polymorphic cell infiltration is seen. There are some eosinophils and fibrocytes among the cells. No Sternberg—Reed giant cells are present (fig. 35 A).

Silver impregnation: The argyrophil network is highly developed and irregular in density (fig. 27).

Clinical course: In spite of various therapeutic measures (cortisone, Sendoxan and x-ray treatments) the disease slowly progressed, the cutaneous infiltrations and glandular swellings enlarging. At the end of 1961, the patient had continuous fever, and his general condition was deteriorating. Exitus.

CASE 27.

Diagnosis: Pro obs mycosis fungoides. Erythrodermia. Rec.no. 1404/60.

A man aged 61. In July 1960, the skin, of the whole body became red and pruritic. He had previously had several different types of eczema. In 1934, —35, —36, —44, —55, —56 and —58 he had been treated at the Department of Dermatology under the following diagnoses: dermatitis arteficialis, eczema seborrhoicum, eczema allergicum ex usu ursol, dermatomycosis and moniliasis. Has suffered from myocarditis for many years. In 1954, sympathectomy for intermittent claudication. Diabetes mellitus was diagnosed in 1954.

Examination in August 1960: The skin of the face and the whole body reddish. The redness is confluent and particularly intense on the skin of the upper arms and back of the hands. It is caused by a diffuse cutaneous infiltration. The skin is smooth, and there is no scaling. On the abdomen there are very dense red pinhead-sized patches with a smooth surface. On the palms of the hands and on the soles of the feet diffuse redness. The lymph nodes are not swollen. The liver and spleen are not enlarged. Roentgenographic examination of the lungs does not reveal any enlarged glands or parenchymal shadows.

Blood count: Hgbn 13.4, erythrocytes 3,950, index 1.08, leukocytes 5,300, staff cells 4.5, segmented cells 66.5, eosinophils 10.5, basophils 0.5, monocytes 7, lymphocytes 11. ESR 13 mm in one hour.

Histology: The epidermis is atrophic and band-like. In the papillary region of the dermis there is perivascular and diffuse cell infiltration, containing lymphocytes and histiocytes and cells of endothelial type with pale nuclei. Some of the histiocytes have large, dark nuclei. Deeper in the dermis no infiltration.

Silver impregnation: In the papillary region of the dermis a zone with a well developed argyrophil network.

Clinical course: The patient was treated with radioactive phosphorus which, after the treatment, was found to have settled in the skin, indicating the immature nature of the infiltration. After the treatment the skin became paler and, during the process of healing, it atrophied and became slightly pigmented.

In April 1963, the condition of the skin was unchanged.

CASE 28.

Diagnosis: Mycosis fungoides. Stadium premycoticum. Rec.no. 178/58.

A man aged 41. In October and November 1957, reddish, rough, and at times pruritic patches appeared on the skin of the trunk and extremities. In 1942, he had suffered from primary syphilis. After five series of combined treatments, the serologic test for syphilis became negative. In 1947, he had jaundice.

Examination in February 1958: On the trunk and extremities there were slightly erythematous, scaling patches, 1 to 5 cm in diameter. On the right buttock was a patch measuring 7 × 15 cm with infiltration and small excoriations covered by a scab. Pea-sized lymph nodes in the axillae and inguinal folds. Liver and spleen not enlarged. Lungs roentgenologically normal.

Blood count: Hgbn 17.5, index 1.13, leukocytes 9,300, staff cells 1, segmented cells 61, eosinophils 2, basophils 0.5, monocytes 3, lymphocytes 32.5. ESR 4 mm in one hour.

Electrophoresis: albumin 55.6, alfa$_1$globulin 3.5, alfa$_2$globulin 9.2, betaglobulin 12.5, gammaglobulin 19.2 per cent.

Total plasma proteins 7.55 per cent.

Histology: A broad zone of the upper dermis is abundantly infiltrated with cells. Among them, histiocytes of variable sizes and shapes with large, dark nuclei are seen, some cells having two nuclei. There are only a few lymphocytes in the specimen. Granulocytes are lacking. There are lymphocytes and histiocytes between the epidermal cells. In places infiltration strands extend deep into the dermis. No mitoses.

Silver impregnation: In the upper third of the dermis a zone containing a well developed argyrophil network is seen.

Clinical course: The patient was treated with x-rays and radioactive phosphorus, the skin lesions becoming smaller and pigmented after the therapy. He then worked as a lumberman in Sweden and, according to a report in the spring of 1961, was undergoing hospital treatment there for the widespread tumor stage of mycosis fungoides. Died in June 1962.

CASE 29.

Diagnosis: Mycosis fungoides. Stadium tumorosum. Rec.no. 541/59.

A woman aged 59. The patient has had reddish, scaling patches on the skin of different sites of the trunk for 6 years. During the year prior to presentation nodules and tumors arose on the skin of a large infiltrated area on the abdomen and sacral region.

Examination in April 1959: The whole skin, even in the apparently healthy places, had a brownish red tinge. On the lower abdomen there was a wide brownish red infiltration with several flat tumors, 2 to 10 cm. in diameter and softer in consistency than the surrounding infiltration. On the skin of the back there was another large infiltrated area in which were a few nodules about 2 cm in diameter. In addition, there were slightly scaling and infiltrated patches, ranging from 2 cm in

diameter to palm-sized, on the upper part of the back, the chest and thighs. There was remarkable generalized reduction of the subcutaneous tissue. Some hazelnut- to prune-sized lymph nodes in the axillae and inguinal folds. On the right side of the chest here was a group of several hazelnut-sized glands. Liver and spleen not enlarged. Lungs roengenologically normal.

Blood count: Hgbn 96, erythrocytes 4,830, index 1.00, leukocytes 8,300, staff cells 2.5, segmented cells 65, eosinophils 3, basophils 1, monocytes 8, lymphocytes 20.5, thrombocytes 450. ESR 65 mm in one hour.

Electrophoresis: albumin 46.5, alfa$_1$globulin 2.3, alfa$_2$globulin 8.0, betaglobulin 15.0, gammaglobulin 28.1 per cent.

Total plasma proteins 7.6 per cent.

Sternal puncture: normal finding.

Histology: A tumor on the abdomen: The reticular part of the dermis is deeply infiltrated. The majority of the cells are histiocytes, among which there are cells with large, dark nuclei. In addition, some lymphocytes, eosinophils and fibrocytes are seen.

Silver impregnation: The cell infiltrations are situated in a well developed argyrophil reticulum.

Histology: Healthy appearing skin of the back: The papillary portion of the dermis is swollen and infiltrated with inflammatory cells, the cells being mainly lymphocytes and histiocytes. Some of the histiocytes are larger than normal and their nuclei are dark. In the epidermal rete a Pautrier's micro-abscess is seen.

