Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Leukemia in Childhood

Volume IX | Friday, May 27, 1938 | Number 29

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
UNIVERSITY OF MINNESOTA

Vol. IX | Friday, May 27, 1938 | Number 29

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Published for the General Staff Meeting each week during the school year, October to May, inclusive.

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William A. O'Brien

I.. LAST WEEK

Date: May 20, 1938

Place: Nurses' Hall
Recreation Room

Time: 12:15 to 1:30 P.M.

Program: Movie: "Boat Builders"

Artificial Fever Therapy
M. M. Cook

Rabies

Discussion: Herman Kesting
B. A. Cvorak
M. M. Cook
Wesley Spink
M. E. Knapp
Irvine McQuarrie
K. W. Stenstrom

Present: 108

Gertrude Gunn,
Record Librarian

II. MOVIE

Title: "The Clock Cleaners"

A Walt Disney Silly Symphony.

Released by: R-K-O.

III. AUTHORS

1. MARGUERITE BOOTH

Was born in Sewickley, Pa. B.A., Smith College, special student Cornell University; M.D., Yale Medical School 1935. Intern in Pediatrics Duke University Hospital, with affiliation at Sydenham Hospital, Baltimore, Md., 1935-36. Intern and Assistant Resident in Pediatrics, University of Minnesota Hospitals 1936-37. Teaching Fellow and Head Resident in Pediatrics, University of Minnesota Hospitals, 1937-38.

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2. RAYMOND R. REMBOLT

Was born in Grand Island, Nebraska; A.B., University of Nebraska, 1933; M.D., 1937. Junior Intern at Lutheran General Hospital, 1935-36. Junior Intern at Evangelical Covenant Hospital, 1936-37. Intern in Pediatrics University of Minnesota Hospitals, 1937-38.

IV. NEXT WEEK

June 3rd will be the "Business Meeting" of the year. Today is the final scientific program for the year 1937-38. During the past year the plan of allotting time to departments to present their reports has been followed. Next week we hope to get an expression of your opinion on many matters. We trust that you will all be present. Perhaps it is a misnomer to call it a business meeting as the executive affairs of the hospital are conducted by the Administration.

During the past year, including today, we had 30 meetings and issued 29 Bulletins, as one meeting was a "good time" affair devoted to the showing of the football pictures of the Golden Gophers.

We will publish the index and summary next week. Anyone desiring back copies to complete files should leave his name with Miss Gunn, who may be able to supply the missing links.

Many of our staff members will be at their last meeting. We are anxious to secure the list of names of those who are leaving for other places on June 30th. In order that those who have to leave at 1:00 o'clock may present their views the discussion will take place at 12:15 instead of at 12:30, as at present. In the meantime try and recall which type of program you like best, as we are anxious to get your reaction on this point.

V. LEUKEMIA IN CHILDHOOD

Marguerite Booth
Raymond R. Rembolt

History

In 1845 Bennett proposed the term "leucocythemia" and Virchow the term "Leukämie" to designate the disease now regarded as leukemia. Two types were later differentiated and called splenomyelogenous leukemia and lymphatic leukemia. Ehrlich, who introduced the differential staining of leukocytes in 1891, distinguished two types of cells: granular leukocytes of bone marrow origin occurring in splenomyelogenous leukemia, and nongranular cells of lymphatic origin noted in lymphatic leukemia. Naegeli was the first to recognize and describe myeloblastic leukemia. In the early part of this century it was found that leukemia affected not only a single organ but the entire body - and that extramedullary metaplasia of myeloid tissue occurs in both physiolggic and pathologic conditions. Reschad and Schilling-Torgau described a third common type - monocytic leukemia - in 1913. Fleischmann in 1915 reported the second case but believes that it changed to a myeloblastic leukemia in the terminal stage. Dameshek and others hold to the theory that this third type of leukemia does exist.

Definition

Leukemia is a systemic disease in which the normal mechanism for the production of formed blood elements is permanently impaired, with the appearance in the peripheral blood of abnormal white cells. The two most prominent features are a marked qualitative change in the leukocytes of the blood, and varying degrees of glandular and splenic enlargement. Leukocytosis may be so high that the blood appears to be a grayish red mixture of pus and blood, separating on standing into a lower layer of red cells and an upper buffy layer of white cells. In other cases, or in different stages of the disease, there may be a normal white count or a leukopenia (aleukemic phase). The blood picture is characterized by an abnormal number of immature white cells which have entered the blood stream from the bone marrow, lymph glands, or other hematopoietic tissue before complete development. The red cells and the platelets are likewise altered, usually showing a great diminution in numbers with consequent anemia and thrombocytopenic hemorrhages. In all leukemias there is marked dysfunction of the hematopoietic system, particularly of the bone marrow - which is reflected by the changes in the circulating blood and by the infiltration of various tissues with immature cells.

Terminology

Great confusion exists in the terminology and classification of diseases of the blood forming organs. Recently there has been a tendency to use the terms leukosis, myelosis, and lymphadenosis for leukemia, myelogenous leukemia and lymphogenous leukemia, respectively. The term leukemia, like the term anemia, has a strong foothold in medical literature, although literally both are incorrect. Hodgkin's disease, lymphosarcoma and lymphatic leukemia belong to the lymphoma or lymphoblastoma group of diseases. Krumbhaar prefers the name lymphatoid diseases instead of Mallory's term lymphoblastoma for various hematopoietic disturbances.

Leukemia is usually classified on the basis of whether it is acute or chronic, leukemic or aleukemic. Subleukemic is perhaps a better term than aleukemic to designate a leukemia without an increase in the leukocyte count although there may be any degree of qualitative alteration in the white blood cells. Autopsy in the human subject or experimental animal reveals no anatomic basis for dividing the disease into acute or chronic varieties or into subleukemia or leukemia. In many cases a subleukemic blood picture will eventually become a frank leukemic type. In classifying the type, the anatomic name of the stain of cells which play the leading rôle in the leukemic process is generally com-

hined with the clinical terms - as acute lymphocytic leukemia, chronic monocytic leukemia, etc.

In order to indicate the origin of the cells involved, some workers designate the type as myelogenous or lymphogenous. Others who favor the neoplastic theory use the nomenclature for neoplastic diseases - such as leukemic lymphoblastoma or myeloblastoma. The origin of the monocyte is still disputed; hence, monocytic leukemia cannot be designated in terms of the origin of the type cell. There are many theories as to its origin: from myeloblasts in the bone marrow, from lymphoid cells, from primitive mesenchyme cells, from fibroblasts, or from macrophages. Downey believing in the reticulo-endothelial origin of the monocyte has used the term reticulo-endotheliosis as a synonym for monocytic leukemia. Sabin, Dameshek, and others support the theory of the existence of monocytes as an independent strain of cells - quite apart from the histiocyte and having a separate cycle of maturation. In recent years leukemic blood leukocytes have been studied by tissue culture in an attempt to determine the origin of the various cell types involved in the leukemias. Nothing definite has as yet been found.

Many combinations of these various terms are in use, but one is seldom consistent in using the same system of terminology for different types of the disease. Forkner suggests a simplified classification including all types of leukemia, dividing them first as to acute and chronic forms, then as to leukemic and subleukemic varieties. Further separation is made depending on the type of cell involved in the leukemic process.

Etiology

The cause of leukemia is still unknown. Three different concepts as to its nature have been advocated - the neoplastic and infectious having more weight than the theory of heredity.

