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# Lymphoblastomas

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# THE LYMPHOBLASTOMAS

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BY

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A spontaneous interest in the field of dermatology is largely responsible for this review of current thought on the relationships which are believed to exist between certain diseases of the lymphatic and reticulo-endothelial system. In addition, the death of a patient attended on the Medical School's outcall service from Hodgkin's disease made an impression sufficiently deep and lasting to serve as an impetus for further study of that affection and its allies.

The "first fatality" might best describe this particular case. "Hodgkin's" was both the clinical and pathological diagnosis, as stated in the hospital records. But the picture failed to tally with textbook descriptions and hastily transcribed lecture notes--and these must substitute temporarily in place of experience. Consultation with staff men was unsatisfactory. The patient failed too rapidly and succumbed to unknown complications. Someone said: "It didn't act quite like Hodgkin's disease." But permission for a postmortem examination was not granted, so the final chapter remains untold.

The futile optimism of this particular patient, the calm resignation of the family, the helplessness of the attendants--all serve now as a stern reminder of

what the future holds for the practitioner of medicine. The insatiable desire to "do something" when everything possible had already been done must be appeased. Scientific advance is as slow as it is certain. Perhaps a thousand men must work a lifetime to make a single deduction possible at the bedside. But as one lifetime of effort is piled upon another, eventually a memorable contribution is made to medical enlightment. That which is unknown today will be known tomorrow.

The lymphoblastomas do not occupy in frequency an outstanding position in the category of disorders which the physician is called upon to diagnose and treat. In 100,000 tissue examinations made by the department of pathology at the University of Michigan from 1895 to 1927 only 506 specimens (.5%) were diagnosed as belonging to this group. During the same period, 2,000 autopsies revealed 83 cases (4.1%).[34] Yet, at the present time, there is widespread interest in lympho-pathology among dermatologists, roentgenologists and pathologists. Their enthusiasm has been aroused by the promise of discovery and accomplishment. The etiology of lymphatic system disease, like many disease entities, had not been defined. Onset is slow and insidious, rarely alarming, but always progressive and unrelenting. Symptoms are

bizarre and perplexing, so that often "atypical" cases of a series outnumber the "typical" examples. No age or class is spared. There is no immunity and treatment is only palliative at its best. A fatal termination is the rule, and apparently, a rule without an exception.

Due in great part to the efforts of Hodgkin and Virchow, these diseases are now recognized by the physician instead of passing unnoticed. Thanks to Roentgen-ray and radium therapy, the victim's expectancy is lengthened and his plight lightened. It is entirely reasonable to expect that the present work of Keim[18-19], Warthin[34], Fraser[14-15], Mallory[24] and others, in delving into the genetic and clinical relationships of lymph gland skin and blood stream affections and formulating a logical grouping and calssification together with definite etiological hypotheses, will aid immeasureably in the final solution of the problem.

## GENERAL CONSIDERATIONS

Though the similarity of many lymphadenoses had long been recognized, it was not until 1924 that Keim[18] first suggested a classification of these diseases as an aid to their interpretation. He held that they were

genetically related and that the variety of clinical pictures which they presented was often dermatological manifestations of the same disease. He termed them lymphoblastomas.

In his group of lymphoblastomas Keim[19] included Hodgkin's disease, lymphatic leukemia, lymphosarcoma and mycosis fungoides. Others, while accepting his lymphoblastic classification, have both limited and expanded the disease conditions in the group. Cannon[8] would associate only Hodgkin's disease and lymphosarcoma. Webster[36] is inclined to omit Hodgkin's disease, but include leukosarcoma. Markowitz[25] limits the class to the leukemias and lymphosarcoma, while Craver[10] recently presented an expansive list of thirty-one conditions which he says "border on the lymphoblastomatous group of diseases." Obviously, in such a diversity of opinions there is a confusion of terminology, and that is what Keim hoped to eliminate.

He firmly agrees with Warthin that diseases of the lymphoblastic group are neoplastic in origin, and hence the condition should be regarded as any tumorous growth with full respect for its tendencies of localization, development and metastases[19]. Mallory[24] has defined

a tumor as "a new formation of cells which proliferate continuously and without control, tend to differentiate from the cells from which they arose under normal conditions, serve no useful purpose, lack an orderly structural arrangement and have, at least for the present time, no assignable cause for their existence." Some lymphatic system tumors grow slowly and the cells have opportune time to continue their growth, often reaching maturity; others proliferate so rapidly that differentiation is impossible and there is an abundance of embryonal forms present.

The one important element in any tumor, Keim[19] insists, is the predominating cell type. From this cell, the neoplasm should be named and "not from some minor characteristic of the method of growth or arrangement of cells." The lymphoblast is the chief cellular element in the vast majority of the diseases under consideration. It is the forerunner of the mature lymphocyte found in the blood stream and later will be described more fully. Hence, the designation of lymphoblastomas for these condition. Keim[19] even goes further in suggesting that the suffix, "blastoma," be used in reference to the predominating cellular constituent in all tumors. Thus, there would be fibroblastomas, osteo-

blastomas, etc.

Warthin[34] and others[1-25-25] have studied exhaustively the genetic relations believed to exist between the lymphoblastomas. He found that the condition "in all forms...is that of a progressive increase in atypical tissue replacing the normal tissues of the body up to a point at which life is no longer possible, or secondary complications may end the picture." He is convinced, beyond doubt, that all are malignant, and infiltrate and metastasize to all reticulo-endothelial and blood-forming organs in the characteristic manner of neoplasms. Moreover, he points out that every case presents a picture of true "tumor cachexia" at its termination, if not earlier.

Though no really mild cases of lymphoblastomas occur, there is sometimes a tendency to regression with a complete suspension of symptoms. This has been noted by Burnam[4] in his experience with mycosis fungoides. However, in spite of frequent x-radiation the termination is invariably fatal. The histo-pathology of lymphoblastomas usually shows a dense lymphoid hyperplasia with lymphoid cells in all stages of development, frequent mototic figures, a few polymorphonuclear cells, eosinophils, plasma cells and fibroblasts. There is

usually a minimum of connective tissue stroma present. The principal differences in the diseases from a histopathologic angle is the point of origin and the degree of cellular differentiation present.

The lymphoblastomas, in many instances, are preceded or accompanied by skin lesions but this is an inconstant feature of the disease. The eruptions are difficult to classify due to their multiplicity of form and instability of character. However, they share certain qualities. First, all are pruritic and persistently so; second, they are often the first tangible evidence of systemic disease; third, there is a tendency for most of the eruptions to become generalized and very frequently they are scaly. Such an onset often brings the patient to the dermatologist, and places considerable responsibility upon his experience and diagnostic ability if the patient's life is to be prolonged.

## HISTOGENESIS OF LYMPHOCYTES

In tissue sections taken from lymphoblastomatous disease, the predominating cellular element in nearly all cases is the lymphoblast--the forerunner of the small lymphocyte. Burnam[4] calls the lymphoblast the "unit or parent cell" in the lymphoblastomas. Keim's[19] basis for

such a classification of lymphatic system disease was the unfailing presence of this type of cell in preponderant numbers. Warthin[34] concluded that all the lymphoblastomas originate from the maternal lymphoblasts in the perivascular reticulo-endothelium. Theories concerning the histogenesis of lymphocytes fall into two principal groups of thought--the hypotheses of the "unitarians" and the "dualists." As will be discussed, the former hold that all hemopoietic cells arise from a single unit, the "hemocytoblast;" the latter contend that cells of the lymphatic and myelogenous order each have a separate, specific stem cell.

The small lymphocyte belongs to the group of non-granular or lymphoid leukocytes, also called agranulocytes, and comprises about 20 to 25% of the colorless corpuscles in normal blood. They are slightly larger than erythrocytes, measuring 6 to 8m in diameter, possess a relatively large nucleus and a thin layer of protoplasm. Taking the shape of the cell, the nucleus also is spherical and is usually indented on one side.

When stained with Romanowsky or Wright's solutions, the nucleus appears very dark blue or purple due to its thick membraneous layer of chromatin. The protoplasm is a pale blue and is massed more on the

indented side of the nucleus. Though classed as non-granular cells, dry smears occasionally reveal variously colored droplet-like granules in the cytoplasm. However, this is but a transient feature of lymphocytes.

In contrast to the "small" lymphocytes, just described, a "large" lymphocyte is also found in the circulating blood. The larger cells owe their size principally to an increase in the amount of protoplasm as the size of the nucleus remains relatively unchanged. In blood smears, the larger lymphocytes are often confused with monocytes.