Silver impregnation: A zone with a well developed argyrophil network is seen in the papillary portion of the dermis. The reticulum is lacking, however, in the denser cell aggregates. The basal membrane is broken below the Pautrier's micro-abscess (fig. 28).

Clinical course: The patient was treated with radioactive phosphorus and x-rays. She died after 5 months' hospitalization.

The examination of autopsy specimens revealed infiltrations extending deep into the dermis. In some areas of the tumor tissue the argyrophil reticulum was poorly developed or lacking (figs. 31 and 32). The lymph nodes showed similar changes. There were no visceral lesions.

CASE 30.

Diagnosis: Mycosis fungoides, stadium tumorosum. Rec.no. 1139/58.

A woman aged 45. In 1953, the patient first observed an itching, reddish and scaling, slightly elevated patch on the skin of the neck. During the following six months similar patches appeared on the shoulders and thighs, below the breasts and on the genitals. She was treated for 3 weeks in a hospital, the diagnosis being eczema seborrhoicum. The eruption subsided somewhat on treatment with ointments, but

reappeared and remained virtually unchanged for two years. After this period, there was progressive exacerbation of the eruption (fig. 42). During the last few months before presentation lumps appeared on the affected areas. Some of these nodules began to suppurate and the patient was feverish at times, the temperature occasionally rising to 40°C.

Suffered in 1930 from scarlatina and pleurisy, in 1937 from nephritis and in 1957 from purulent pleurisy.

Examination in October 1958: The skin of the whole trunk was scaling slightly. In places there were large reddish areas. Infiltrated and scaling patches of skin, 0.8 to 7 cm in diameter, were present all over the body, and flat tumor-like growths, 2 to 9 cm in diameter, on the left cheek, scalp, neck, chest and right labium majus. Some of the tumors were ulcerating. There were some separate, fingertip-sized lymph nodes in the inguinal folds. The liver and spleen were not enlarged.

Roentgenographic examination of the lungs: Adhesive pleurisy. Calcium deposits in the hili. At each apex, but especially on the right, slight mottling due to inveterate inflammatory changes was seen.

Blood count: Hgbn 12.7, erythrocytes 4,420, index 1.01, leukocytes 12,400, staff cells 1.0, segmented cells 80.5, eosinophils 5.0, basophils 1.0, monocytes 2.5, lymphocytes 10.0. ESR 29 mm in one hour.

Sternal puncture: In places only fat globules, reticulum cells and broken nuclei were seen in the punctate. The plasma cells were increased in number, appearing isolated or in groups. The bone marrow was fairly abundant. Leukopoiesis was active and myelometamyelocytic. The granules of the myelocytes were coarse. Erythropoiesis was rather scanty and normoblastic, and thrombopoiesis normal.

Histology: An infiltration: In the upper dermis dense inflammatory cell infiltrations are seen, in places extending even deeper to the dermis. There are dark staining histiocytes among the cells.

Silver impregnation: Well developed argyrophil reticulum as perivascular islets.

Histology: A tumor: A large polymorphic cellular infiltration (fig. 35, B) comprises the upper and middle dermis, the infiltration containing, in addition to pale-nucleated cells, histiocytes with dark nuclei, eosinophils, some neutrophils, lymphocytes and plasma cells. Some of the histiocytes have two nuclei. There are few mitotic figures.

Silver impregnation: A well developed argyrophil network is seen in the area of the tumor (fig. 29).

Clinical course: The patient was treated with radioactive phosphorus and x-rays and later with Sanamycin and Degranol, the therapy only producing temporary improvement. The entire cutaneous surface gradually became erythematous and infiltrated and covered with tumors and ulcerations.

The patient died in December 1959. In the last weeks of life she suffered from continuous fever, cough and hoarseness. Tubercle bacilli were found in the sputum. Leukopenia, thrombocytopenia and anemia were detected.

In addition to mycosis fungoides, autopsy revealed lesions limited to the skin, changes due to miliary tuberculosis in the larynx, lungs, paratracheal and hepatic lymph nodes and lymph nodes of the liver hilus. Terminally, fibrinous bronchopneumonia was observed in the right lung.

CASE 31.

Diagnosis: Mycosis fungoides, stadium tumorosum. Rec.no. 606/59.

A man aged 67. In 1956, reddish and scaling patches appeared first on the dorsa of the feet and later on various other sites of the body. Within the last year prior to presentation some of the patches swelled to nodules, began to suppurate and were covered by a purulent scab.

Examination in April 1959: In different sites of the skin there were purplish infiltrations, 0.5 to 10 cm in diameter, tumors covered by scabs and flat ulcerations (fig. 43). The patient was fatigued and feverish. In the axillae and inguinal folds fingertip-sized freely movable lymph nodes were palpable. The liver and spleen were not enlarged. Lungs roentgenologically normal.

Blood count: Hgbn 12.5, erythrocytes 3,990, index 1.00, leukocytes 9,400, staff cells 3.0, segmented cells 57.0, eosinophils 1.0, basophils 0.5, monocytes 10.0, lymphocytes 28.5. ESR 48 mm in one hour.

Electrophoresis: albumin 45.9, alfa$_1$globulin 5.8, alfa$_2$globulin 11.1, betaglobulin 7.2, gammaglobulin 30.0 per cent.

Total plasma proteins 7.3 per cent.

Histology: A tumor: The acanthotic epidermis forms elongated pegs surrounded by mesodermal cells. There are dense cellular infiltrates in the deep parts of the dermis, too. The majority of the cells are dark-staining reticulohistiocytes, many of which have large nuclei. Some of the cells have pale nuclei, resembling endothelial cells. In addition, there are a few eosinophils in the specimen.

Silver impregnation: A well developed argyrophil reticulum forms a framework for the tumor tissue. The network surrounds the blood vessels and is seen in the figure as an oblique section around the epidermal processes (fig. 30).

Clinical course: The patient died after 4 months of hospitalization. Autopsy revealed that the specific lesions were confined to the skin.

CASE 32.

Diagnosis: Mycosis fungoides. Stadium tumorosum. Rec.no.470/57.

A woman aged 48. The patient had suffered from the present skin disorder since 1955. Reddish, pruritic patches appeared on various parts of the body, some lesions developing into cushion-like nodules. A few patches healed, leaving brownish areas on the skin, the process taking 2 to 3 months. But new patches continuously appeared and the disease progressed.

Examination in June 1957: Everywhere on the skin there were purplish infiltrations, 5 to 15 cm in diameter, some being annular and others soft tumors with a

considerable fluid content. In the axillae and inguinal folds some fingertip-sized, firm lymph nodes were palpable. The liver and spleen were not enlarged. Lungs roentgenologically normal.