I. Theory of Neoplasm

Some obervers claim that the leukemias belong in the group of neoplasti diseases, with close relationship to lymphosarcoma, leukosarcoma and Hodgkin's disease. In 1902 Babes advanced the theory of the neoplastic nature of leukemia, which was later subscribed to by Ewing and others. Three cases of lymphosarcoma have been reported by Evans and Leucutia, which changed into lymphatic leukemia (leukosarcoma) as soon as the bone marrow became involved by foci of lymphosarcoma. There are many features in leukemia which suggest a relationship to cancer inasmuch as a type of body cell appears to lose its ability to mature. In this respect it is somewhat suggestive of the process which affects the red blood cells in pernicious anemia. Some of the neoplastic characters of the white blood cells in leukemia are:

(1) Uncontrolled growth

(2) Tendency to form secondary foci of growth (metastasis).

(3) Progress to a fatal termination with cachexia.

(4) Neoplastic type of metabolic rate of the cells.

(5) Maturation with roentgen ray irradiation.

(6) Failure to transmit the disease by inoculation of human beings with the blood of affected patients.

(7) Birth of perfectly normal children by leukemic mothers.

(8) Failure to isolate an infectious agent from leukemic blood or tissues.

The neoplastic theory gains strong experimental support from the laboratory work of MacDowell and Richter and of Furth on the transmissible leukemia of mice. They conclude that leukemia is transmissible in mice only when living leukemic cells are injected into a susceptible host, and that the nature of the resultant growth is

CLASSIFICATION OF LEUKEMIA (LEUCEMIA, LEUKOSIS, LEUCOCYTHEMIA)

Clinical Designation	General Type of Leukemia	Cell of Origin	Specific Type of Leukemia	Synonyms Depending on Common Usage, on Course of Disease or on Clinical or Hematologic Characteristics
Leukemia or Subleukemic (Aleukemic) Leukemia (Acute or Chronic)	Myelogenous (arising from cells of bone marrow)	Myeloblast	NEUTROPHILIC Leukemia	Myelogenous, myeloid, myelocytic or myeloblastic leukemia; myelosis.
			Eosinophilocytic Leukemia	Eosinophilic leukemia
			Basophilocytic Leukemia	Basophilic leukemia
			Chloroleukemia	Chloroma or chloroleukosarcoma
		Myeloblast and megaloblast	Erythroleukemia	Leukemia associated with erythremia
		Megakaryoblast	Megakaryocytic Leukemia	
	Lymphogenous (arising from cells of lymphoid tissue)	Lymphoblast	LYMPHOCYTIC Leukemia	Lymphogenous, lymphoid, lymphatic or lymphoblastic leukemia; lymphoblastoma leukaemicum; lymphadenosis.
			Leukosarcoma	Lymphosarcoma associated with leukemia
	Lymphogenous or myelogenous	Primitive mesenchyme cell	Stem cell leukemia	Hemohistioblastic, embryonal or lymphoidocytic leukemia.
		Plasma cell, myeloblast and lymphoblast	Plasma cell leukemia	Plasmacytoma with leukemia or multiple myeloma with leukemia.
	Disputed	Monoblast	MONOCYTIC Leukemia	Histiocytic leukemia; reticulosis; reticulo-endotheliosis, reticulum cell leukemia; reticulosarcoma.

*The common types are given in capital letters.

that of a tumor with or without a leukemic blood picture.

Furth, Ferris and Reznikoff claim that leukemia in man is essentially the same disease as that in mice, and that both acute and chronic forms, myeloid as well as lymphoid, are neoplastic. Experimental evidence shows that the leukemic blood cells of mice are malignant, with characteristics of their own, and that leukemia-like carcinoma can be produced by various chemical (benzene, indole) or physical (x-ray) agents. They believe that lymphosarcoma and lymphoid leukemia are related diseases. In experimental lymphoid leukemia in mice, the malignant blood cells may localize as huge tumors (lymphosarcomas), or may diffusely invade the blood-forming tissues but not the blood stream (aleukemic leukemia), or may invade the blood stream as a classic leukemia.

2. Theory of Infection

The theory of the infectious origin of leukemia is advocated by clinicians who have noted a similarity in the clinical and pathologic picture to that of an infectious process. This hypothesis is applicable particularly to acute leukemia with its prostration, intoxication, purpura and septic type of fever. The occurrence of leukemia in series suggests a mild epidemic character. Pierce has reported 41 cases of leukemia in children, in which there was a high incidence of antecedent infection (49%). Ellermann and Furth have shown that experimental leukemia in fowls is due to an infectious agent - by transmitting the disease by inoculations with cell free filtrates of blood and organs of leukemic chicks. In no other animal has the disease been reproduced without the introduction of living leukemic cells into the host. This conflict in experimental evidence makes one doubt whether leukemia in mice is the same condition as that in fowls. Many workers still believe that the acute and the chronic leukemias are different in character, the acute forms having much in common with infections and the chronic having more similarity to tumors of lymphoid or myeloid tissues. A number of investigators have produced leukemoid blood pictures by inoculating animals with streptococcus and staphylococcus obtained from the spleen and lymph nodes of leukemic patients, but they are not true leukemias.

3. Theory of Heredity

The concept of the etiology of leukemia, that a constitutional inferiority of the hematopoietic organs predisposes to an unstable response to infections, is supported by a number of observers. This is suggested by the occurrence of leukemia in families having other types of diseases of the blood forming tissues - such as anemia, agranulocytosis, infectious mononucleosis, etc. It may be that there is some factor which regulates the maturation of the granular cells just as the liver fraction seems to control erythropoiesis. One may postulate a deficiency in this regulatory factor due to a hereditary tendency to abnormal toxic reaction in infections, and as a result, a flooding of the peripheral blood with quantities of immature blood cells.

Hereditary factors in experimental animal leukemias are well known. As regards man, the genetics of leukemia have not yet been extensively studied. Ardashnikov investigated thirty-three family histories and found but three familial cases. Only seventeen authentic instances of familial leukemia are known. The majority of these are of the lymphatic type. There has been no recorded case of the disease in both husband and wife. As a rule, parent and child, or brothers and sisters are affected, three cases in one family being the maximum. Curschmann cites a case of leukemia in a man whose father had died of the same disease nearly fifty years before. These facts are against the theory of common environmental influences including infection, and they favor the hypothesis that heredity is an influential factor in the etiology of leukemia.

Pathology

Leukemia is considered as a system-

ic disease, beginning as a local process and spreading throughout the body until at autopsy there is wide dissemination. The usual structural changes are those of hyperplasia of the bone marrow and lymph nodes associated with variable degrees of infiltration in the viscera, bones, meninges and skin. The pathologic findings in leukemia are confined chiefly to the blood and the blood forming organs. They are much the same in the various clinical forms and differ from one another only in degree and in the type of predominating cell found. The marrow, spleen, and lymphatic tissue show the greatest and most constant changes. The normal bright yellow "fat marrow" in the shafts of the long bones is replaced by a grayish pink, firm, homogeneous, markedly cellular tissue. Small islands of active erythropoiesis may be left. Granular myelocytes and polymorphonuclear leukocytes predominate in the myelocytic form, while in the monocytic and lymphocytic types, the nongranular mononuclear cells are most numerous. The lymph nodes and lymphatic tissue vary greatly in involvement, since often most of them are but slightly enlarged. All involved tissues show complete obliteration of their normal architecture, the tissue being replaced by fibrosis and a diffuse mass of immature cells, either granular or mononuclear, which are large with pale staining nuclei and many mitotic figures.