The hemopoiesis of the lymphocytes is closely related to the problems presented by the lymphoblastomas. In all of the diseases included in this group, the significant feature is an uncontrolled, bizarre production of lymphocytic cells either in the circulating blood, the regional lymph glands, the skin or in a metastatic propensity elsewhere. Keim[18-19] and other investigators insist that the course taken by these cells determines the clinical entity which results, and is accordingly named lymphosarcoma, lymphatic leukemia or whatever it may be.

The lymphoid tissue in the body, whence the lymphocytes arise, includes the lymph nodes, tonsillar

tissue, spleen, the gastro-intestinal tract and probably also the skin. Some investigators[7] now believe that all the tissues of the body are involved. Such lymphoid tissue presents a diffuse ground substance, comprised of follicles, or primary nodules, in the middle of which is a germinal center, or secondary nodule. There are sinus passages between the cellular structures for the circulation of lymph which are formed by a loose arrangement of the fibrillar meshworks. The constituents of this tissue include the framework or stroma, and the free, round cells contained in the meshes of the network.

The much abused term, "reticulum"[24] has often been used with reference to either the fibrous framework of this stroma, or to the fixed cells of the stroma, or to both. All such references, while somewhat misleading, are more or less correct, as the fixed cells of the lymphoid tissue are reticular cells and the fibers are reticular fibers. In the meshes of this cellular, or reticular, synctium are the free cells or lymphocytes. They are densely crowded together in the stroma, obscuring the reticular cells from view in most stains.

In the words of Maximow[24]: "The three types of

lymphocytes are connected with each other by an uninterrupted series of transitional forms. This is explained by their close genetic interrelationships. It is generally believed that the medium-sized lymphocytes originate from the division of large lymphocytes, while the small ones are the daughter cells of the medium-sized. The lymphocytes proliferate only by mitosis. Some authors believe the large lymphocytes of the lymphoid tissue to be the stem cell of the small lymphocytes of the blood and therefore call them "lymphoblasts." In the small lymphocytes mitoses are extremely rare under normal conditions. The opinions are divided as to whether a small lymphocyte can turn into a large one.

"The representatives of the dualistic theory of hemopoiëses deny this possibility. To them the small lymphocyte is the highly differentiated end stage of a cell lineage. They believe that it cannot be transformed into any other cell and cannot turn back into a large lymphocyte capable of proliferation. After having circulated in the blood, it perishes and, doing this, performs its function in some unknown way according to these authors.

"The unitarians, on the contrary, believe that the small lymphocyte is an undifferentiated cell and

that it keeps unrestricted all the potencies of development which are characteristic of the large and medium-sized lymphocytes. It is merely a temporary stage of the lymphocytic cell typed. After the small lymphocyte has reached a suitable age--the time necessary for the maturation is not known--it may again be transformed through hypertrophy into a medium-sized and a large lymphocyte and again regain the ability to divide under suitable external conditions. This, of course, does not exclude the possibility of their transformations into other kinds of blood and connective tissue cells. The transformation of a small lymphocyte into a large one need not occur at the place of origin of the lymphoid tissue; this may, and indeed, usually does happen in other places of the body, after the small lymphocyte has circulated in the blood.

"....the sum of all the facts speaks more in favor of the unitarian than of the dualistic theory. From the viewpoint of the first theory, the genetic relationships of the blood cells appear in a much simpler and clearer light and their artificial subdivision into numerous cell lineages on the basis of minute, inconstant, structural differences becomes unnecessary."

Hodgkin's disease, first described in 1832, is "an affection characterized by painless progressive enlargement of the lymph nodes, and frequently the spleen, often accompanied by fever and, in the late stages, by cachexia and anemia.[22]" From both a clinical and histopathological viewpoint, it is definitely a part of the group of lymphoblastomes in the opinion of many investigators.

The disease is found most frequently in younger adults and occurs more often in men than in women. While considered at various times to be related to tuberculosis, neoplasms and infections, the cause of Hodgkin's disease is unknown. It may begin with an enlargement of any of regional lymph glands in the body. Warthin[34] states the left cervical glands are the mediastinal and retroperitioneal, in the order named. This glandular hypertrophy is painless and often the patient does not seek medical aid in the early stages of the disease.

The patient may complain early of an intense and distressing pruritus. In fact, this symptom may cause more concern than the glandular enlargement. Skin eruptions and herpes zoster[10] may accompany the itching, further clouding the diagnosis. The spleen

is enlarged in about 60% of cases, and the liver is often palpable. As the malady progresses, there is marked cachexia, dyspnea due to mediastinal involvement, and sometimes, dysphagia. Throughout its course, the blood picture in typical cases is normal and the blood pressure is low.

In the opinion of Cannon[8], Hodgkin's disease is often preceded "years before" by changes in the skins, nails and hair. In a series of thirty-three cases, Cole[9] found that thirteen presented skin lesions. He says they are often unnoticed because they are not looked for by the average physician. An excoriated, pruritic papule is the most common lesion and should make one immediately suspicious of Hodgkin's disease in an early stage. Cannon[9], who says that 98% of his cases have had so-called toxic or secondary skin symptoms lists such findings as: changes in pigmentation, dryness, thickening, roughening, scaling, follicular papules simulating goose flesh and feeling like sandpaper to touch, papules, vesico-papules, excoriated papules, urticaria-like lesions, dermatographism, transient swellings, erythematous macular areas, hemorrhages, icterus, exfoliative dermatitis, alopecia and dystrophy of nails.

When the diagnosis of Hodgkin's is made, Warthin[34] says the patient's expectancy is from three to five years. Due to its many atypical presentations, however, he emphasizes the difficulty of diagnosing the disease and describs the usual histological picture of "atypical lymphocytes, lymphoblasts, plasma cells, mono and polynuclear eosinophils, myeloid cells, fibroblastic cells and the multinucleated 'Hodgkin's' or 'Dorothy Reed' giant cell." The eosinophils and Dorothy Reed cells must be present, he stated, for a positive diagnosis based on tissue examination. Cases in which the requirements of the clinical picture are fulfilled and these special cells are absent on the slides, are known as "atypical" Hodgkins. In many reported series of the disease[2-3-5-6-11-16-17], the number of atypical cases is surprisingly large and their resemblance to the other disease entities under discussion is interesting and gratifying.

Various classifications of Hodgkin's Disease have been presented. That of Longcope and McAlpin[22] i thoroughly acceptable:

1. Acute forms in which the patient dies in a month or two.

2. A localized form in which it is confined for two or three years to a particular group of lymph glands, with generalization only in the final stages.

3. A mediastinal form, which produces the most distressing symptoms.

4. A latent form, confined generally to the deep nodes in the thorax or abdomen, and confused with a large variety of conditions.

5. A splenic form, confined principally to that organ, which is rare.

6. Another rare form in which the involvement includes the periosteum and bone marrow.

The differential diagnosis lies chiefly between the other pathological conditions, discussed herewith, which bear such a close genetic relationship. Tuberculosis of the cervical lymph nodes and gummatous lymph glands must be remembered. Treatment is palliative only, consisting of radium or X-Ray therapy. Arsenic, in the form of Fowler's solution, is the only drug of value.

Two cases of Hodgkin's disease are included in this review. The first, reported by Dr. Moses Barron[2],

is of the type most frequently encountered, but which also shows an interesting skin manifestation. The other case, reported by Dr. James R. Lisa[21], is an unusual form in which the skin is the principal and earliest seat of the pathological process.

Case 1.--History.--Mrs. H.C., aged 56, was first seen on September 14, 1922, complaining of pain in the precordium and edema of the legs. The family and past history were negative. The patient had always been well up until the present illness. A hysterectomy had been performed when she was 44; menopause had been present since then. The patient was well until the spring of 1919, when she developed small lumps in the back of the neck and then a large mass below the angle of the right side of the jaw. This increased to the size of an orange, when it was treated with radium, after which it gradually disappeared. The following year she was entirely well. In April, 1920, she developed a rash like measles, which was associated with fever, and was confined to bed for three weeks. In July, 1921, she again developed a fever. At this time she was told that the urine was bad. In the fall of 1921, she began to feel tired; her mouth was dry; she was very thirsty, drank large quantities of water and urinated frequently. In April, 1922, she fell down and bruised herself, and was confined to bed for thirteen weeks. She was treated for heart disease and diabetes at the same time. At that time she again developed a pink rash over the body composed of discrete papules from 3 to 10 mm. in diameter. These were definitely raised and indurated.