Blood count: Hgbn 12.1/85, erythrocytes 4.78, index 0.89, leukocytes 8,200, staff cells 3.0, segmented cells 73.0, eosinophils 6.5, basophils 1.0, monocytes 4, lymphocytes 12.5, thrombocytes 327,000. ESR 27 mm in one hour.

Electrophoresis: albumin + alfa$_1$globulin 55.1, alfa$_2$globulin 8.5, betaglobulin 8.3, gammaglobulin 28.1 per cent.

Total plasma proteins 8.0 per cent.

Histology: A tumor: Below the basally destroyed and degenerated epidermis there is tumor tissue, rich in cells, extending to the subcutis. The majority of the cells are large dark-staining histiocytes. Abundant mitotic figures are seen in them. Other large cells with pale nuclei are present. In addition, some eosinophils and a few plasma cells are seen, as well as a remarkable amount of disintegrating nuclei and nuclear debris. In the area of the tumor there are blood vessels with hyalinized walls, in places containing pale enlarged endothelial cells, of very large size. In addition, there are lacunae lined by a single layer of endothelial cells. Erythrocytes pass freely between the tumor cells.

Silver impregnation: In the tumor area abundant argyrophil fibers are visible. The network is not continuous, however. There are cell aggregates with a poorly developed reticulum.

Clinical course: The patient was treated with radioactive phosphorus and x-rays, the therapy resulting in some fading of the erythema and decrease in the size of the tumors. The condition rapidly deteriorated, however. Infiltrated patches, tumors and ulcerations appeared side by side on the skin. The blood count showed leukopenia and thrombocytopenia.

The patient died in the fall of 1958.

At autopsy the lesions were shown to be confined to the skin.

CASE 33.

Diagnosis: Mycosis fungoides d'emblee. Rec.no. 977/58.

A woman aged 56. In 1955, a reddish, occasionally oozing area appeared on the back. In 1957, the patient observed two small slightly scaling lumps on the left upper arm and consulted a doctor on that account. The histologic diagnosis was mycosis fungoides, and she was treated with x-rays, during which the lumps on the arms disappeared and the eruption on the back became somewhat drier, but soon after discontinuance of the treatment the area became elevated into a tumor (fig. 44). A week prior to presentation the patient again observed a small nodule on the right forearm and on the nape of the neck.

Thirty years before the examination the right ovary had been removed because of inflammation. Ten years before, the patient had suffered from a dry, scaling eruption on different sites of the body.

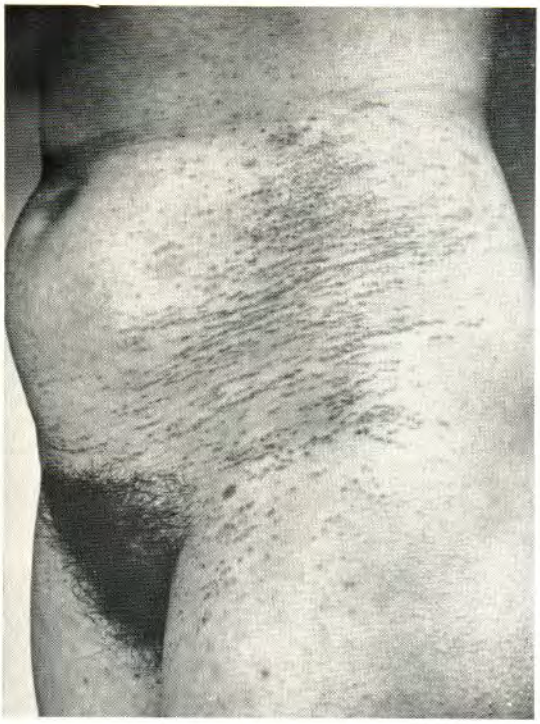


Fig. 36
Poikiloderma congenitale. Case 8.

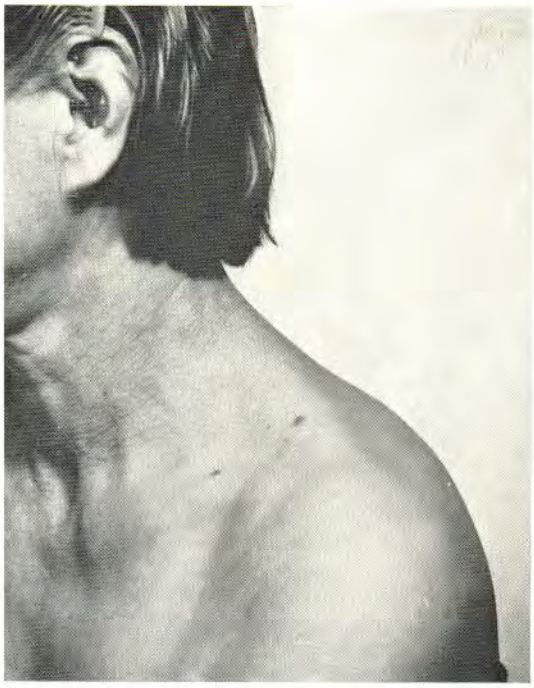


Fig. 37
Lymphadenosis cutis benigna. Case 12.

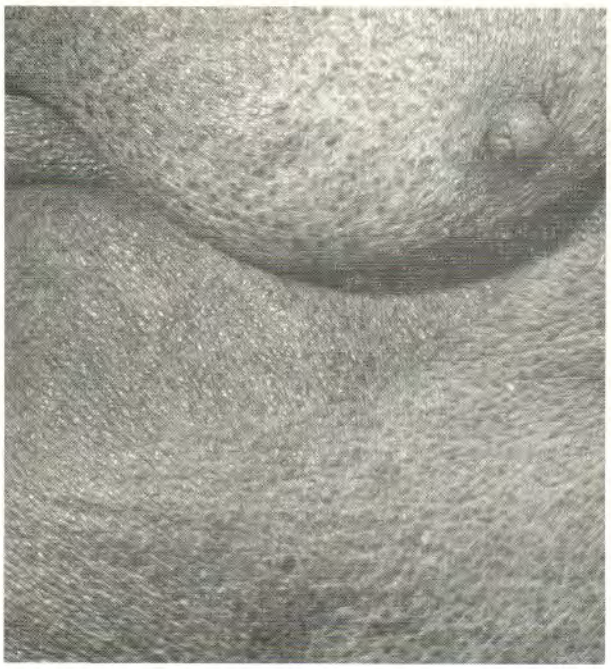


Fig. 38

Lymphocytic lymphoma, poorly differentiated (lymphosarcomatous erythroderma). Case 16.