It is said that any organ or tissue except teeth and nails may be infiltrated. In acute leukemia hemorrhages are common in the skin, mucous and serous membranes and the ocular fundi. The spleen is always enlarged, sometimes to enormous proportions. Its normal shape is preserved, its consistency firm and the edges sharp. The pulp and vessels are crowded with abnormal cells of the predominating type. The malpighian bodies are obliterated by myeloid cells in the myelocytic type, while the pulp is packed with lymphoid cells in lymphocytic leukemia. Cellular infiltration is seen frequently in the liver, kidneys, pancreas, and adrenals, and to a less degree in the skin, nervous system or smooth muscle. Bony lesions include subperiosteal infiltration, generalized or localized osteoporosis, irregular cortical absorption and softening without compression of the spine, and fractures in the long bones which must be differentiated from hyperparathyroidism, erythroblastic anemia, and metastases from neuroblastoma. The skull, spine, pelvic bone and upper ends of the femora and humeri are most frequently involved. Falconer and Leonard in a series of cases in the lymphomatoid group of diseases report the incidence of pulmonary involvement as follows: Hodgkin's disease, 31%, lymphosarcoma, 36%; and lymphatic leukemia, 30%.

Incidence

Leukemia occurs in many animals, particularly in fowls, and to a less extent in horses, cattle, dogs, pigs, rats, and mice. In man the incidence has been variously estimated as occurring in from 1 to 3 cases among every 1000 hospital admissions. Race, country, occupation and season play no important role. Leukemia occurs with varying frequency at any time during life. Acute leukemia is chiefly a disease of childhood and early adult life, commencing usually before 25 years of age. Chronic myelogenous leukemia is more frequent in the fourth and fifth decades, and chronic lymphatic leukemia in the sixth and seventh decades. It has been found that about 70% of all cases are under 30 years of age, and 55% under 20 years. Males are more subject to leukemia than females - in the proportion of 2 to 1. The course of the disease is identical in the two sexes. The disproportion in sex incidence does not apply to younger children up to 5 or 6 years.

Lereboullet and Baize in a review of 113 cases of acute leukemia in children up to 16 years report a high incidence in infancy, 25 in the first year and 64 during the first 4 years, which decreases strikingly with increasing age. They had several congenital cases. In Cooke's series of 50 children with acute leukemia, the age incidence in boys is about the same up to 15 years, but the girls show a decrease in the older age group. In his group of 142 cases of leukemia of all ages, the average age of acute leukemia patients is

less than 20 years, for those with chronic myelogenous leukemia, 40; and for those with chronic lymphatic leukemia, 57. Chronic myelogenous leukemia was more frequent than any other single type during adult life; in childhood he had only three cases.

Symptoms

1. Acute Leukemia - with or without leukocytosis.

The first clinical manifestation of leukemia is ease of fatigue. Increasing pallor soon develops, and it may be several weeks before a physician is consulted for these complaints or for some other more alarming symptoms. At times the patient becomes ill with dramatic suddenness as in an infection with high fever, chills, vomiting, joint pains, apathy and lemon yellow pallor, followed soon by ulcerative stomatitis, multiple hemorrhages and splenomegaly. There is individual variation but in most cases there is an insidious onset with loss of weight, progressive anemia, weakness, waxy pallor, skin hemorrhages, fever and enlarged spleen. These cardinal signs of leukemia lead one to suspect the diagnosis, but this must be confirmed by the hematology or sternal puncture.

The symptoms are protean and, as a whole, fall into four groups:

(1) Associated with an increase in the basal metabolic rate (nervousness, profuse perspiration, loss of weight).

(2) Associated with infiltrated organs and glands (pressure symptoms, arthralgia, stomatitis, cyanosis, cough, hemoptysis, hematemesis, constipation, diarrhea, melena, frequency of urination, etc.).

(3) Associated with anemia, thrombocytopenia, and myocardial insufficiency (hemorrhages, dyspnea, palpitation, edema, fatigue, hemic cardiac murmurs).

(4) Associated with abnormal metabolism following the gradual progress of the disease (cachexia).

Hemorrhages are the rule. The most common sites from the mucous membranes are the mouth and nose. Severe epistaxis may be the presenting symptom. Purpuric cutaneous lesions occur in multiple petechiae or ecchymoses, usually on the trunk or extremities. There are often hemorrhages in the gastrointestinal or urinary tract, in the vagina or into the joints. Tonsillectomy may cause fatal bleeding. Retinal hemorrhages are considered by some clinicians to be pathognomonic of leukemia. Swelling and ulceration of the gums, cheek, and tonsils in many cases progress to form necrotic, gangrenous lesions. Mediastinal enlargement of the thymic area may be an early symptom with dyspnea from pressure on the trachea.

Hyperplasia of the hematopoietic organs is almost always present, noted particularly in the lymph nodes and spleen. The cervical nodes are generally enlarged, sometimes the first sign to attract attention. The enlargement is usually slight, the nodes being small, firm, palpable, and discrete. The anterior cervical group is more frequently involved and may show visible tumors. In a few cases the submandibular glands may attain huge size causing marked cervical deformity. In the child splenomegaly is more constant than in the adult, especially in the younger group. The spleen is firm, smooth and somewhat tender to palpation, in the majority of cases not reaching the umbilicus, but occasionally filling more than half of the abdomen. The liver is generally hypertrophied, but to a less extent than the spleen. Leukemic infiltration of the stomach has been described (Rigler), while Haining reports a case of monocytic leukemia with intestinal obstruction due to infiltration. Rheumatoid pain may play a prominent role and may be the initial chief complaint. Continued fever occurs, frequently becoming high and septic in type toward the end of the disease. At times abdominal pain simulates appendicitis; leukemic infiltration and perforation of the appendix have been noted at autopsy.

Schwab and Weiss report 334 cases of

acute leukemia, 20.5% of which had neurologic signs excluding retinal lesions. Nervous manifestations may assume the form of facial paralysis, Jacksonian epilepsy, convulsions, exophthalmos, meningeal irritation, and deafness. Cerebral hemorrhage is a most serious complication leading to death in a few hours. Other symptoms occur, such as profound anorexia, nausea and vomiting, vertigo, dyspnea, infiltrating skin nodules (leukemia cutis) and sanguineous pericardial effusion. Due to infiltration of the kidneys with embryonal cells, there occasionally are nephritic symptoms, albuminuria and hematuria. Common to all leukemias is an excess of uric acid and purine bases in the urine, parallel with intensive destruction of the leukocytes.

2. Chronic Myelogenous Leukemia

Chronic myelogenous leukemia is relatively rare in children - usually occurring in later childhood - but presents essentially the same picture as in the adult. Ease of fatigue, progressive loss of weight and strength, and an increase in the size of the abdomen due to the characteristic enormous enlargement of the spleen are early manifestations. The spleen is generally not tender but causes pain in a certain number of cases. The liver is moderately enlarged. In contrast to lymphatic leukemia, there is little gross hypertrophy of the lymph nodes. Following an insidious onset, the course is gradual, and there is usually little discomfort for several weeks or months. Pains in the extremities are not uncommon. In the later stages, there are hemorrhages from the mucous membranes, rather than into the skin as noted in acute leukemia, particularly from nose, gums and rectum. Hemorrhage or leukemic infiltration may cause Ménière's syndrome, if in the labyrinth, dimness of vision, if in the retina or optic nerve, or exophthalmos, if in the orbit. A marked rise in the basal metabolism is found, up to 40-50% of the normal. Febrile attacks occur but the elevation of temperature is not as high as in acute leukemia. Among the later symptoms are anemia, dyspnea, abdominal distress, edema, ascites, and occasional priapism. Skin lesions are much less frequent in myelogenous leukemia.

3. Chronic Lymphatic Leukemia

Chronic lymphatic leukemia does not occur in childhood. It is much less common than the myelogenous variety. The general symptoms closely resemble those of myelogenous leukemia and only examination of the blood can differentiate them. The most conspicuous feature is enlargement of the lymph nodes, cervical, axillary, inguinal, and mediastinal; these are firm, discrete, noninflammatory, and painless. The spleen and liver are not as large as in myelogenous leukemia. Hypertrophied tonsils may be an early symptom associated with weakness and anorexia. Leukemides and specific cutaneous lesions (leukemia cutis) are frequent. In the terminal stage one sees cardio-respiratory and digestive symptoms with profound anemia.