Examination.--On examination in September, 1922, the patient was found to be well nourished, with a pulse rate of 72, a blood pressure of 162 systolic and 70 diastolic, and an extensive papular rash over the whole body--front, back, abdomen, arms, forearms and thighs. The tonsils were large; there was gingivitis of the lower teeth, with a plate for the upper. There were large lymph nodes in the posterior and supraclavicular triangles of the neck, the largest measuring 2 cm. in diameter. The right maxillary and right axillary nodes were the size of walnuts, the right inguinal nodes

the size of hen's eggs, and the left inguinal nodes the size of hazelnuts. All nodes were discrete and freely movable. Cardiac dulness was increased both to the right and to the left, with increased mediastinal dulness; there was a soft systolic murmur at the apex transmitted to the axilla. The chest showed poor expansion with lagging on the left side. The spleen and liver were not palpable. The biceps, triceps and knee reflexes were exaggerated.

The first examination of the urine showed sugar + + +; subsequently it was normal. Blood examination on September 14 revealed a hemoglobin of 86 per cent, red blood count 5,200,000, leukocytes 5,800, with a differential count of polymorphonuclears 64 per cent, lymphocytes 23 per cent, large mononuclears 5 per cent, transitionals 3 per cent and eosinophils 4 per cent. On December 11 the hemoglobin was 54 per cent, the white count 3,400, with eosinophils 7 per cent. On March 24, 1923, the hemoglobin was 34 per cent, the red count 1,900,000 the white count 1,800 and a few normoblasts.

Clinical Notes.--Dec. 11, 1922: The condition was better; the skin rash had disappeared.

December 26: The patient felt very weak; the spleen was markedly enlarged, 10 cm. below the costal margin; the liver, to the level of the umbilicus.

Jan. 2, 1923: The patient felt weak; her appetite was poor; the spleen and liver were very large; the skin rash reappeared with a papular eruption from 1 mm. to 1 cm. in diameter.

March 1: The patient entered St. Mary's Hospital. Her temperature was 102 F.; it was irregular for about ten days, ranging between 97 and 101 F., then to normal from then on; the pulse rate varied from 110 to 130; respiration, from 20 to 40. Physical examination showed very large superficial lymph nodes, the liver receded to 1 cm. below the costal margin and the spleen to 3 cm. below the costal margin. The patient showed marked dyspnea, accompanied by deep cyanosis of the finger-nails and lips. The lower half of the right part of the chest was fixed, the breath sounds absent.

March 13: The patient was much worse. The right side of the chest was full of fluid, and generalized edema was developing.

March 14: One thousand cubic centimeters of clear amber fluid was aspirated from the right side of the chest; breathing was a little easier.

March 19: There were signs of fluid reaccumulating. Severe dyspnea was present.

March 20: Fifteen hundred cubic centimeters of similar fluid was aspirated.

March 22: The patient was much worse. Anemia was profound. There was a purpuric rash over the right arm, the right shoulder and the back. Urine showed one plus albumin, one plus hyaline and three plus granular casts.

The patient died on March 25, 1923.

Biopsy of the skin showed infiltration into the corium with small lymphocytes and a few large reticular cells, but no characteristic Dorothy Reed cells. Biopsy of a cervical node showed extensive hyperplasia of lymphoid tissue with areas of fibrosis and a few eosinophils. The diagnosis was Hodgkin's disease.

The patient had been given six roentgen-ray treatments with some reduction in the size of the nodes, but there was no clinical relief. Necropsy was not performed.

Comment -- This is a usual case of Hodgkin's extending over a period of four years which presents an accompanying skin eruption. On first appearance of the rash, together with a fever, a diagnosis of measles was made. It disappeared, only to occur again as the more or less typical erythematous papule often found in Hodgkin's. However, in contrast to the fol-

lowing case, in this instance the characteristic features of the histological section were missing. In place of the Dorothy Reed cells there was a diffuse lymphocytic infiltration of the corium together with a few large reticular cells.

In other respects, the case is a typical example of Hodgkin's disease.

Case 2.-- A white man, 56 years old, was admitted to the service of Dro. John Carroll at the City Hospital on March 8, 1927, because of extreme weakness and loss of weight. He had lost weight for six months, and three months prior to admission nodules had appeared on the trunk. No other relevant fact could be elecited. He was extremely emaciated and weak. On the face were large fungoid-like masses with ulcerated surfaces. Scattered over the entire body--on the scalp, trunk and thighs--were innumerable subcutaneous masses, varying in size from that of a pea to that of a walnut, some slightly tender and some with a marked degree of hemorrhage. The skin over the anterolateral and posterior aspects of the upper part of the arms and forearms and the anterolateral aspects of the legs was pigmented a deep brown-gray, was inelastic and was so nodular that it gave a cobblestone appearance.

The cervical and axillary glands were moderately enlarged, discrete, not attached to surrounding structures and slightly painful. Masses were not palpable in the abdomen. Roentgen examination revealed no enlargement of the mediastinal glands.

The course was progressive, and death occurred on March 27. The temperature varied from 97 to 99.2 F.

Autopsy.-- All glands were only moderately enlarged and had the histologic characteristics of Hodgkin's disease. Nodules were found in the heart, liver, kidneys and suprarenals.

The skin of the arm presented an interesting picture. On incision it cut with the resistance of cartilage and was firmly resilient; the cut surface had a homogeneous, waxy translucence. Histologically the epidermis was preserved but atrophic. The dermis was diffusely involved by a dense sheet of extremely cellular structure, with a fine intercellular network and a sprinkling of lymphocytes and polymorphonuclears. Monocytes with horseshoe nuclei were present in small numbers, also typical Ree-Sternberg cells. An occasional mitosis was found.

The diagnosis was Hodgkin's disease.

Comment--This report is presented as an "atypical" case of Hodgkin's in which the skin is the primary seat of involvement and in which dermatological symptoms were the first evidence of the disease. Such a condition is rare, though skin manifestations, as has been mentioned, do not occur infrequently in Hodgkin's disease. Here, the glandular and systemic involvement appeared secondary to the skin findings.

In addition, seldom do skin lesions in Hodgkin's disease have the diagnostic Sternberg-Reed histology as was found in this case. It was likewise present in sections of the lymph glands. There was no doubt about the diagnosis, but if the multinuclear giant cells had been absent from the skin sections it is quite likely that this would have been considered as one of the bizarre types of leukemia cutis imposed on a Hodgkin's or lymphosarcoma. The rarity of conclusive evidence of

Hodgkin's disease from skin lesions leads to the belief that it is probably present in more instances than are reported, or in other words, that the above case is a lymphoblastoma of the Hodgkin's type.

## Lymphosarcoma

Lymphosarcoma is difficult to establish as a distinct disease entity. It closely resembles Hodgkin's disease in that it causes a painless enlargement of the lymph glands, but with a more rapid progression of symptoms. The two diseases are often confounded and many investigators are unwilling to admit that they are separate afflictions. Textbooks, notably the latest (third) edition of Cecil's "Textbook of Medicine[22]," in which the two diseases are considered synonymously, appear disinclined to differentiate between the two conditions. Usually the description of lymphosarcoma is minimized or entirely omitted at the expense of a lengthy review of Hodgkin's disease.

When the clinical picture of Hodgkin's disease is present, but the specific features are missing from the tissue section, the diagnosis isapt to be either "atypical" Hodgkin's or lymphosarcoma. Webster,[35] who upholds Keim's lymphoblastomatous theory, reported

ten cases of lymphosarcoma, all of which presented similar findings. Five of the cases showed intestinal lymph gland involvement, one the mesenteric glands and in four the mediastinal glands. Contrary to typical Hodgkins these cases were all in young individuals, were marked by abdominal discomfort and a rapidly fatal course. In each case there was malaise, loss of weight and tumor masses. Were these cases "typical" lymphosarcoma or "atypical" Hodgkin's disease?

In addition, Webster[35] states that "lymphosarcoma" is a very general term, "including everything from a localized tumor to a general invasion" of the blood stream, lymph gland system and bone marrow. Burnam[4] holds that differentiation between Hodgkin's disease and lymphosarcoma is made only on the basis of histologic structure. The individual cells of lymphosarcoma, he finds, are more irregular in shape with larger nuclei and present more frequent mitotic figures than those of normal lymphoid tissue. But such a picture differs hardly at all from ordinary hyperplastic infections, tuberculosis, lymphatic leukemia and "isolated early" Hodgkin's. In the latter disease, there is a great variety of cellular elements, a delicate reticulum, large and small lymphocytes, plasma cells, eosinophiles and

the giant Sternberg-Reed cell. Yet, the demarkation between these two, apparently clear-cut, descriptions is often vague and indefinite. Border-line cases merge into each other, so that the diagnosis becomes dependent on the predominating features of the clinical picture.