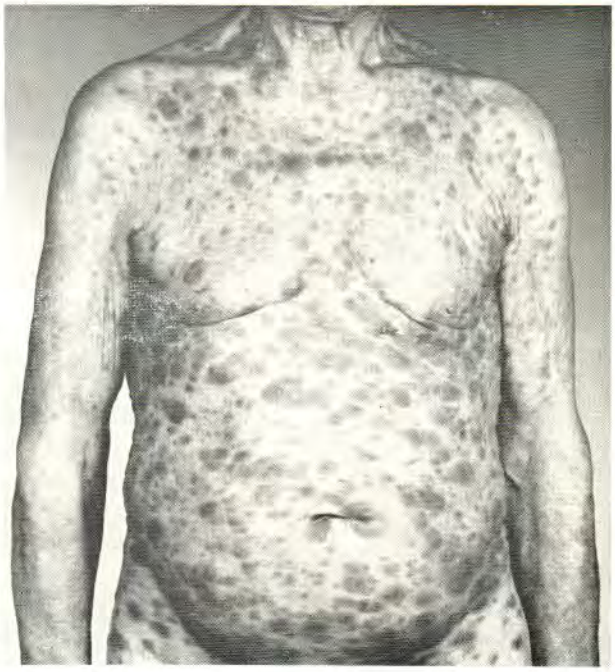


Fig. 39

Lymphocytic lymphoma, poorly differentiated (primary cutaneous lymphosarcomatosis) Case 18.

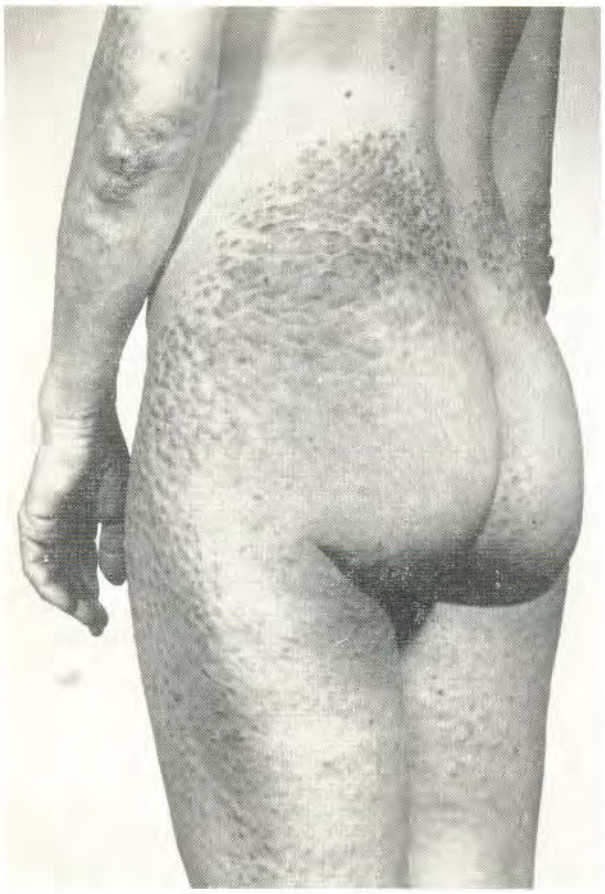


Fig. 40

Reticulum cell lymphoma, well differentatied (monocytic cutaneous leukemia). Case 19.

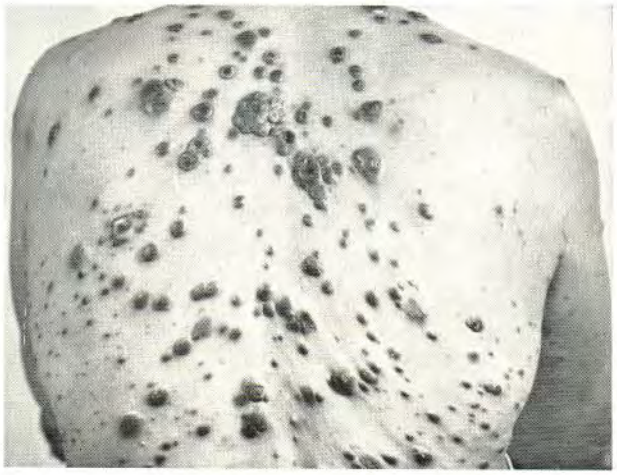


Fig. 41

Reticulum cell lymphoma, poorly differentiated (primary cutaneous reticulosarcomatosis). Case 22.

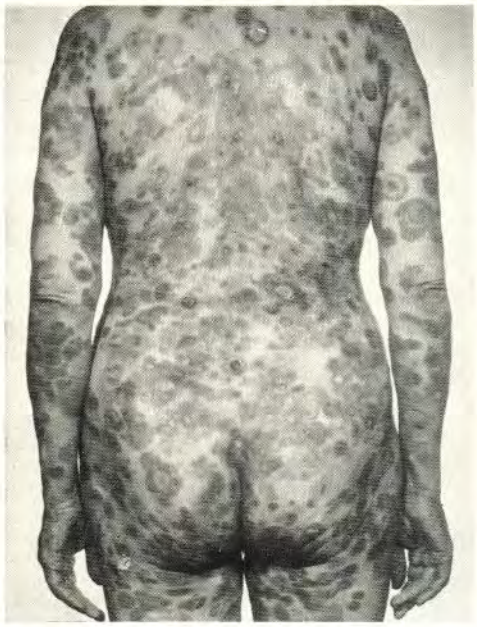


Fig. 42
Mycosis fungoides. Case 30.

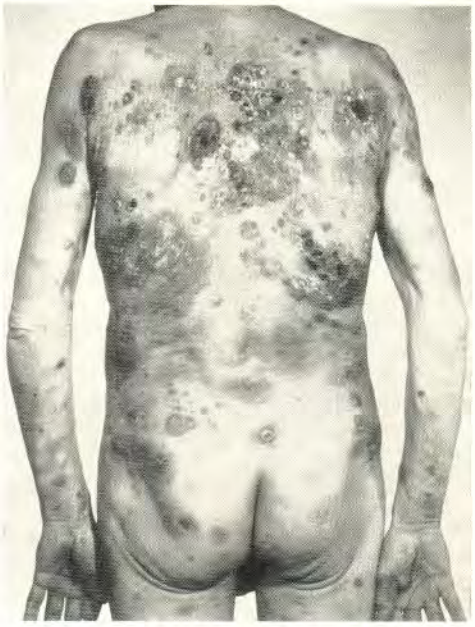


Fig. 43
Mycosis fungoides. Case 31.