4. Monocytic Leukemia

Since Dameshek reviewed the literature and reported 10 cases of monocytic leukemia in 1930, others have increased the list. Recently Klumpp and Evans added 8, and in 1937, Osgood described 6 new cases, making also an analysis of 127 previously reported. These workers believe monocytic leukemia is a relatively common condition. Rosenthal found only 2% in 455 cases, while Doan, using his more sensitive supravital staining technique, estimates it as 15% in his series of 75 cases of leukemia. The general opinion prevails that the incidence of each type of leukemia is approximately that of the particular cell types in the normal differential count from a blood smear: an average of 66% myelogenous leukemia, 25% lymphatic, and 5% monocytic.

Monocytic leukemia is an acute type with a short clinical course ranging from 1 month to 2 years. It differs little clinically from the other acute leukemias except in age limits. The ages reported have been from 1 to 28 years, the majority around 40 years. It is characterized by an abrupt onset of oral

symptoms in 60% of the cases, marked tendency to swelling of the gums, and the frequent association of stomatitis, fever, and hemorrhages from the mucous membranes. The liver and spleen are usually enlarged, but the lymph nodes are less involved than in the other type of leukemia. Progressive pallor and weakness are parallel to the degree of anemia and thrombocytopenia with its hemorrhagic diathesis. Other symptoms, less frequent but definitely related to the disease, are pain in bones and joints, cutaneous papules and nodules, and monocytic infiltrative tumors. Secondary staphylococcus infection of the skin with furunculosis and carbuncles is not uncommon. The course of this disease is progressively downward. Osgood suggests that the term monocytic leukemia be used in preference to reticulosis or reticulo-endotheliosis.

5. Other Types

Chloroma or chloroleukemia, at first thought to be a distinct disease, is now considered a modified form of leukemia. It is a disease with localized tumor masses of greenish color, always associated with myelogenous leukemia. All the characteristic findings of leukemia are present: symptoms, blood picture, and infiltration of organs, and in addition, the local tumor-like infiltration. These multiple tumors have a predilection for periosteum and dura, the skull bones - especially the orbits, being most frequently involved. Pressure symptoms from the mechanical effect of the tumors are in evidence. The green pigment in the tumors is apparently a lipochrome and contains iron. Kandel has reviewed 175 cases found in the literature and reported three more. Congenital leukemia is a rare occurrence. Only 30 known cases of leukemia complicated by pregnancy have been found. Recent cases during pregnancy are described by Mehta and by Erf anf Fine. Abt cites six cases in the newborn period, one of which was in a stillborn infant in the seventh month of gestation. Leukemia, however, is not transmitted from mother to child, leukemic mother having given birth to normal children. In no authentic case has leukemia been found in the offspring of leukemic mothers. Leukemia in the neonatal period must be differentiated from erythroblastosis neonatorum and congenital syphilis. Plasma cell leukemia is reported occasionally - associated often with multiple myeloma. Plasma cells resemble other leukocytes in potentialities for leukocytosis, infiltration, tumor formation, and leukemic infiltration. Stem cell leukemia is a term applied when very immature cells predominate. Lymphosarcoma associated with leukemia is known as leukosarcoma. Erythroleukemia is a rare type of leukemia accompanied by polycythemia. Many observers believe that leukemia and polycythemia rubra vera are closely related, the latter sometimes changing into a leukemia.

Blood Picture

1. Acute Leukemia

The morphologic characteristics of the blood picture of acute leukemia are:

(1) Abnormal nongranular mononuclear cells - 80-95% of leukocytes regardless of total count (leukocytosis or leukopenia).

(2) Agranulocytosis, granular cells only 1-15% of white cell count: myelocytes, immature neutrophilic polymorphonuclear cells (juvenile and staff type) and segmented cells.

(3) Anemia with frequent red counts of 1,000,000 and a hemoglobin content of 20%. Anemia usually secondary in type, but may resemble pernicious anemia, especially when there is leukopenia. Occasionally, normoblasts, megaloblasts and reticulocytes during rare temporary remission.

(4) Thrombocytopenia, below 150,000, and often below 100,000, with prolonged bleeding time, normal clotting time and poor retraction of clot.

The number of circulating leukocytes is greatly variable during the course of the disease and in different patient ranging from 250 to 1,000,000 per c.mm.

the average being from 20,000 to 200,000. In a few days' time the count may drop from 100,000 to 6,000, or suddenly rise to that extent in another case. There may be normal white cell counts or the so-called aleukemic leukemia (with leukopenia) may have counts less than 5000 for long periods. These leukemias constitute a diagnostic problem, but the stained blood smear sooner or later will show the typical abnormal nongranular cells. These stem cells or undifferentiated cells are large, round or oval elements, having a large, irregular, eccentric nucleus with a narrow border of hyaline protoplasm. Stained by the Giemsa method, the nucleus is pale violet with a fine chromatic structure and contains vacuoles and a deeper stained nucleolus, while the cytoplasm is deep azure. There has been considerable controversy concerning these abnormal agranulocytes - whether they originate in the lymphatic tissue and are lymphoid in origin or whether they come from the bone marrow and are therefore myeloid. The peroxidase reaction is not successful in identifying myeloid cells by the presence of granules since the true myeloblasts, like the lymphocytic series, are peroxidase negative. These nongranular leukemic cells show an increase in protease, as do the myelocyte and polymorphonuclear leukocyte, while lymphoid cells do not possess this proteolytic activity. This fact leads one to believe that these stem cells are myelogenous in origin.

2. Chronic Myelogenous Leukemia

(1) Leukocytosis of 40,000-500,000, usually over 200,000.

(2) Predominant cell - mature polymorphonuclear leukocyte - with 10-30% myelocytes, and 10-25% juvenile and staff cells. 95-99% of white blood cells are of myeloid origin. Eosinophilia occasionally 50-80% ("eosinophilic leukemia").

(3) Anemia moderate at first (red blood count - 2,500,000 - 3,000,000), more marked in later stages and improved during spontaneous or therapeutic remissions.

(4) Platelets usually increase

(5) Peroxidase test positive only for myelocytes up to mature polymorphonuclears.

(6) Indophenol blue (synthesis test positive - Kracke).

(7) Increase in protease.

There is no other disease in which so many different types of cells are seen in the blood smear.

3. Chronic Lymphatic Leukemia

(1) Leukocytosis of 40,000-500,000, usually over 100,000.

(2) Extreme lymphocytosis with 90-99% small lymphocytes. Smudge forms constant.

(3) Anemia less marked than in other types - red blood count may be normal in early stage.

(4) Thrombocytopenia marked.

(5) Peroxidase test negative.

(6) Indophenol blue synthesis test negative.

(7) No protease.

4. Monocytic Leukemia

(1) Leukocytosis usually up to 320,000 but white blood count may go as low as 600.

(2) Predominant cell (50-75%) monocyte and promonocyte.

(3) Red blood count markedly decreased in terminal stages.

(4) Thrombocytopenia toward the end.

(5) Indophenol blue synthesis test negative.

(6) Peroxidase test positive.

There seems to be an association between the degree of monocytosis and the duration of the illness. In the fulminating cases, the number of monocytes in the peripheral blood is great, or else rapidly increases to high levels, while in the slowly progressing cases, the absolute number of monocytes is only moderately elevated.