Skin manifestations in lymphosarcoma are less common than in any of the lymphoblastomas. When present, they are non-specific in character but usually generalized in distribution. The eruption appears as an excoriated urticaria-like papule, often with circumscribed purpuric areas. Itching is a constant feature and may be present even in the absence of skin findings.

There are several cases reported in the literature of lymphosarcoma developing, either typically or atypically, and in some strange manner terminating as Hodgkin's or lymphatic leukemia. Following is the case of Drs. David H. Flashman and Simon S. Leopold,[13] which serves well as an example of the definite relationship established by the lymphoblastic theory.

Case 3.--The patient, Edward B., white, aged sixty years, in July, 1926, noticed a swelling in the right inguinal region. This gradually increased in size and in March, 1927, lymphedema of the right leg and genitalia developed. He was admitted to the surgical division of the University Hospital on July 2,

1927, when a lymph node was removed from the inguinal region. The pathologic diagnosis by Dr. A. E. Bothe was lymphosarcoma. Roentgen ray examination on July1, 1927, was negative for mediastinal glands, but showed in the pelvis a large mass which did not appear to be springing from the bone. Physical examination showed a general lymphadenopathy due to a moderate number of discrete, soft, nontender lymph nodes, from 0.5 to 2 cm. in diameter, and a large firm mass in the pelvis. The leukocyte count at this time was 7300 cells per c.mm. The patient was referred to Dr. Henry Pancoast for Roentgen ray therapy and was treated three times a week from July 12, 1927, to November 17, 1927. While he was under this treatment, numerous leukocyte counts were made, ranging between 5000 and 7000 per c.mm. The differential count showed 50 to 60 per cent neutrophils, 30 to 40 per cent lymphocytes, 3 to 10 per cent large mononuclear cells, and 2 to 3 per cent eosinophils. The percentage of neutrophils gradually diminished, and that of lymphocytes gradually increased. The erythrocytes ranged between 3,500,000 and 4,000,000 per c.mm. and the hemoglobin between 72 and 85 per cent. In September the mass in the abdomen was noted to be much smaller and the patient felt better.

About November 1, 1927, the patient developed a gradually increasing jaundice, and began to complain of weakness, anorexia, nausea, and palpitation. On November 10, 1927, the leukocyte count was noted to be 96,000 and on November 17, 1927, it was 100,000 per c.mm. The differential count showed 90 per cent small lymphocytes.

On November 21, 1927, he was admitted to the medical division of the University Hospital on the service of Dr. Alfred Stengel. The outstanding findings on physical examination were a vaguely defined, deep-seated mass in the right side of the abdomen, moderate jaundice, generalized adenopathy, signs of fluid in the right chest and marked enlargement of the liver. The spleen was not palpable. The blood count in November 22, 1927, was as follows: Red blood cells, 2,960,000; hemoglobin, 59 per cent; white blood cells, 96,000, and a differential count of small lymphocytes, 97 per cent; neutrophils, 2 per cent, and large mononuclear cells, 1 per cent. The Wassermann reaction was negative.

At this time the clinical diagnosis of leuosarcoma was made although the site of the primary invasive tumor was not definitely known. It was assumed, however, because of the Roentgen ray examination on July 1, 1927, which showed a large mass in the pelvis, that it had its origin in the retroperitoneal lymph nodes.

On December 1, 1927, the leukocyte count had risen to 288,000 with 96 per cent small lymphocytes, and on December 3, 1927, a few hours before death, the leukocyte count was 444,000. The average temperature was 100, the average pulse 100, and the average respiration 23.

Surgical Specimen.--(Inguinal lymph node removed July 2, 1927.) The gross specimen was noted as being part of a lymph node 2.5 by 2.5 by 2 cm. On section it was light pink in color, with pin-point hemorrhagic areas. The capsule was noted as being in places 2 mm. in thickness.

Microscopic Examination.--Throughout the node, there is an irregular alternation of lighter staining areas with darker areas. The darker zones contain chiefly small lymphoid cells, while the lighter zones contain many larger cells which stain less intensely, show numerous mitotic figures, and are less compactly arranged. In places the lighter portions are round, resembling germinal centers. The sinuses and original architecture have been replaced by tumor. There is marked infiltration of the tumor from 1 to 2 mm. beyond the original capsule, which in places has been replaced by the neoplasm. The lymphoid cells outside the capsule are less densely compact than those in the node. The cells have the same characters as in the tumor tissue found at autopsy and will be described later.

Autopsy Findings.--The autopsy was performed on December 3, 1927, two hours postmortem, by Dr. D. H. Flashman. Leukosarcomatosis, with primary lymphosarcoma of the retroperitoneal lymph nodes, and metastases to inguinal, mesenteric, gastric, mediastinal, axillary and cervical lymph nodes; heart; lungs; liver; spleen; kidneys; ureters; prostate; gall bladder; pancreas; suprarenal glands; stomach; duodenum; bone

marrow of the right femur; thyroid; and blood (lymphatic leukemia). Lungs: Emphysema, atelectasis and healed apical tuberculosis. Liver, kidney, pancreas and suprarenals: Parenchymatous degeneration. Bone marrow of right tibia and lumbar vertebrae: Hyperplasia. Kidneys: Right--hydronephrosis, and chronic focal glomerulonephritis; left--hypertrophy.

Comment--The author is inclined to designate this rare combination of lymphosarcoma and lymphatic leukemia as leukosarcoma. It appears as another example of the similarity of the diseases of the lymphoblastic group which, seemingly, are able to change occasionally from one clinical entity to another. In this case, and other recorded instances of such a transition, there is usually a motivating stimulus--X-ray therapy (as in this case), a severe secondary or unrelated infection, etc.

Evans and Leucutia[12] advanced the idea, substantiated by Flashman and Leopold[13] that all cases of Lymphosarcoma would eventually develop into lymphatic sarcoma "if they lived long enough." The only successful means of prolonging life in lymphosarcoma is by the use of X-ray treatment, however, so the assumption is of little value.

## Lymphatic Leukemia

Lymphatic leukemia, in either the acute or chronic forms, appealed to Keim[19] as a "circulating metastases" of neoplastic tissue. When the disease definitely invades skin or lymph glands, he suggests that the clinical diagnosis should be changed to conform with the findings. Like any of the leukemias, it is a disease producing abnormal white blood cells with a quantitative increase in their number, due to a hyperactivity of the hemopoietic organs involved. In lymphatic leukemia, the hyperplasia of the lymph glands and spleen produces an excess of atypical lymphocytes, as opposed to the granulocytic leucocytosis of myelogenous leukemia. The etiologic factor responsible for the hyperactivity and hyperplasia of the blood forming organs, resulting in lymphatic leukemia, is not yet known.

Predisposing factors are obscure. Evans and Leucutia[12] have reported three cases of lymphosarcoma which developed into lymphatic leukemia when the bone marrow became involved. Kato and Brunschwig[17] found that two of their cases of lymphosarcoma in children terminated fatally soon after X-radiation with the symptoms and findings of acute lymphatic leukemia. Webster[35] had a case beginning with a localized tumor of the chest which also developed lymphatic leukemia following X-ray

therapy. Others have reported the onset of the malady in close sequence to a tonsillectomy, or a tooth extraction. Many feel that it has a definite relation to infection as opposed to its neoplastic characteristics. The disease begins insidiously, it attacks males twice and as often as females, and occurs most frequently in the fourth and fifth decades of life.

Like typical Hodgkin's, lymphatic leukemia may begin with a painless enlargement of regional lymph glands, often the cervical group. In other instances, there may be an enlarged tonsil, a loss of weight, a pronounced weakness, a mass in the abdomen, or any findings consistent with the laymen's interpretation of "anemia," which offer opportunity to the clinician for diagnosis of lymphatic leukemia. There may be a low grade temperature increase accompanying the complaints. In some atypical cases, there is no enlargement of the superficial glands and such conditions, while rare, tend to bind the condition more closely to the lymphoblastic theory. Enlargement of the spleen and liver are almost constant findings.