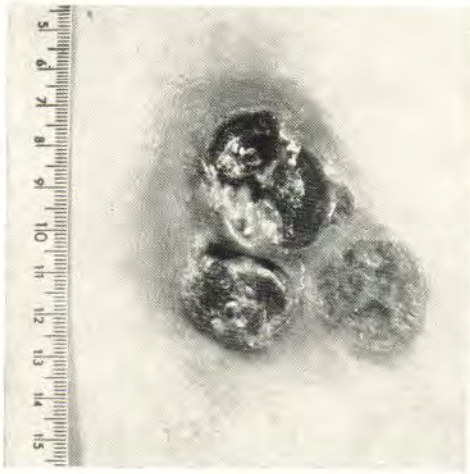


Fig. 44
Mycosis fungoides d'emblee. Case 33.

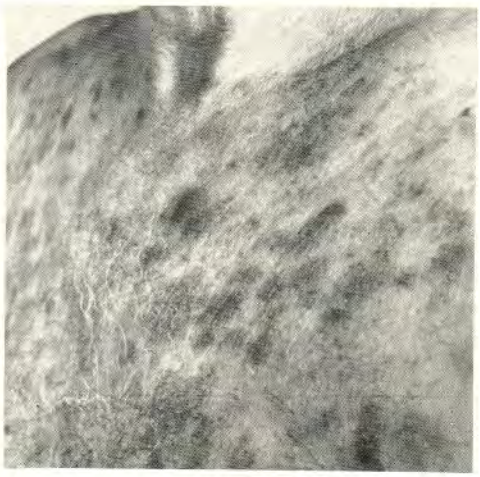


Fig. 45
Cutaneous leukemia, stem cell type. Case 34.

Examination in September 1958: In the middle of the neck there was a 5 × 6 cm wide, well demarcated, purplish tumor with flat nodules. The elevated area was surrounded by a pigmented zone due to the x-ray treatment. On the right forearm was a papule covered with a yellowish scurf, 4 mm in diameter. There was a similar papule on the back of the head. No palpable lymph nodes. Liver and spleen not enlarged. Lungs roentgenologically normal.

Blood count: Hgbn 14.3, erythrocytes 4,380, leukocytes 5,400, segmented cells 48.0, eosinophils 3.5, monocytes 8.0, lymphocytes 40.5. ESR 11 mm in one hour.

Electrophoresis: albumin + alfa$_1$globulin 74.4, alfa$_2$globulin 6.8, beta 9.2, gammaglobulin 9.6 per cent.

Total plasma proteins 6.8 per cent.

Sternal puncture: The bone marrow was rich in reticular cells. The plasma cells were augmented in number. Active normoblastic erythropoiesis. Myelometamyelocytic leukopoiesis. Eosinophils somewhat augmented.

Histology: A papule: The epidermis is thickened and hyperkeratotic, the center of the papule ulcerating. Around the ulceration the epidermal cells are large and variable in shape and size, resembling those seen in Bowen's disease. In the upper dermis there is a principally perivascular inflammatory cell infiltration consisting of large dark-staining histiocytes.

Silver impregnation: In the upper dermis a well developed argyrophil network is seen.

Histology: A tumor: In the specimen there is polymorphic cell infiltration, typical of the tumor stage of mycosis fungoides, with large-nucleated, dark-staining histiocytes and pale-nucleated cells resembling endothelial cells. Some eosinophils, broken nuclei and nuclear debris are also seen.

Silver impregnation: A regular, well developed argyrophilic reticulum is seen.

Clinical course: X-ray treatment caused rapid diminution in the size of the tumor area on the back. New lesions appeared, however, on the thighs, scalp, right upper arm and chest.

In March 1959, a little, fingertip-sized shadow was seen in the lower lobe of the right lung. Three months later, several infiltration shadows with clear-cut margins were visible in both lungs. The general condition of the patient quickly deteriorated and he died in July 1959, showing signs of right-sided hemiplegia.

Report of the autopsy: Immediately below the foramen magnum an extradural tumor about 2 cm in diameter, is encountered. The consistency of the brain is normal. The brain ventricles are symmetric; no focal changes are observed. The lower aspect of the cerebellum shows no lesions due to elevated intracranial pressure.

In the posterior wall of the left ventricle of the heart there is a round, soft, pale tumor, 7 mm in diameter. Similar tissue is present in the anterior wall of the right atrium immediately to the right of the auricle.

On the surface of the lungs, a fresh, easily detachable fibrinous exudate is detected. The lungs are full of pea- to walnut-sized, relatively soft, pale tumors, the

cut surfaces of which show hemorrhages. The tumors are spherical and located near the lung surface. In the lung parenchyma between the tumors there are small bronchopneumonic changes and turbid, blood-colored fluid can be pressed from the cut surface of the lungs. The mediastinal glands are not swollen and there are no metastases in them.

In the right kidney there are three, in the left two pea- to walnut-sized tumors. They are principally located in the cortical layer, the biggest, however, extending to the medulla. In their cut surfaces some hemorrhages are seen.

In the posterior wall of the uterus there is a rather soft, well-limited tumor, the size of a thumb-tip. The tumor is macroscopically encapsulated and can be easily detached with the fingers from the surrounding tissue.

Microscopic examination of autopsy specimens:

Histology: An early skin tumor: The epidermis is slightly hyperkeratotic and acanthotic. In the papillary part of the dermis there is pronounced cell infiltration. Deeper in the corium there are large perivascular cellular infiltrations. The majority of the cells are large hyperchromatic histiocytes.

Silver impregnation: The cell infiltrations are located in a regular, well developed argyrophil reticulum.

Histology of soft tumors in the brain, heart, lungs, kidneys and uterus:

All these tumors are similar in structure. There are abundant large hyperchromatic and in places multinuclear cells. Some neutrophils and eosinophils are present. The tumors are not growing expansively; on the contrary, in the middle of the lung tumors, for instance, alveolar walls are still present.

Silver impregnation: In the lung tumor, kidney tumor, and myoma of the uterus, a well developed argyrophil supporting network is visible.

CASE 34.

Diagnosis: Stem cell lymphoma, generalized. Rec.no. 684/60.

A man aged 60. In December 1959, a thumbnail-sized purplish patch appeared on the forehead. Further patches gradually appeared on the forehead, chest (fig. 45) and back. Some of the patches turned into nodules. They were neither tender nor pruritic.

In 1918, the patient had pneumonia as a complication of influenza. In 1952, he was hospitalized for 6 weeks for cardiac infarction. In 1958, leukoplakia was found on the mucous membrane of the left cheek. The condition was healed by treatment with x-rays.

Examination in March 1960: The eruption was localized principally on the forehead, chest and back. A few isolated nodules were present on the cheeks, upper arms, thighs and legs. The eruption consisted of intracutaneous infiltrations and nodules, ranging in size from that of a bean to a prune. The skin around the nodules was mottled with yellowish brown spots due to hemorrhages, the largest measuring two cm in diameter.

In the left supraclavicular fossa a pea-sized lymph node, and in both inguinal folds 3 cm long pencil-thick glandular strands were palpated. The liver and spleen were not enlarged.