Diagnosis

It is difficult to separate the acute or chronic leukoses on a clinical basis. Although usually associated with splenomegaly or lymphadenopathy from which the diagnosis is suspected, leukemia cannot be differentiated until a hematologic examination is made. The diagnosis of leukemia can usually be made from the blood count and, what is more significant, from the blood smear. Until recently leukemia was regarded as a disorder characterized by a persistent increase in the number of white blood cells. According to the present conception of the disease and the recognition of subleukemic states, an increase in the number of white cells is not an essential diagnostic factor. The most reliable criterion for the diagnosis of any leukemia is a preponderance of immature cells regardless of the total number. The difficulty in diagnosis is due to the many variations that may occur both in the clinical picture and in the laboratory observations.

Without a careful blood examination, leukemia may readily be mistaken for other conditions because of the initial symptoms in mouth and throat, fever and hemorrhagic tendency. These lead one to think of diphtheria, ulcerative stomatitis, scurvy, purpura hemorrhagica, and endocarditis. When leukocytosis is present, as in the majority of cases, leukemia may come first to mind. Leukopenia, however, may mark the entire course of the disease, or be present in certain phases. Abt has listed two groups of differentiation in leukemia in childhood.

Group 1. Differentiation When Leukocytosis is Present

A. Nonleukemic conditions simulating leukemia.

1. Pertussis.
2. Pneumonia.
3. Sepsis.
4. Von Jaksch's pseudoleukemic anemia.
5. Cooley's Mediterranean erythroblastic anemia.
6. Infectious mononucleosis.
7. Mediastinal tumor (thymoma or lymphosarcoma).
8. Niemann-Pick's essential lipoid histiocytosis.

B. Leukemia simulating other conditions.

1. Simulating mediastinal tumor.
2. Simulating rheumatism.
3. Simulating diarrhea.
4. Simulating parotitis. (Mickulicz' disease).

Group 2. Differentiation When Leukopenia is Present

A. Nonleukemic Conditions Simulating Leukemia.

1. Sepsis with leukopenia.
2. Agranulocytosis.
3. Gaucher's disease.
4. Aplastic anemia.
5. Malaria.
6. Nonlipoid splenohepatomegaly; Letterer-Siwe's disease.

B. Aleukemic leukemia simulating other conditions.

1. Simulating sepsis.
2. Simulating appendicitis.
3. Simulating aplastic anemia.

After careful weighing of the clinical findings and of the blood picture, diagnosis may still be uncertain. Roentgenograms may be of material assistance

where there are bone lesions. Prominent signs of some leukemias may be pain in the long bones as in osteomyelitis; pain around joints resembling acute rheumatic fever; periosteal reactions as in scurvy or luetic periostitis; spontaneous fractures in local osteolytic processes; bulky tumors of single bones; chloroma; or osteolytic lesions, as in multiple myeloma. One case of unusual interest was reported by Clark, in which the roentgenogram revealed a marked disturbance in the calcium content of the bones of the entire skeleton, particularly in the pelvis and femora. The blood calcium was found to be 19.3 mg./100 cc. and persisted at high levels until the end. This was attributed to leukemic infiltration of the parathyroid gland. Biopsy of an enlarged lymph node may assist in the differentiation but it is often impossible to tell from a histologic preparation of a lymph node alone whether one is dealing with a leukemia, lymphosarcoma, leukosarcoma, or Hodgkin's disease. The architecture is destroyed by an invasion of small lymphocytes so that biopsy gives no clear picture of any certain disease.

Of major importance in the diagnosis of leukemia is the sternal puncture. Simultaneous studies of the bone marrow and the circulating blood in living subjects is a relatively recently developed diagnostic procedure. The peripheral blood often fails to furnish accurate information concerning underlying abnormalities in the blood forming organs. Changes at the sources of blood cells are probably visible earlier than in the blood, and distinguishing characteristics of different pathologic states may be seen in the bone marrow. Kingery has published a report of 15 ambiguous cases in which sternal puncture has furnished information of noteworthy diagnostic accuracy - which blood examination or biopsy of a node was unable to give. They describe their technique with a spinal needle. It is simple, applicable to ambulatory patients, and free from unpleasant symptoms or sequelae. The positive value of sternal puncture is in the various types of leukemia, while its negative value is in Hodgkin's disease and lymphosarcoma. Dameshek's sternal method is the trephining technique and while the hematopoietic pattern can be better identified, the technique is more complicated, and there is the possibility of postoperative hemorrhage.

The criteria for diagnosis of leukemia from a sternal puncture are as follows:

1. Lymphatic leukemia -	
lymphocytes	$>20\%$
or large lymphocytes	>5-20%
2. Myelogenous leukemia -	
premyelocytes	$>20\%$
or myeloblasts	$>4\%$
Suggestive of myelogenous leukemia -	
premyelocytes	10-20%
or myeloblasts	2-4%
Nucleated cells in normal bone marrow	$<70,000$/ c.mm.

Splenic puncture is seldom used as a diagnostic tool. Weil believes that it should be done more frequently, the chief contraindication being a hemorrhagic tendency. It is done with a needle under local anesthesia; splenic pulp is aspirated and spread on slides for staining. The splenogram gives much the same picture that the marrow puncture does. It may be a guide to prognosis and treatment, more than 20% of primitive cells indicating a grave outlook and therapy not indicated. Splenic puncture is not without risk, there being a 1% mortality from postoperative hemorrhage.

Leukemia should be differentiated from the various conditions associated with localized or generalized lymphadenopathy. Lymphocytic leukemia is in many ways similar to Hodgkin's disease and lymphosarcoma, but the blood picture generally is sufficient to differentiate it. Hodgkin's disease more prevalent in the second and third decades produces progressive painless enlargement of a group of nodes which remain firm, discrete and free from suppuration and adhesions. Lymphosarcoma, occurring in the age limits from 25-55 years, may involve any lym-

phoid tissue. Accessible involved nodes show unilateral or unequal disturbances, almost bony hardness, early fusion between nodes, and adhesions to adjacent tissues. The nodes are not tender and do not suppurate, but they cause serious pressure symptoms. Tuberculous cervical adenopathy is characterized by inflammatory reaction with tenderness, edema, suppuration, fusion of nodes, and adhesions to the skin and underlying tissues. Mikulicz' disease is a disease with chronic, symmetrical, painless enlargement of the lacrimal and salivary glands - which is not leukemic.

A number of diseases have been mentioned with leukemoid blood pictures but without tissue changes. Others that may be included are smallpox, chronic infection, such as tuberculosis, hemolytic icterus, polycythemia vera, during anemic phase, pernicious anemia, Banti's disease, active regeneration following anemia or severe hemorrhage, certain chemical poisoning - as arsenic, or mustard-gas or mercury, and malignant tumors of the lymphoid system. With regard to the latter, it may be said that in true leukemia, there is a disturbance of all the elements of the blood - while in blood dyscrasias based on tumors of the lymphoid system, tumor cells are present but the rest of the cellular elements are not affected.

Acute leukemia may be confused with acute benign lymphadenosis or infectious mononucleosis. Both are diseases of childhood or young adults. Both are characterized clinically by a sudden onset, high fever, generalized adenopathy and acute pharyngitis and tonsillitis. The blood count reveals a relative and absolute lymphocytosis. In 1923 Downey and McKinlay reported nine cases of benign lymphadenosis with criteria for differentiating it from leukemia and for separating the various types of the atypical lymphocytes found in the blood. They are described as highly differentiated, mature, "leukocytoid" lymphocytes. Paul and Bunnell in 1932 found that the heterophile antibody reaction is positive in infectious mononucleosis and negative in other lymphadenopathies. Weinstein and Fitz-Hugh confirmed this in 16 cases of leukemia in which the heterophile antibody titer was uniformly at a low level.

Therapy

Marked improvement in the clinical condition of the leukemic patient with decrease in organ enlargement and reversal of the blood status toward the normal may occur in three ways. It may come about spontaneously without apparent cause; it may result from intercurrent acute infection; or it may follow therapeutic effort, particularly x-ray irradiation.