Various skin lesions may occur as the disease progresses. Craver[10] states that they are usually present in all cases and consist of "papulovesicular

lesions, blebs, bullae, hemorrhagic lesions, nodules and infiltrations." In addition, there may be localized necrotic patches on the orae mucous membranes, he has found. Dermatologists, however, are inclined to consider the skin manifestations of this disease under the grouping of leukemia cutis, (lymphadenosis cutis or lymphogranulomatosis cutis). Pusey[29] claims the term, leukemia cutis, is a misnomer and suggests that differentiation must be made between lesions appearing in aleukemia lymphadenopathy, as Hodgkin's, in contrast to those accompanying the definite leukemic conditions.

In the circumscribed leukemia cutis[29], the disease produces flat patches of infiltration or tumor-like masses from pea to fist-size in the skin. These lesions appear most frequently on the face, but also on the scalp, arms and backs of the hands; more rarely on the nipples, abdomen, scrotum and penis. After a rather rapid development, growth is arrested and the lesions may persist or disappear without scarring. The patient is usually free of subjective symptoms.

The universal leukemia cutis[29] is seldom seen, though in Keim's[19] classical group of 20 cases of lymphoblastoma three were recorded. The picture here is inclined to be atypical. In Keim's three cases, two

presented an extensive scaling dermatitis covering the entire body with a generalized lymph gland enlargement. The other case was free of scales, but was characterized by a universal reddish-brown hyperpigmentation, not especially thickened or infiltrated. Here also, there was an enlargement of the lymph glands. All three cases presented nearly identical initial complaints--a persistent, intensely pruritic eruption which did not respond to ordinary medication.

In sections of universal leukemia cutis, large lymphocytes tend to predominate, with numerous mitotic figures, but with an absence of connective tissue proliferation. In describing the histological picture, Arndt[1] says it is "a continuous, diffuse, pure, lymphocytic infiltration of the upper two-thirds of the derma, going down to the lower third of the cutis propria and the subcutaneous tissue in the form of perivascular and periglandular cell collections."

While a diagnosis of lymphatic leukemia may be suspicioned by the enlarged lymph glands, palpable spleen and general evidence of anemia, it is confirmed by the blood findings. In the early stage the red cell count and hemoglobin content are often within normal limits. The white count, however, averages

between 100,000 and 200,000 cells per cubic millimeter. In the differential count, there is striking lymphocytosis, ranging from 90 to 99 per cent with both a relative and absolute decrease in all other leucocytes. The lymphocytes do not differ markedly from those found in normal blood. Later in the course of the malady, there is anisocytosis, poikilocytosis, polychromasia and bosophilic stippling of the red cells.

A few cases of lymphatic leukemia run an acute, rapid course with death occurring in a few days or weeks. The condition is often confused with many other diseases, especially if examination of a stain blood smear is not made. For the most part, however, lymphatic leukemia runs a longer course, usually terminating fatally in three to four years. Treatment, while only palliative, consists of x-radiation and radium therapy. Arsenic as Fowler's solution is used when they are not available.

Two cases of lymphatic leukemia, both of which were marked by overwhelming skin lesions, are herewith presented from the literature. The first is Keim's[14] classical case of universal leukemia cutis, which because of its important bearing on the lymphoblastic theory, is recorded in the complete detail of the

author's original report. The second case is that of Dr. F. R. Schmidt[31], a record of leukemia cutis in a child.

Case 4.-- History.--J.W.P., a man, aged 56, a carpenter, was seen on Oct. 12, 1919, complaining of a generalized eruption. The family history was in no way related to the complaint. At the age of 21, the patient had had gonorrhea without attendant complications or resultant sequelae. There was no history of syphilis. At the age of 50, a fine papular and vesicular eruption had appeared on both lower legs, which was extremely pruritic. This was treated as an "eczema," but did not respond to the therapy instituted; it gradually extended, until four years later the entire body was involved. Baths and many ointments had been used; nothing, however, seemed to influence favorably the course of the eruption. During the past year, he had been unable to work because of the marked fissuring of the palms, which, together with the sensations of chilliness and puritus, constituted his chief complaints.

Examination.--The patient was a well nourished and well preserved man, just beyond middle life, who walked into the clinic. He did not appear strikingly ill, and was unusually cheerful and optimistic for one with such an extensive eruption. Involving the entire cutaneous envelop was an extensive scaling dermatitis, which was associated with a dull reddish discoloration. The exfoliation was abundant, being most marked on the extremities, and consisted of various sized flakes, the largest of which was the size of a quarter. They were thin, dry, brittle and of a dirty gray tinge. The underlying skin was smooth, red and shiny, and, except for a few artificially produced lesions where the scale had been pulled down to the "quick," there was no tendency toward weeping or bleeding. The skin appeared thickened and edematous, but to palpation was found to be firm and diffusely infiltrated, giving it the sensation one would expect from pliable leather. Associated with this thickening was a marked accentuation of the natural folds and lines of cleavage, which

was particularly striking on the flexor surfaces and about the joints.

The palms and to a lesser extent the ventral surface of each finger and thumb presented a diffuse overgrowth which took the form of short, fine, dirty brown filaments of epithelium. The natural folds of the hands fissured through this thickened epidermis, the combination of fissuring and thickening prohibiting complete extension of the fingers without marked pain. The soles and the ventral surface of each toe were involved in a similar though less extensive process.

Almost surrounding the malleoli of each foot and extending upward over the anterior surface of the lower one third of the leg were discrete and confluent papillomatous lesions. The individual lesions were about the size of a glass-headed pin and studded the anterior surface of the leg just above the ankle. The confluent lesions extended up from the sole in a 2 inch (5cm.) papillomatous band, which practically encircled the instep. The surface of this epidermal overgrowth was distinctly verrucous, irregularly furrowed, dirty gray, with a suggestion of brown, and was raised approximately 0.5 cm. above the surrounding skin. The lesions were not painful or eroded and were relatively superficial. The dorsal surface of the fingers and toes, and to a lesser extent that of the hands and wrists, presented many of these smaller papillomas, which later developed into hypertrophic warty lesions.

The hair of the beard, axillae, pubis and body was almost completely absent, while the eyebrows, eyelases and hair of the scalp was much thinned and lusterless.

Both lower eyelids presented a moderate secondary ectropion, with resultant hypertrophic conjunctivitis. The other visible mucous membranes apparently did not share in the process. Many carious teeth were present in both the upper and the lower jaw.

Neither the spleen nor the liver could be palpated; a striking general adenopathy, however, was present, the enlarged glands being firm to palpation,

painless and freely movable. The individual glands varied in size from that of an olive to that of a small orange, the largest of which were found in the groin.

No increased mediastinal dulness could be determined, but the heart was found to be slightly enlarged. Radiographically, the mediastinum was found to be entirely clear, with no displacement of the trachea. The heart was found to be slightly increased in its long diameter. On roentgen-ray examination of the chest, it was found to be voluminous, long, deep and well illuminated throughout, without unusual opacities in the pleuritic or lung field. Examination of the urine did not reveal any evidence of nephritis, and the Wassermann reaction of the blood was negative.

A tentative diagnosis was made of "dermatitis exfoliativa," etiology undetermined, and the patient was admitted to the hospital for further study. A blood count performed the next day revealed: hemoglobin, 86 per cent (Sahli); red blood cells, 4,350,000; white blood cells, 30,500; differential count 200 cells. The differential count revealed: polymorphonuclear neutrophils, 28.5; polymorphonuclear eosinophils, 0.5; small lymphocytes, 56.5; large lymphocytes, 10; large mononuclears, 4, and transitionals, 0.5 per cent. From this and other similar blood counts, a diagnosis of chronic lymphatic leukemia was established, and several small pieces of skin were removed from the abdomen for microscopic study. Microscopic examination revealed the epidermis to be somewhat atrophic with a relative increase in the stratum corneum. The papillary layer of the corium showed a moderate infiltration with lymphocytes arranged in small centers of growth. Obviously, a generalized lymphocytoma was being dealt with, and while the microscopic picture of the skin did not exactly coincide with that described by Reihl and Arndt, when viewed in the light of the clinical and hematologic observations, it established a tentative diagnosis of a true universal lymphadenosis. A second microscopic examination of the skin of the trunk, made on Jan. 7, 1920, revealed a similar although more striking picture. The epidermis showed some hyperkeratosis and acanthosis, with beginning lengthening of the papillae and early diffuse lymphoblastomatous infiltration. The atypical lymphoid hyperplasia of the primitive lymph nodes of the papillary corium was well shown. Apparently, the infiltration of the papillary

layer of the corium had its beginning in the primitive lymph nodes. In the hyperplastic lymph node in the center of the lower field, there were many lightly staining lymphoblasts. Several other microscopic examinations of the skin were made during the first year that the patient was under observation, each showing a similar microscopic picture with a gradual extension of the lymphocytic infiltrate. A biopsy, performed on May 5, 1921, revealed the characteristic lymphoblastic infiltration of the skin, which will be discussed in detail in conjunction with the observations at necropsy.