X-ray examination of the lungs. Glandular hyperplasia was observed in both hili. No parenchymatous changes.

Blood count: Hgbn 13.3/86, erythrocytes 4,850, index 0.88, leukocytes 3,800, staff cells 3.5, segmented cells 35.5, eosinophils 1.5, basophils 0.5, monocytes 9.0, lymphocytes 49.5, myelocytes 0.5, thrombocytes 460,000. ESR 28 mm in one hour.

Electrophoresis: albumin 63, alfa$_1$globulin 3.9, alfa$_2$globulin 6.5, betaglobulin 11.5, gammaglobulin 15.1 per cent.

Total plasma proteins 6.7 per cent.

Sternal puncture: The marrow is poor in cells and erythropoiesis is depressed. The exact identification of the cells is difficult, the cells being either lymphoid reticulocytes or myeloblasts. The cell structure is compact, and there are one to two nucleoli. Some mitotic figure are seen. The specimen is susceptible of interpretation either as badly differentiated lymphoma of the lymphoreticular tissue or as incipient granulocytic leukemia.

Histology: A skin nodule: Large, deep cellular infiltrations with hemorrhages are seen in the dermis. The cells are uniform stem cells with pale nuclei (fig. 35, C).

Silver impregnation: Between split collagenous fibers there are cell groups poorly surrounded by argyrophil fibers. No reticular network is visible in these cell aggregates (fig. 33).

Clinical course: The patient was treated with Sendoxan and grenz rays. The nodules disappeared, leaving pigmented spots on the skin. After temporary granulocytopenia caused by the treatment slight leukocytosis was observed. Among the cells some myelocytes, promyelocytes and paramyeloblasts were found. At the same time the lymph nodes, liver and spleen were enlarged. Cortisone was given and the glands, liver and spleen were reduced in size. The general condition of the patient continued to deteriorate, however, and the number of paramyeloblasts in the blood rose, being between 18.5 and 20.0 per cent during the last weeks of life. The patient died in June 1961, after an acute attack of diarrhea.

At autopsy, large, firm, and pale conglomerations of lymph nodes were found around the aorta in the upper parts of the abdominal cavity. The spleen was large, weighing 310 g. It was firmer than normal and mottled with dark red and a yellowish color. The right kidney weighed 210 g, the left 190 g. The cut surface of the kidneys was paler than normal and the boundary between the cortex and medulla was indistinct in many places. The marrow of the femur was bright red in color as were also the vertebral bodies.

Histology: A lymph node: The lymph node is thoroughly infiltrated with leukemic cells. They are mainly large cells, the nuclei of which are large and often horseshoe-shaped. Profuse fibrosis is seen.

Liver: On the lower surface of the liver there is a lymph node conglomeration,

from which round cell infiltration extends to the liver, where it is seen as islets. The greater part of the cells are monocytes, very closely resembling lymphocytes. There are signs of biliary stasis and fatty degeneration in the parenchyma.

Spleen: Great disintegration of spleen structure. Monocytic infiltration as above can be discerned, however.

Bone marrow: The marrow is very rich in cells. The vast majority of these have large nuclei and scant cytoplasm, their structure most closely resembling that of myeloblasts.

Kidney: Strands of cellular infiltrate, consisting principally of monocytes, are seen in the specimens.

VIII. REFERENCES

Alibert, J. L. c.f. *Shelley, W. B. & Crissey, J. T.:* Classics in clinical dermatology. Charles C. Thomas, Springfield, Illinois, U.S.A., 1953, p. 31.

Amorati, A. & Longhi, A. & Roversi, L. Abstract: Excerpta Med., Section 13 (Dermat.) 5:469, 1951.

Arndt, G.: Kernstudien zur Unterscheidung von Regeneration und Geschwulstbildung. Z. Krebsforsch. 41:393, 1935.

Biasiadecki, cited by Bluefarb.

Bluefarb, S. M.: Cutaneous manifestations of the malignant lymphomas. Charles C. Thomas, Springfield, Illinois, U.S.A., 1959.

— Leukemia cutis. Charles C. Thomas, Springfield, Illinois, U.S.A., 1960.

— The cutaneous manifestations of the benign inflammatory reticuloses. Charles C. Thomas, Springfield, Illinois, U.S.A., 1960.

Borst, M.: Die Kerngrösse der Krebszellen. S.-B. phys.-med. Ges. Würzburgh, 1910, s. 24.

Brill, N. E. & Baehr, G. & Rosenthal, N.: Generalized giant lymph follicle hyperplasia of lymph nodes and spleen. J. Amer. med. Ass. 84:668, 1925.

Brofelt, S. A.: Pathologisch-anatomische und klinische Studien über Leukoplakien der Lippe und deren Verhältnis zum Karzinom. Arb. path. Inst. Univ. Helsinki. N.F. 5:34, 1928.

Bäfverstedt, B.: Über lymphadenosis benigna cutis. Acta derm.-venereol. Suppl. 11, 1943.

— Lymphadenosis benigna cutis as a symptom of malignant tumors Ibid., 33:171, 1953.

Clara, M.: Über die Kerngrössen der Leberzellen. Z. mikr.-anat. Forsch. 22:145, 1930.

Custer, R. P. & Bernhard, W. G.: The interrelationship of Hodgkin's disease and other lymphatic tumors. Amer. J. med. Sci 216:625, 1948.

Custer, R. P.: An atlas of the blood and bone marrow. W.B. Saunders Co., Philadelphia and London, 1949.

Damashek, W. & Gunz, F.: Leukemia. Grune & Stratton, New York and London, 1960, p. 86.

Dostrovsky, A. & Sagher, F.: Poikiloderma as the initial stage of mycosis fungoides. Arch. Derm. Syph. (Chic.) 51:182, 1945.

Dublin, W. B.: Reticulum. Arch. Path. 41:299, 1946.

Dunn, Th. B.: Normal and pathologic anatomy of the reticular tissue in laboratory mice. J. nat. Cancer Inst. 14, 1954.

Ehrich, W.: Die polymeren Kerngrössen als Ausdruck der Krebsanaplasie. Z. Krebsforsch. 44: 308, 1936.

Engelbreth-Holm, J.: On leukaemia research. In Ciba Foundation Symposium on leukaemia research. J. & A. Churchill, Ltd., London, 1954.

Evans, W. R.: Histological appearances of tumours, Livingstone, London, 1956.

Feyrter, F.: Über den Kernpolymorphismus einiger Zellarten in der Leiche und im Operat. Frankfurter Z. Path. 70:740, 1960.

Fisher and *Yates:* In *Siegel, S.:* Nonparametric Statistics. McGraw—Hill Book Co., New York, 1956.