Clinicians have noted for a long time that intercurrent infections during the course of leukemia are associated with a decrease in the number of leukocytes. In the last decade artificial production of fever by malarial inoculations has been studied with variable reports as to the effective response. In most of the cases the fall in the white blood cells was quite transitory.

The medical literature abounds in suggestions regarding effective medicinal measures. Leukocytolysis, or reduction in the number of white blood cells, may be accomplished by several methods: chemical, biologic, or physical. Numerous remedies were tried for leukemia before irradiation. Since the etiology is still obscure, no specific remedy is known, and the treatment is essentially symptomatic. The chief purpose is to produce:

(1) Improvement of general condition by rest, diet, and sedatives.

(2) Increase of strength and efficiency by blood transfusions and roentgenotherapy.

Among the many therapeutic substances that have been advocated are lead, arsenic, antimony, sulphur, iodine, benzol, quinine, malarial inoculations, liver extract, ventriculin, embryonic extract (fetal liver), tuberculin, and nuclein. Many of these are toxic and their use entails considerable risk; few of them afford much palliation.

1. Chemical

Before the advent of the roentgen rays the method of treatment in most common use was with arsenic in the form of Fowler's solution. After the general employment of irradiation, arsenic fell into relative disuse, but recently attention has once more been called to its value in chronic myelogenous leukemia by Forkner. It has practically no influence in chronic lymphatic leukemia. In 1936 Stephens and Lawrence reported 7 cases of chronic myelogenous leukemia treated with prolonged courses of potassium arsenite. To be effective, the drug should be given in rapidly increasing doses until toxic symptoms appear, then continued in amounts as large as can be tolerated, a regime which can be maintained for over a year without serious reactions. They conclude that arsenic is an efficient palliative, especially when accompanying or alternating with radiotherapy. Kandel and LeRoy also find that arsenic therapy and x-ray treatment are not antagonistic, and that a remission of the leukocytosis may be induced with arsenic as soon as the postirradiation decline of the leukocyte count ceases. The toxic reactions of inorganic arsenic are either transient, mild symptoms (conjunctivitis, coryza, nausea, diarrhea) or the more serious complications: polyneuritis, cirrhosis of the liver with ascites, or cutaneous pigmentation and painful plantar and palmar hyperkeratoses. Organic arsenicals (arsphenamine) are more dangerous and have produced little improvement in the leukocyte count.

Benzol has had a somewhat similar history as arsenic, but has not regained its early favor. Von Korányi (1912) introduced this drug in the treatment of leukemia. It is ingested in large doses in capsules. Improvement of the general condition is dependent upon reduction in the excessive number of leukocytes. Its administration must be discontinued if the red cells decrease to below 2,000,000. Benzol is contraindicated in albuminuria, in anemia, in toxic effects on the liver and kidneys, and in hemorrhages due to thrombopenia. Its effects are less easily controlled than arsenic, and aplasia of the red bone marrow is a theoretic, if not an actual danger. Antimony and other drugs have produced similar remissions, but their employment has been disappointing and far inferior to irradiation for that purpose.

2. Biologic Method

Leukocytolytic substances have been demonstrated in leukemia. An antileukocytic serum produced from leukemic white blood cells has been used in cases of leukemia but the beneficial response was only transitory.

3. Physical Method

Radiotherapy, although not curative, is undoubtedly of the greatest therapeutic value in chronic myelogenous and chronic lymphatic leukemia. Irradiation is slightly more efficacious in relief of symptoms in the myelogenous variety. It is generally conceded that radiation therapy is without symptomatic effect in the acute cases, the disease progressing toward the fatal end at a speedy pace. Because roentgen irradiation, even in small doses, has been followed by an increase in toxicity and rapid death, its use is contraindicated in acute leukemia. Rosenthal and Harris, however, disagree with this verdict. Since the roentgen ray was first tried in leukemia by Senn in 1903, it has been used with increasing and justifiable popularity.

Radium, in the form of surface application or packs, was first used only when deep x-ray therapy was not available - or in patients unable to be moved from their homes. Although large quantities of radium are required and it presents difficulties in application, in recent years, it has become more widely used. Leucutia reports good results with radium packs in leukemia. Fricke (1928) showed definite and impressive palliation with radium therapy in 157 patients, and this year Fricke and Watkins present 16 cases of unusual borderline types of leukemia, many with leukopenia. They believe that radium is the most satisfactory therapeutic agent in these obscure cases with low leukocyte counts. Roentgenotherapy covers a larger portal and the effect of

the treatment is usually too sudden and drastic. The best results are obtained in leukopenia with very cautious and well controlled radium.

Roentgenotherapy is at the present time accepted by the majority of clinicians as the therapeutic method of choice in the treatment of chronic forms of leukemia in producing temporary remissions which may persist for some months or even years. No definite plan of treatment can be outlined in advance; the patient must be considered as an individual, and the therapy given according to his response. The marked radiosensitivity of leukemic tissue, particularly in children, and the lability of the blood count necessitate extreme caution. Since leukemia is incurable and palliative radiation must be continued for long periods, marked reactions should be avoided and the radiation must be the smallest amount that will produce beneficial results. Small fractional treatments are tolerated better than larger ones. The size of the dose and intervals between radiations must be determined by the patient's condition and a careful check of the blood count. It is unnecessary, even harmful, to attempt to reduce the leukocytes to normal or below normal. Symptomatic relief and general improvement may be accomplished with the white cell count around 10,000-30,000. There is always the hazard of a secondary aplastic anemia. Too heavy dosage may precipitate the same condition observed in the terminal stage of the disease when anemia and thrombopenia become the dominant features. A sudden drop in the leukocyte count may be followed by a clinical agtravation or even by cachexia.

Further treatment is guided by the activity of the leukemia, controlled by periodic blood examination, and a strict surveillance of the patient's general condition. Anemia is no contraindication. As soon as there is a change in the blood count, quantitative or qualitative, an increase in the mediastinal shadow, a recurrence in the enlargement of spleen or lymph nodes, a rise in the basal metabolic rate or deterioration in the physical state, irradiation is repeated. A number of remissions may be produced in this manner, but gradually the therapy becomes less effective, and as the disease progresses, it shows complete resistance to any form of therapy.

There is virtual chaos concerning the technique of irradiation. The areas to be irradiated are a subject of controversy. Leucutia in a review of 2725 cases and personal observation of 129 has concluded that, in view of the fact that palliation is all that can be produced and that some effect may be expected from every radiation, the technique is not of such paramount importance. There have been good results claimed from medium penetrating rays with layer doses, from harder rays with smaller fractionated doses, and from radium packs, whether irradiation is made over spleen, lymphatic system, in lymphatic leukemia, long bones in myelogenous leukemia, great vessels of the chest, bones of the thorax, kidneys, entire trunk, or even the entire body in the form of teleroentgenotherapy. David believes that the therapeutic agent should directly attack the centers of cell proliferation and advocates first treating the bone marrow (vertebrae, ribs, scapula, sternum and long tubular bones) - later applying roentgen rays to the spleen and peripheral glands.

Craver prefers the Heublein method of prolonged low intensity irradiation of the whole body - over a period of 2-30 days in a ward where the entire bodies of four patients can be irradiated simultaneously with the tube at some distance. Treatment is given for 16-20 hours daily. Enlarged spleens in myelogenous leukemia should be irradiated locally preliminary to teleroentgenotherapy. Langer, who emphasizes the importance of the vegetative nervous system in the production of leukemia and related diseases, recommends roentgen treatment over the vegetative nervous system with small fields instead of using teleroentgenotherapy.