Course and Treatment.-- When the patient was admitted, he was immediately treated with baths, and wet dressings were applied to the hands and feet in an effort to heal the bothersome fissures. A salicylic acid and petrolatum ointment containing a mild antipruritic was applied to the body, face and scalp. Under this regimen, the symptoms of chilliness and pruritus abated, and the scaling soon became much less marked. He remained in the hospital about six weeks.

The patient returned to the hospital in about a month, and with the exception of several short visits to his home, was under observation continually until the time of death, four years later.

Local treatment consisted for the most part of baths, wet dressings and various ointments and pastes containing keratolytic and antipruritic drugs. Under this therapy, the scaling remained fine and branny and never returned to the abundant large flakes which were seen at the time of his first examination. The pruritus was likewise relieved, but he was never entirely free from this symptom, which was especially persistent over the face. He frequently complained of spontaneous pain, especially in the legs. During the course of his illness, he received doses of arsenic in various forms without any noticeable improvement in the clinical condition or alteration in the blood picture.

Several months after he was readmitted to the hospital, both the spleen and the liver became enlarged so that they were distinctly palpable. This seemingly was a variable factor and not related to roentgen-ray therapy, as for periods of months these two organs could be readily felt at the costal margin,

while at other times no manuever or position seemed to bring them within the palpating fingers.

The leukocytosis varied from 25,000 on March 27, 1920, to 85,000 on Nov. 25, 1923, while the hemoglobin reading was never below 68 per cent. The red blood cells on a great number of counts averaged 3,500,000. In the differential picture, the red cells were usually fairly normal in appearance. Frequently, there was some moderate central pallor. Platelets were invariably diminished. The predominating white cell was a medium-sized lymphocyte with a small amount of fragile cytoplasm, in type about midway between the ordinary large and small lymphocyte of normal blood. There was an absolute, permanent and progressive increase in the percentage of lymphocytes, the maximum occurring on Oct. 25, 1923, at which time 94.5 per cent of lymphocytes were counted.

Early in the course of the disease, I was able to control the number of young forms in the blood picture with roentgenization of the spleen and tibae, but later roentgen-ray therapy did not seem to influence the type of white cell present. Repeated roentgen-ray exposures of the skin never produced any striking clinical change, although the pruritus was temporarily relieved. The papillomatous lesions on the extremities were extremely rebellious to treatment. They were not influenced by the roentgen ray, and I was able to control their growth only by the use of strong keratolytics. Numerous interesting suggestions were offered by visitors to the clinic, but after a trial of these measures, I would invariably have to resort to the salicylic acid plaster. Later in the course of the disease, these lesions extended so that the upper forearms and legs presented a transitional epidermal change, with the atrophy on the proximal side and the marked hypertrophy increasing as the distal phalanges were approached.

The patient's appetite was uniformly good, and his weight curve showed little fluctuation. The relatively slight impairment of his general health was a rather striking feature of the long continued illness, a fact which I know characterizes this type of new growth. The enlargement of the superficial lymph glands was slowly progressive and entirely asymptomatic, and showed no tendency to break down until one

month before death. At this time, an acute swelling the size of a lemon appeared in the right deep posterior cervical chain of lymph glands, which promptly softened, necessitating deep incision and drainage. A small teacupful of thick yellowish purulent material was evacuated, following which operation prompt healing occurred.

On two occasions during his stay in the hospital, the patient developed definite signs of bronchopneumonia, with involvement of the pleura, from which he rapidly recovered. On Jan. 17, 1924, he again developed bronchopneumonia and pleuritis. On January 22, the temperature, pulse rate and respirations were 103.6 F., 120 and 32, respectively: respiratory embarrassment and cough were marked, and on the following day respirations ceased.

Autopsy.--There was marked congestion and edema of the meninges of the brain, lymphatic leukemia in the meningeal vessels, congestion, edema and atrophy of the brain substance, with lymphatic leukemia of the vessels. Congestion, edema and atrophy were present in the spinal cord.

There was marked pigmentation of the posterior lobe of the hypophysis; also marked congestion, increase of basophils and chromatophores, excessive colloid in the intermediate lobe and numerous brain sand concretions. Much brain sand was present in the pineal gland.

Examination of the heart revealed subepicardial fatty infiltration with serous atrophy, marked atherosclerosis of the coronaries, marked atrophy of the heart muscle and subendocardial fatty degenerative infiltration. There was advanced atherosclerosis of the aorta.

Examination of the lungs revealed acute fibrinopurulent pleuritis, acute hemorrhagic prurulent lobular pneumonia, chronic passive congestion, localized emphysema and some peribronchial infiltration.

Lymphoblastoma and moderate anthracosis were found in the bronchial nodes. There were numerous islets of thymic tissue with many calcified corpuscles of Hassall. The lymphoid tissue was of the lymphoblast-

omatous type. There was an old nodular colloid goiter, with an increase of stroma. The colloid on the whole was reduced. There was no epithelial hypertrophy.

Examination of the sternal marrow revealed an increase of lymphocytes and a diminution of myelocytes. There was no lymphoid marrow in the tibia.

There was a lymphoblastomatous hyperplasia of the spleen. There was a chronic catarrh of the intestines. An old chronic obliterative appendix was present. There was marked atrophy of the stomach and a chronic catarrh; postmortem change had occurred. There was a marked nutmeg liver with lymphatic leukemia. The pancreas showed postmortem change; there was atrophy with an increase of stroma. The gallbladder showed postmortem change; otherwise it was normal. Chronic parenchymatous degenerative nephritis was present, also a secondary contracted kidney and well advanced arteriosclerosis.

There were marked lipoidosis and atrophy of the suprarenal chords and chronic passive congestion. The zona pigmentosa was markedly pigmented. The seminal vesicles did not contain sperm. There was no atrophy. There were postmortem desquamation of the prostate, and slight chronic cystitis of the bladder. The epididymis was dilated. There was no sperm. There was complete fibrosis of the seminiferous tubules of the testes, with marked hyperplasia and hypertrophy of the interstitial cells, with lipoidosis and pigmentation. All the vessels showed lymphatic leukemia, and there were localized lymphatic infiltrations.

The skin showed leukemic lymphoblastoma. The epidermis was atrophic, and the papillary layer showed a diffuse lymphoblastomatous infiltration. An increase of leukocytes in the vessels was everywhere apparent. With low power magnification, the line of demarcation between the infiltrated papillary layer and the lower part of the corium was easily seen. The site of the original nodes was represented by the nodular character of this infiltration. Everywhere, the skin showed a marked leukemic lymphoblastomatous infiltration of the papillary layer. The complete absence of hair follicles and gland structures accentuated the striking resemblance to lymphosarcoma. With higher magnification, the cells were seen to be small round cells of

the lymphocyte series. The blood vessels showed the picture of lymphatic leukemia. There was leukemic lymphoblastoma of the lymph nodes. Throughout the atypical lymphoid tissue were many highly staining lymphoblasts. This was a typical picture of lymphatic leukemia.

Pathologic Diagnosis.--The diagnosis was: lymphatic leukemia, leukemic lymphoblastoma of the skin, spleen, lymph nodes, bone marrow and liver (leukemia cutis): terminal lobular pneumonia: acute fibrinopurulent pleuritis; right-sided empyema; cardiac dilatation with relative tricuspid and pulmonary insufficiency; subepicardial fatty infiltration with serous atrophy; atrophy and fatty degenerative infiltration of the myocardium; advanced atherosclerosis of the aorta and coronary arteries; chronic parenchymatous degenerative nephritis; secondary contracted kidney with arteriosclerosis; nutmeg liver; passive congestion, atrophy and parenchymatous degeneration of all the organs; lipoidosis of the suprarenal glands; roentgen-ray fibrosis of the testes, with hypertrophy of the interstitial cells; cysts of the epididymis and subcutaneous fibrosarcoma.

Comment.- It is interesting to note in this case that in the first examination, Keim[19] stated that there was a question of a diagnosis of pityriasis rubra. This, however, was discounted in view of the progressive increase of lymphocytes in the blood and the changes in the skin sections taken for microscopic examination.