Foot, N. C. & Day, H. A,: The occurrence of reticulum in tumours. Amer. J. Path. 1:431, 1925.

Fraser, J. F.: Mycosis fungoides. Arch. Derm. Syph. (Chic.) 12:814, 1925.

Frenk, E.: Zur Histologie der Fibrome und Histiocytome der Haut. Hautartzt 12:15, 1961.

Fresen, O.: Pathomorphologie des rethothelialen Systems. Verh. dtsch. Ges. Path. 37:15, 1953.

Friedman, I. A. & Leithold, S. L.: The diagnosis of leukemia. In: *Bluefarb, S. M.:* Leukemia cutis, Charles C. Thomas, Springfield, Illinois, U.S.A., 1960, p. 404.

Gall, E. A. & Mallory, T. B.: Malignant lymphoma. A clinico-pathologic survey of 618 cases. Amer. J. Path. 18:381, 1942.

Gans, O. & Steigleder, G. K.: Histologie der Hautkrankheiten II Bd. Springer-Verlag, Berlin—Göttingen—Heidelberg, 1957.

Gerwig, cited by Bluefarb.

Gottron, H. A.: Zur Leukämie der Haut. Ned. Klin. 33:373, 1937.

— Retikulosen der Haut. In: *Gottron, H. A. & Schönfelt,* W. Dermatologie und Venerologie, Bd. IV, S. 501, Georg Thieme Verlag, Stuttgart, 1960.

Götz, H.: Die Acrodermatitis chronica atrophicans Herxheimer als Infektionskrankheit. Hautartzt 5:491, 1954.

Hadfield, G. & Harrison, C. V.: Reticulosis and reticulosarcoma. In: *Hadfield, G.:* Recent advances in pathology, ed. 6, p. 82, J. & A. Churchill, Ltd, London, 1953.

Harrison, C. V.: Benign Hodgkin's disease (Hodgkin's paragranuloma). J. Path. Bakt. 64:513, 1952.

Haumeder, E.: Vergleichende Kern- und Nucleolenmessungen an verschiedenen Organgeweben mit besonderer Berücksichtigung den malignen Tumorzellen. Z. Krebsforschung 40: 105, 1934.

Hauser, W.: Zur Kenntnis der Akrodermatitis chronica atrophicans. Arch. Derm. Syph. (Berlin) 199:350, 1955.

Heiberg, K. A.: Über die Erklärung einer Verschiedenheit der Krebszellen von anderen Zellen. Nord. med. Ark. 41, 1908.

Heiberg, cited by Engelbreth-Holm.

Heidenhain, M.: Plasma und Zelle. Verlag von Gustav Fisher, Jena, 1907.

Heite, H. J. & Socha, P.: Häufigkeitsanalytische Untersuchungen zur Symptomatologie der Mycosis fungoides. Arch. Derm. Syph. (Berlin) 193:118, 1951.

Herrath & Dettmer: In *von Herrath, E.:* Die Morphologie des Retothelialen Systems. Verh. dtsch. Ges. Path. Gustav Fisher Verlag, Stuttgart, 37:13, 1953.

Hertwig, G.: Der Aufbau des Zentralnervensystems aus Zellen deren Kernvolumen sich verhalten wie 1:2:4:8:16. Ein Beweis für das rythmische Kernwachstum durch Volumenverdoppelung. S. ber. Naturf. Ges. Rostock 3:73, 1932.

Herzberg, J.: Reticulosarcomatöse Umwandlung multipler subcutaner Lymphocytome bei Acrodermatitis chr. atrophicans. Derm. Wschr. 125:422, 1952.

Herzberg, J. & Überschär, K. H.: Die Mycosis fungoides als neoplastische Erkrankung des erweiterten retikuloendothelialen Systems. Derm. Wschr. 123:316, 1951.

Hodgkin, T. c.f. *Jadasshon, J.:* Handbuch der Haut- und Geschlechtskrankheiten. Bd VIII/1 p. 272, Julius Springer, Berlin 1929.

Holsti, R. L. & Voutilainen, A.: Über kombinierte Röntgen- und Radiophosphorbehandlung bei Mycosis fungoides. Strahlentherapie 111:139, 1960.

Homma, H.: Über Gitterfasern in normaler menschlicher Haut. Wien. klin. Wschr. 35:149, 1922.

Jacobj, W.: Über das rythmische Wachstum der Zellen durch Verdoppelung ihres Volumens. Arch. Entwickl.-Mech. Org. 106:124, 1925.

Jaffé, cited by Bluefarb.

Jackson, H.: The classification and prognosis of Hodgkin's disease and allied disorders. Surg. Gynec. Obstet. 64:465, 1937.

Jackson and *Parker*, cited by Bluefarb.

Järvi, O. & Teir, H.: Experimental alterations of cell size and mitotic activity in the outer orbital gland of the white rat. Acta path. microbiol. scand. 24:401, 1951.

Keim, H.: The lymphoblastomas, their interrelationships. Arch. Derm. Syph. (Chic.) 19:533, 1929.

Klossner, A. R.: Studien über Zellstrukturen in den epithelialen Mammatumoren und in den Epithelien der Fibromatosis diffusa Mammae (Dietrich) Arb. path. Inst. Univ. Helsinki. N.F. 6:81, 1930.

Knoth, W.: Zur Cyto- und Histogenese und zur klinischen Einteilung der reticulohistiocytären Erkrankungen der Haut. Arch. klin. exp. Derm. 209:130, 1957.

— Die diagnostische Bedeutung des Gitterfasernachweises bei Dermatosen. Arch. klin. exp. Derm. 206:744, 1958.

— Reticulosarcomatose auf dem Boden von Akrodermatitis chronica atrophicans und Serumeiweissuntersuchungen bei blastomatösen reticulohistiocytären Krankungen der Haut. Hautartzt 9:456, 1958.

Kruskall-Wallis cited by Siegel.

Kundrat, H.: Über Lymphosarkomatosis. Wien. klin. Wschr. 6:211, 1893.

Lever, W. F.: Histopathology of the skin. J. B. Lippincott Co., Philadelphia, London, Montreal, 1949.

Lumb, G. & Newton, K. A.: Prognosis in tumors of lymphoid tissue. An analysis of 602 cases. Cancer 10:976, 1957.

Mackenzie, D. H.: Reticulin pattern in tumours of lymphoid tissue. Brit. J. Cancer 13:38, 1959.

Mall and *Siegfried*, cited by Maximov.

Mallory, F. B. & Parker, F.: Reticulum. Amer. J. Path. 3:515, 1927.

Marshall, A. H. E.: An outline of the cytology and pathology of the reticular tissue. Oliver and Boyd, Edinburgh, London, 1956.