The leukemic patient should receive supportive treatment of various kinds. His feeling of well being depends to a large extent upon the state of the red cells and hemoglobin. Results of x-ray therapy have greatly improved

since massive doses of iron have been administered throughout the course of the illness. In marked anemia and tendency to hemorrhage multiple transfusions are indicated for temporary amelioration, but they have no effect on the circulating leukocytes or in altering the course of the disease. Liver extracts, ventriculin and various extracts of spleen have been used with but minimal response. Nucleotide, which has a favorable effect in stimulating the production of granular leukocytes in certain types of agranulocytosis has been of no value in the treatment of subleukemic leukemia.

Israels in 1935 studied the effect of Lugol's solution in chronic lymphatic leukemia. Although in some cases the iodine caused a reduction in the white cell count, the failure of symptomatic relief, the lack of improvement in the anemia when present and the uninterrupted course of the condition suggest that the leukemic process itself was unaffected. Isaacs believes that Lugol's solution has a definite effect, especially in chronic lymphatic leukemia, in relieving some of the symptoms associated with a high basal metabolic rate.

Operative procedures are contraindicated because of the low resistance to infection and the bleeding tendency. A rapid exodus is apt to follow dental extraction for removal of foci of infection. Tonsillectomy and splenectomy are of no value, and even hasten the fatal termination, especially in acute leukemia.

Prognosis

Acute leukemia is invariably fatal in a few weeks or months, all treatment being of no avail in affecting the rapid course of the disease. Although the ultimate prognosis in chronic leukemia is bad, and no instance has been reported of recovery in a case in which the diagnosis of leukemia was unquestioned, therapy such as arsenic or radiation therapy, may produce temporary remissions for many months or years. Forkner (1937) has reviewed the subject of spontaneous remissions and reported cures of leukemia. One remarkable feature of leukemia is the great variation in the length of its course. It may be fulminating or greatly prolonged and relatively benign. Occasionally myelogenous leukemia lasts for 10 years or more, but a long course is more common in lymphatic leukemia. Treatment cannot extend the clinical course of chronic leukemia beyond a certain limited period, but it vastly improves the quality of life remaining to the patient and promotes his activity and happiness. The improvement in the general condition after course of x-rays is usually dramatic. The disease, however, always proceeds, by exacerbations and remissions to a fatal termination. The immediate prognosis may be estimated with some accuracy by observing the effects of treatment on the hemoglobin and red blood cells. A steady rise gives a good immediate prognosis, while a fall indicates the probability of an early fatal issue.

Nathanson and Welch (1937) in a report on life expectancy and incidence of malignant disease estimate that 50% of the patients with acute leukemia are dead in 2 months, 75% in 6 months, and the remainder within a year. The average survival in chronic lymphatic leukemia is 3.45 years. In 96 cases of acute and chronic lymphatic leukemia, only 18% were living five years after onset. In 141 cases of acute and chronic myelogenous leukemia, 22% were living after a five year period. Isaacs also has found that the average duration of life in chronic leukemia is about 3½ years. Leucutia claims that radiation therapy increases the expectation of life very little, perhaps with about 1/4 to 1/3 of the usual duration without treatment. It is said, however, that the patient's working efficiency is increased at least 60% throughout the entire course of the disease as a result of radiation therapy.

ANALYSIS OF LEUKEMIA ON THE PEDIATRIC SERVICE IN THE UNIVERSITY OF MINNESOTA HOSPITALS - 1922 to MAY 23, 1938

The following analysis includes all available case records of leukemia up to the age of 16 years, admitted to the Pediatric Service in the Minnesota University Hospitals from January 1, 1922 to May 23, 1938. No records are obtainable for the years 1925-1928. In some instances comparison is made with similar studies of other observers.

Year	No. of Cases
1922	1
1923	1
1924	0
1925)	
1926) no records available	
1927)	
1928	1
1929	2
1930	2
1931	2
1932	1
1933	5
1934	3
1935	7
1936	9
1937	8
1-1-38 to 5-23-38	3
Total	45

Classification

The cases reviewed in this series fall into the following classification. Diagnosis was established in 58% of the cases by autopsy findings.

	Number of Cases	Per Cent of Total Number
Acute Lymphatic Leukemia (LYMPHOCYTIC)	35	78%
Myelogenous (NEUTROPHILIC)	6	13%
a. Acute 2 cases		
b. Chronic 4 cases		
Reticulo-endotheliosis (MONOCYTIC)	2	4.5%
a. Reticulo-sarcoma 1 case		
b. Leukemic Reticulo-Endotheliosis 1 case		
Atypical	2	4.5%
	45	100. %

Etiology

a. Yearly incidence

In the following table, the number of cases per year which are included in this survey are shown.

b. Age and Sex

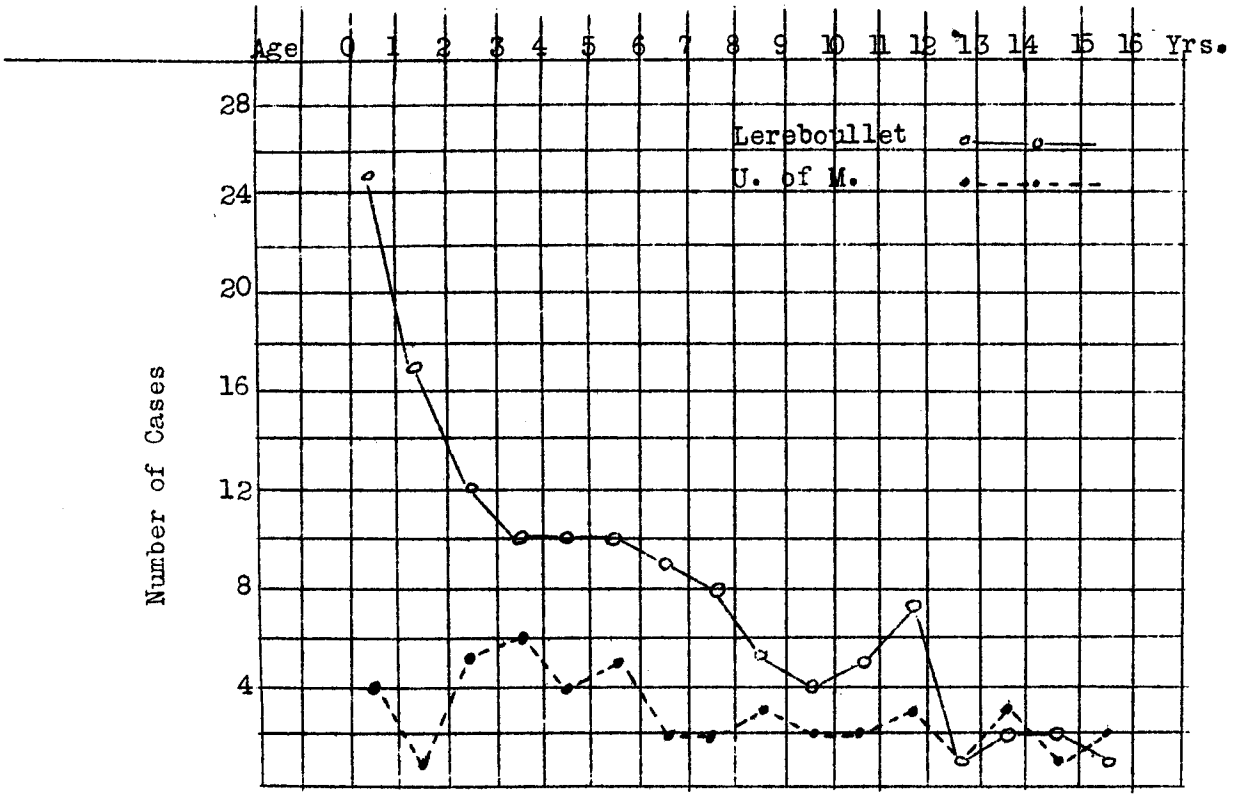
The age and sex incidence was similar for all types of leukemia. The following table represents these findings in this series.