Case 5.--History.--B. C., a white girl, aged 2 years, whose parents were healthy, had whooping cough at the age of 1 year, after which she suffered from frequent attacks of bronchitis.

Her mother stated that shortly after birth she noticed on the back of the infant's neck two

small lumps which became larger, until at 1 year of age each had attained the size of a dime. On Dec. 15, 1928, a diagnosis of nevus was made and excision was advised. The lesions were hard, freely movable, painless and flat like buttons in the skin, and the color of a bruise. There was no palpable adenopathy, and the child appeared in good health, though everybody remarked on her "pasty" color. She was not seen again until July, 1929.

Examination.--On July 6, 1929, the child presented a healthy appearance. She was well nourished, alert and seemed mormal except for the pale, waxlike skin. The spleen was not palpable, and the liver was not enlarged. The left tonsil was injected and enlarged.

On the right posterior side of the neck were two discrete, smooth surfaced nodules, each the size of a hazelnut and protruding dome-fashion above the level of the skin. The lesions were hard, freely movable, had no connection with the underlying tissue and varied in color from brown to purple.

The Wassermann reaction of the blood was negative. A roentgenogram of the lungs did not reveal any enlarged lymph glands, but there was evidence of some infiltration along both the upper lobes.

Course.--Three months later, two button-like, slightly infiltrated, dime-sized plaques, resembling bruised spots, appeared on the abdomen. At that time two small lumps reappeared in the postoperative scar on the neck. These four lesions almost disappeared from time to time. During October and November, the patient received deep roentgen therapy, without apparent benefit. The lymph glands and spleen were not palpable or enlarged throughout this period.

In November the child became acutely ill with a severe sore throat, extreme weakness and a high fever. A suppurating discharge from the left ear stopped after a few days. It is interesting to note that following this illness the child's general condition seemed to improve and that the lesions of the skin grew smaller. The parents then took the child to a warm climate, where she died in February, 1930. The father described the child's condition previous to death as pitiable, for she was apathetic, weak and

without interest in her surroundings. The skin looked like wax and was covered with many boils which gave off a foul odor. Autopsy was not performed.

Examination of the Blood.--Complete studies of the blood were made at frequent intervals. Dr. Jaffe' reported that about one third of the lymphocytes were large and of lymphoblastic type. Many others were not so large, but slightly larger than the normal lymphocyte. The nuclei were lightly stained. The oxydase reaction was negative.

Histologic Examination.--On July 6, 1929, both nodes on the neck were excised and examined by Dr. R. H. Jaffe, who reported that the epidermis was normal, but that the cutis was everywhere invaded by actively proliferating lymphatic tissue. This infiltration was very dense in the subcutaneous fat tissue. Under high magnification, the character of the lymphoid cells, with their tendency to groups themselves, was clearly seen around the capillaries and glandular elements.

Comment--The summary of the blood picture in this case, omitted from the above report, shows a progressive decrease in the hemoglobin and red cells from 80% and 4,720,000 to 65% and 3,860,000 over a period of six months. During the acute illness described the white count rose to 20,200, then rapidly fell to 3,800. The lymphocytosis was marked throughout the course of the disease, with a low of 60% and high mark of 98%. Myeloblasts were absent from the smears at all times and eosinophiles were seen only on two occasions. Monocytes disappeared in the terminal stages.

The author[31] added that of the lymphoid cells seen in the blood smears about one-third resembled lymphoblasts and were larger than the normal lymphocyte.

## Mycosis Fungoides

Mycosis fungoides was first described by Alibert[29] in 1806 as a clinical syndrome with lesions in the papillary layer of the skin. Since that time, its etiology has been in almost constant dispute and is still obscure, the cases reported have been often atypical and related to other diseases of the lymphatic system, and no adequate treatment has been discovered to prevent it from always being fatal. A possible hereditary relationship may exist as Cameron[7] recently reported the disease in mother and daughter for the first time.

Manifesting itself usually by a premycotic stage, featured by circumscribed areas of dermatitis which are intensely pruritic, mycosis fungoides progresses rather inconstantly to a second stage--that of infiltration. The early lesions vary in outline and size, though all appear in some shade of red or reddish brown. There may be areas of dry dermatitis, which are confused with "eczemas," psoriasis and urticarial patches. Often there are moist "weeping" lesions. As the patches become infiltrated, sharply defined, elevated placques and nodules appear. Their size varies from that of a pea to a

hazel nut, and they are usually pink to dark red in color.

The duration of these first two stages is variable and periods of remission have been noted, though the pruritus rarely disappears. Usually, however, each phase of the disease occupies months or years. In the final, or fungoid stage, the placques and nodules develop into prominent tumors up to the size of a grapefruit. At first they are solid masses, but later vegetate and ulcerate. They may be sessile, pedunculated or lobulated and present a multiplicity of colors. Often, the smaller, adjacent tumors coalesce to form foul-smelling suppurating masses of granulation tissue.

Apart from the intense and persistent itching, along with progressive weakness and cachexia, the patient is usually without subjective complaints until the final stages. As the tumors break down and ulcerate, secondary pyogenic infection, with considerable invasion of the parts, is the usual story. Death occurs within a year or two after the onset of the fungoid stage. As in the other lymphoblastomas, treatment is directed toward relieving the symptoms, especially the pruritus, and arresting the disease

temporarily by x-radiation.

Investigators have been largely concerned with the cause of mycosis fungoides, probably in the hope that therein lies a cure for a disease which progresses from such a commonplace beginning to a fatal end in spite of all attempts to check it. Theories of an infectious and neoplastic origin both have their adherents. Fraser[14], in reporting some atypical cases, stated: "The question of whether the lesion in mycosis fungoides is inflammatory or neoplastic again faces us. In the present series, and in Keim's[19] cases, the lesions were unquestionable neoplastic. Are the lesions in mycosis fungoides always neoplastic, or are they always inflammatory as practically every textbook would have us believe? Or are the lesions inflammatory in the early stage of the disease and later transformed into a neoplastic process? In a recent article, I analyzed these questions and concluded that the lesions were neoplastic from the beginning. The inflammatory features which often dominate the histologic picture, especially in the early, or prefungoid dermatoses, were interpreted as a reaction to the development of tumor cells." Keim[19] takes a similar stand on the question. Warthin[34] says the lesions are "neoplastic in type...

showing true infiltrations and metastases." Symmer,[33] however, is inclined to consider mycosis fungoides only as a disease syndrome, not as an entity in itself. He stated that from his series "the postmortem and histologic observations show that mycosis fungoides is the cutaneous expression of at least three different diseases of the lymph node system: Hodgkin's disease, a variety of round cell sarcoma arising from the connective tissue reticulum of lymph nodes and elsewhere, and lymphosarcoma, originating in the lymphoid cells of the lymph nodes and of other lymphoid structures--in short, that mycosis fungoides as an independent form of disease does not exist."

Case 6.--History-Mrs. L. P., a white housewife, age 54, was first seen at the University of Nebraska dispensary on September 28, 1931. She was referred to the department of dermatology due to a persistent, intensely pruritic eruption on the chest and back, upper extremities and around the hips and sacral region, which was of about one year's duration. The eruption had at first tended to be oozing in character, but during the past month it had become dry and slightly scaly. The patient also complained of fulness after eating, gas on the stomach and chronic constipation.

Past Illnesses-The patient had measles, smallpox and pertussis in childhood without sequelae. A thyroidectomy had been performed at St. Joseph's hospital, Omaha, in 1922.

Family History-The father was dead at 58 from "bowel trouble." The mother died at age 45 from un-

known causes. One brother died at 35 from carcinoma of the stomach. Two sisters were living and well. There had been nine pregnancies of which three were miscarriages. Six children were living and well. There was no family history of skin diseases, tuberculosis, diabetes, heart disease or insanity.

Examination - The record reads: "The patient exhibited a rather multiform lesion distributed mainly over the anterior thorax, thighs and sacral region. There was considerable erythema, infiltration and occasional oozing. The characteristic lesion seemed to be a pinhead to pea-sized pinkish papule. Widely distributed over involved areas were brown patches of pigmentation, seated upon the site of former eruption."

Diagnosis - Dr. C. C. Tomlinson made a diagnosis of mycosis fungoides and the patient was advised to return to the clinic for further examination and treatment regime.