Maximow, A.: Das Mesenchym als Quelle der verschiedenen Arten der Bindesubstanzen, des Blutes, der Blutbildenden Gewebe und des Endothels. In: *v. Mollendorff, W.:* Handbuch der mikroskopischen Anatomie des Menschen. Bd II, s. 231, 1927.

Maximow, A. & Bloom, W.: A Textbook of Histology. W. B. Saunders Co., Philadelphia, London, 1950.

Montagna, W.: The structure and function of skin. Academic press inc. Publishers, New York, 1956.

Montgomery, H.: Mycosis fungoides, lymphoblastoma of the skin and allied conditions as general diseases. Oxford Med. 4:44, 1936.

Mustakallio, S.: Untersuchungen über den mikroskopischen Bau und die Natur der Ostitis fibrosa localisata. Arb. path. Inst. Univ. Helsinki. N.F. 8:37, 1935.

Niethammer, M.: Beiträge zur Frage der Ätiologie und zur Therapie der Mycosis fungoides. Arch. Derm. Syph. (Berlin) 179:484, 1940.

Nomikos, B.: Vergleichende Untersuchungen über die Kerngrösse bei den verschiedenartigsten epithelialen Neubildungen insbesondere bei Carsinomen. Inaug. Diss. Kgl. Bayer. Julius-Maximiliano-Universität Würzburg, 1910.

Oliver, E. A.: Mycosis fungoides, report of three cases of the tumor d'emblee type. Arch. Derm. Syph. (Chic.) 10:183, 1924.

— Mycosis fungoides with poikiloderma-like changes. Arch. Derm. Syph. (Chic.) 33:267, 1936.

Ormsby, O. S.: Mycosis fungoides. Arch. Derm. Syph. (Chic.) 29:159, 1934.

Paltauf, R. & Zumbusch, L.: Mycosis fungoides der Haut und inneren Organen. Arch. Derm. Syph. (Berlin) 118:699, 1913.

Paschoud, J. M.: Die Lymphadenosis benigna cutis (L.a.b.c.) als übertragbare Infektionskrankheit. Hautarzt 9:153, 1958.

Peiser, B. & Brandenburg, W.: Beitrag zur Klinik und Histopatologie der Mycosis fungoides: Granulomatöse Reticulo-histiocytose mit Übergang in Reticulosarkom. Z. Haut.- u. Geschl.-Kr. 26:61, 1959.

Putkonen, T.: A case of cutaneous leukemia, presented to the Finnish Dermatologic Society, April 1959.

Rappaport, H. & Winter, W. J. & Hicks, E. B.: Follicular lymphoma. A re-evaluation of its position in the scheme of malignant lymphoma, based on a survey of 253 cases. Cancer 9:792, 1956.

Reed, cited by Bluefarb.

Rentzow, H.: Über die Kerngrösse der Retikuloendothelien bei Lymphogranulomatose und Tuberculose. Inaug. Diss. Rostock, 1935.

Repsilber, M.: Über die Kerngrössen einiger Lymphknotengeschwulste. Inaug. Diss. Rostock 1936.

Robb-Smith, A. H. T.: Reticulosis and reticulosarcoma: a histological classification. J. Path. Bact. 47:457, 1938.

Rosenthal, N. & Harris, W.: Leukemia, diagnoses and treatment. J. Amer. med. Ass. 104:702, 1935.

Rosenthal, S. K.: Beiträge zur Kenntnis der exfoliativen generalisierten erythrodermien. Arch. Derm. Syph. (Berlin) 164:82, 1931.

Saxen, A.: Pathologisch-anatomische und klinische Studien über die primären von der Nasenkavität und den angrenzenden Nebenhöhlen ausgehenden Papillome und Karzinome. Arb. path. Inst. Univ. Helsinki. N.F. 4:1, 1926.

Schairer, E.: Kernmessungen und Chromosomenzählungen an menschlichen Geschwulsten. Z. Krebsforsch. 43:1, 1936.

Schilling & Reschad, cited by Gottron.

Siegel, S.: Nonparametric Statistics, pp. 152—54, 184—194. McGraw—Hill Book Co., New York, 1956.

Sonck, C. E.: Primäre Reticulumzellsarkomatose der Haut. Proc. of North. Derm. Soc. Helsinki, 1956.

Steigleder, G. K. & Hunscha, H. G.: Die Reticulosarkomatosen der Haut. Arch. klin. exp. Derm. 205:435, 1958.

*Stenius, F.:*Studien über Pathologie und Klinik der Papillome und Karzinome der Harnblase. Arb. path. Inst. Univ. Helsinki, N.F. 3:27, 1925.

Sugerbaker, E. D. & Craver, L. F.: Lymphosarcoma. A study of 196 cases with biopsy. J. Amer. med. Ass. 115:112, 1940.

Symmers, D.: Clinical significance of the pathologic changes in giant follicular lymphadenopathy. Arch. Path. 34:385, 1942.

Szodorey, L.: The structure of the junction of the epidermis and the corium. Arch. Derm. Syph. (Chic.) 23:920, 1931.

Teir, H.: Über Zellteilung und Kernklassenbildung in der Glandula orbitalis externa der Ratte. Acta path. microbiol. scand. Suppl. LI, Helsinki, 1944.

Thesleff, C.: Studien über das Ulcus rodens einschliesslich seiner Zellstrukturen. Arb. path. Inst. Univ. Helsinki. N.F. 7:51, 1933.

Tzanck, A. & Dreyfuss, A. & Levy, S.: La ponction sternale dans le mycosis fongoide. Sang 12:110, 1938.

Warthin, A. S.: The genetic neoplastic relationships of Hodgkin's disease, aleukemic and leukemic lymphoblastoma and mycosis fungoides. Ann. Surg. 93:153, 1931.

Way, S. C.: Reticulum or lattice fibers. Arch. Derm. Syph. (Chic.) 55:478, 1947.

Way, S. C. & Klövekorn, G. H.: Hautkrankheiten und Gitterfasern. Derm. Z. 48:139, 1926.

Weidman, A.: Beiträge zur Kenntnis des Granuloma fungoides. Derm. Wschr. 94:777, 1932.

Vidal & Brocq, cited by Bluefarb.

a. *Winer, L. H.:* Mycosis fungoides. Arch. Derm. Syph. (Chic.) 56:480, 1947.

b. *Winer, K.:* Skin manifestations of internal disorders. The C. V. Mosby Co., St.Louis, 1947.

Vorbeck, cited by Repsilber.

Zurhelle, E.: Über den Anteil feinster Bindegewebsfibrillen, den sogen. Gitterfasern, am Aufbau syphilitischer und anderer Hautefflorezenzen, gleichzeitig ein Beitrag zu ihrer Konsistenz insbesondere zur Härte des Primäraffektes. Derm. Z. 35:251, 1922.