First admission - The patient was next heard from when admitted to the Douglas county hospital on November 17, 1933. During the interim she stated that she had sought treatment at the Creighton medical college's clinic and had used various proprietary applications. She now complained of multiple nodular growths on each forearm, around the right shoulder and on the anterior surface of the right side of the chest. There was still a skin eruption, now generalized and scaly, which continued to itch constantly.

The patient stated that she had been advised to seek x-ray treatment but was without funds even to secure ordinary prescriptions which she had obtained in the clinics as anti-pruritic measures. About one year ago (late in 1932), she noticed several small "growths" which first appeared in the right axilla and on the upper right arm. They were about the size of a hazelnut and painless. They grew larger, coalesced to form a large mass, ulcerated and emitted a foul discharge. This lesion, which had taken on the appearance of a cauliflower, gradually closed up. Similarly, a smaller growth in the left shoulder region and another about the right elbow developed into an ulcerated mass but in time stopped discharging. Five months ago, a mass on the inner surface of the right

arm enlarged, broke down and remained in an ulcerated state for two months. There had also been a similar growth on the posterior aspect of the right knee joint.

History by systems - (a) Gastrointestinal: There were pains in "the pit of the stomach," apparently aggravated by food. Gas pains still persisted, as noted in the first contact. There was weight loss of 18 pounds in the past six months. (b) Cardio-respiratory: Patient had been bothered by palpatation previous to her thyroidectomy. There had been shortness of breath for several years and swelling of the feet two months ago. (c) Genito-urinary: Frequency 3-4 times. Menses began at age 13 and had always been regular every 28 days until the menopause at age 52. Patient was married at age 17 and has six living children out of nine pregnancies. There were three miscarriages. Syphilis and gonorrhea were denied. (d) Neuromuscular: The patient stated that she has always been nervous, but less so since her goiter was removed.

Physical examination: - The patient was a well developed but poorly nourished white woman of about the stated age. Her face had a puffy appearance. Eyes reacted sluggishly to light, the teeth were carious and the tongue was coated and furrowed. The tonsils were enlarged and a post-nasal discharge was noted. The heart was rapid but regular. The lungs, abdomen and extremities were negative.

There was a generalized skin eruption over the entire trunk and extremities. The face was free of skin manifestations except for a macular eruption on the left eyelid. The lesions on the body were erythematous, pruritic and characterized by a "crusted pustule with an inflamed base." There were also many nodules distributed over various parts of the body: one in the right axilla and extending along the midaxillary line, another on the upper right arm, another on the medial aspect of the upper left arm, and several smaller nodules on the volar surface of the left forearm. These lesions, with the exception of the last mention, were definitely lobulated, about the size of a teacup, erythematous, ulcerated and with a foul-smelling discharge.

Laboratory - The urine was negative except for

a few pus cells. The blood Wassermann was negative. Blood studies presented no unusual findings. The hemoglobin ranged from 80 to 85%, the red count from 3,800,000 to 4,200,000 and the white count from 6,500 to 10,500. The differential on admission was monocytes 10%, segmented froms 54%, staff forms 6%, eosinphils 12%, small lymphocytes 8%, large lymphocytes 10%. The differential count on November 30, 1933,: monocytes 4%, segmented forms 74%, staff forms 2%, eosinophils 6%, small lymphocytes 14%, large lymphocytes 4%. No other laboratory procedures were carried out.

Pathological report - Following a study of biopsy specimens, Dr. J. P. Tollman stated: "There are two sections. One of these is from the skin surface in which the most striking feature is the presence of small round cells a very short distance beneath the epithelium. These cells have much the appearance of lymphocytes although some of them are rather irregular in shape and give the impression of being fibroblastic in origin. Occasional multinucleated cells with two to four nuclei are found. These nuclei are vesicular in character and the cytoplasm is clear and slightly acidophilic in reaction. There may be a slight increase in fibrous tissue immediately beneath the epithelium. The whole corium has the appearance of edema. The epithelium shows no striking change.

"The second section is from the tumor mass and is composed almost entirely of small round cells closely packed together with a minimum of supporting tissue. Mitotic figures are fairly frequent. There is a very thin epithelium on the surface which is also being infiltrated by these small round cells.

"I see no way to distinguish sharply between mycosis fungoides and leukemia cutis in this case. The section of skin more closely resembles the former but the section from the tumor has the appearance of leukemic infiltration. We interpret the tumor mass as a further development of a reaction seen in the first slide described, and for that reason diagnose this as a leukemia cutis."

Dr. Carl B. Russum made a diagnosis of mycosis fungoides on other biopsy specimens studied independently.

Course - The patient was in the hospital 21 days and received symptomatic treatment only. She was dismissed on December 8, 1933, with a final diagnosis of "lymphosarcoma, unimproved," and referred to Dr. J. F. Kelly who gave the patient a Roentgen-ray treatment in his office. Subsequently, she was sent to the x-ray therapy department of the University hospital where Dr. H. H. Heitzman began a series of treatments on January 24, 1934. Radiation over the fungating masses on the right arm and left chest was 2 al., 130 K.V., beginning with 50R and ascending to 260 R. Additional treatments were given on January 29-31; Februrary 12-14; March 13-28, 1934.

The patient lost ground rapidly during January and February, was bed-ridden at home and carried to the hospital for treatment by her husband and a son. When seen on March 28 her left arm was about twice its normal size, edematous and tender. She had lost the use of her arm a few days before and the only possible movement in the extremity was a slight motion of the fingers. In view of an evident secondary pyogenic involvement, hospitalization was urged.

Second admission - The patient was readmitted to the Douglas county hospital on March 31, 1934. The temperature was 99.6, pulse 120 and respiration 24. Treatment was symptomatic; hot magnesium sulphate packs to the left arm, and morphine (gr. $\frac{1}{4}$ p.r.n.) for pain and sedation. A blood count on April 6, 1934 showed hemoglobin of 70%, 3,400,000 red cells, 9,850 white cells and a differential as follows: monocytes 6%, segmented forms 72%, staff forms 8%, eosinophils 2%, small lymphocytes 8% and large lymphocytes 4%. The urine was negative.

The patient was seen last April 7, 1934. She was unhappy in the hospital and cognizant of her decline. There was a slight scaly, erythematous eruption on the dorsal surface of the left wrist. The entire left arm gave the patient considerable pain. It was still very edematous and completely paralyzed. A generalized eruption around the neck, back and thorax, noted on her first admission, still persisted. The pruritus, however, had disappeared. The tumor mass on the right chest caused no complaints.

Comment.-- This case, followed for about four and one half years, is more or less a typical example of mycosis fungoides. When first seen, the disease was in the period of early infiltration following the pre-mycotic invasion. Without treatment, it progressed fairly rapidly to the stage of multiple fungating tumors. Often, these growths are distributed over the entire body. In this case, at least up to the present, the active masses are limited to the chest and upper extremities.

While the clinical diagnosis was made without hesitancy, it is of interest to note that the pathological opinion was divided between mycosis fungoides and leukemia cutis. This is entirely in keeping with the lymphblastic theory that these diseases have a common genetic relationship, but present various clinical manifestations.

The appearance of a secondary infection, with death resulting from a septicemia or pneumonia, is the usual course.

## Summary

1. Hodgkin's disease, lymphatic leukemia, lymphosarcoma and mycosis fungoides have been grouped together as the lymphoblastomas because of their genetic and clinical interrelationships.

2. The etiology of lymphoblastomas is unknown. Treatment by Roentgen-ray is only palliative as they are eventually fatal.

3. The theory that the lymphoblastomas are the manifestation of a "circulating metastases"[19] in the blood stream, eventually affecting all the tissues of the body, has been accepted by many investigators.

4. Cells of the lymphocytic series are always present in large numbers, often in an overwhelming preponderance, in tissue specimens taken from the lymphoblastomatous disease.

5. The lymphoblastomas may be preceded or accompanied by eruptive skin lesions, but this is an inconstant feature. Generalized, persistent pruritus is nearly always the initial subjective symptom.

6. From a clinical standpoint, the lymphoblastomas are often interchangeable. The case may begin as one

lymphoblastoma and terminate as another.

7. Pathological differential diagnosis of the lymphoblastomas from tissue sections is usually impossible.

8. The clinical picture and dermatological manifestations of Hodgkin's disease, lymphatic leukemia, lymphosarcoma and mycosis fungoides are discussed independently.

9. Five cases of lymphoblastoma from the current literature, with an additional case personally observed, are included to show the definite relationships existing between the clinical and pathologic pictures.

10. In view of present knowledge, the lymphoblastomas should be considered as various clinical manifestations of the same disease, probably of neoplastic origin.

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