Age-Years	No. Males	No. Females	Total
0 - 1	3	1	4
1 - 2	1	-	1
2 - 3	3	1	4
3 - 4	3	3	6
4 - 5	3	1	4
5 - 6	3	2	5
6 - 7	2	-	2
7 - 8	1	1	2
8 - 9	2	1	3
9 - 10	1	1	2
10 - 11	2	-	2
11 - 12	1	2	3
12 - 13	-	1	1
13 - 14	2	1	3
14 - 15	1	-	1
15 - 16	2	0	2
Totals	30	15	45

	Diagnosis	Age
Youngest case -	Atypical Leukemia	2 months
Oldest case -	Leukemic Reticulo-endotheliosis	15½ years
Average age for entire group		6.4 years
Percentage of cases under 6 years		53.3%

30 cases occurred in males and 15 in females (ratio 2:1).

A comparison of our findings regarding age incidence of the entire group is made with that of P. Lereboullet and P. Baize.



c. Predisposing factors (questionable)

(1) Family history.

The family history was reported in 43 of the 45 cases. There was no blood dyscrasia in the family reported in any case with one exception. In that case a second cousin to the patient was reported to have had an illness at the age of 2 years during which time the abdomen became very large, bluish green spots developed over the body, and he died after 2 months. It is true, however, that family history records of this group were not detailed in many instances. Therefore, these results may be of questionable significance.

(2) Previous infectious diseases

12 cases (27%) of the group had the history of an infectious process shortly preceding the onset of the first manifestation. The following table presents these findings.

Type of Infection	No. of Cases
Pneumonia	4
Pertussis	3
Otitis Media	3
Axillary Abscess	1
Pyuria	1
Upper Respiratory Infection	1

Symptomatology

a. Initial Manifestations.

The relative frequency in occurrence of various initial manifestations is indicated below. Comparison is made with the results of a corresponding study of 50 cases of acute leukemia reported by J. V. Cooke.

Symptoms	Cooke's Series		U. of M. Hospital Series			
			Lymphatic Leukemia		All Cases	
	Number of Cases	Percentage	Number of Cases	Percentage	Number of Cases	Percentage
Asthenia)	17	) 34%	2	5.7%	4	9%
Pallor)		)	16	45.7%	16	36%
Rheumatoid pains	5	10%	5	14 %	8	18%
Cervical Glandular Enlargement	9	18%	4	11 %	5	11%
Large abdomen	1	2%	1	2.9%	3	7%
Skin hemorrhages	7	14%	2	6 %	3	7%
Localized swelling			2	6 %	2	4%
Cough-dyspnea	5	10%	1	2.9%	2	4%
Anorexia			1	2.9%	1	2%
Abdominal pain	2	4%	1	2.9%	1	2%
Stomatitis	2	4%				
Neuropathic symptoms	2	4%				
	50 cases		35 cases		45 cases	

Symptomatology

b. Onset.

The following figures indicate as nearly as possible the period of time elapsing between onset of the first symptom and hospital admission.

Diagnosis	Number of Cases	Shortest Period Days	Longest Period Days	Average Period Days
Acute Lymphatic (LYMPHOCYTIC)	35	4	210	60
Myelogenous (NEUTROPHILIC)				
a. Acute	2	21	42	31.5
b. Chronic	4	21	821	293
Reticuloendotheliosis (MONOCYTIC)	2	6	35	20.5
Atypical	2	16	60	38
Entire Series	45	4	821	76.8

c. Clinical Symptoms previous to hospital admission.

Since the general symptoms of all varieties of leukemia are very much alike, the following analysis is of the entire series. Only those manifestations specifically stated in the history as being present are tabulated.

Analysis of Symptoms	Cases in which Present	Percentage of Occurrence
Asthenia	37	82%
Pallor	29	64%
Anorexia	24*	53%
Fever	16**	36%
Large abdomen	16***	36%
Rheumatoid pains	16	36%
Skin hemorrhages	13	29%
Epistaxis	12	27%
Cervical gland enlargement	12	27%
Cough - dyspnea	12	27%
General gland enlargement	10	22%
Abdominal pain	8	18%
Stomatitis	6	13%
Buccal bleeding	5	11%
Subcutaneous tumors	1	2%
Enlarged tonsils	1	2%
Pyuria	1	2%
Localized swelling	1	2%

* 16 had hemoglobin less than 50%.
** 8 had previous or associated infectious disease clinically demonstrable.
*** 4 occurred in myelogenous group.

Those underlined are considered by Ramsay to be the chief symptoms.

Physical Findings

Anaylsis of the physical findings at the time of hospital admission is likewise made of the entire series due to no significant differences between the various types. An attempt has been made to estimate the degree to which each is present. This is represented in the following table.

Analysis of Physical findings	DEGREE				Cases in which Present	Percentage of Occurrence
	Slight	Moderate	Marked	Extreme		
Pallor	-	15	18	3	36	80%
Splenomegaly	4	14	13	3	34	76%
General gland enlargement	11	18	3	-	32	71%
Hepatomegaly	-	22	6	-	28	62%
Cervical gland enlargement	5	16	5	-	26	58%
Enlarged tonsils	1	14	2	1	18	40%
Skin petechiae	2	8	4	-	14	31%
Buccal bleeding	3	5	-	-	8	22%
Stomatitis	2	5	2	-	9	20%
Localized swelling	1	5	1	-	7	16%
Retinal hemorrhage	-	2	1	-	3	8%
Scalp tumors	-	1	-	-	1	2%

Diagnostic Procedures

a. Blood Findings

The blood pictures for the cases of Acute Lymphatic (LYMPHOCYTIC) and Myelogenous (NEUTROPHILIC) Leukemias are tabulated separately. They represent findings at the time of hospital admission. Comparison is made with findings of Mills and Ramsay.

Acute Lymphatic Leukemia (LYMPHOCYTIC)

Analysis of Blood	U. of M. Hospital Series				Mills *** Aver. of 14 Cases	Ramsay ** Aver. of 70 Cases
	No. of Cases	Maximum	Minimum	Average		
Hemoglobin	35	85%	10%	36.8%	36.1%	31%
Erythrocytes	33	3,510,000	690,000	1,741,212	2,319,000	1,946,000
Leucocytes	35	1,254,000	900	61,426	6,507	210,245
Polymorphonuclears	34	65%	0	17.8%		
Lymphocytes	34	100%	30%	78.7%		
Monocytes	34	28%	0	1.4%		
Myelocytes	34	7%	0	0.3%		
Immature or atypical cells*	23	100%	0	24.7%		
Reticulocytes	14	11.1%	0.1%	2.9%		
Platelets	25	300,000	7,000	101,768		

* 12 additional cases were reported as having immature or atypical cells present, but no percentages were given. These are not included in the calculation.

** All cases were under the age of 8 years.

*** All cases were under the age of 13½ years.

Myelogenous Leukemia (NEUTROPHILIC)

Blood Analysis	U. of M. Hospital Series				Ramsay*
	No. of Cases	Maximum	Minimum	Average	Aver. of 19 Cases
Hemoglobin	6	68	20	47	31.8
Erythrocytes	6	3,830,000	770,000	2,320,000	2,114,800
Leucocytes	6	341,000	7,000	158,983	139,020
Polymorphonuclears	6	51	5	39.6	38.7
Lymphocytes	6	94	4	29.3	25.0
Monocytes	6	3	0	1.0	
Myelocytes	6	20	6	13.7	)
Promyelocytes	6	18	0	7.5	) 32.0
Metamyelocytes	6	15	0	5.3	)
Immature or atypical cells	6	45	4	14.5	
Stem cells	6	9	0	3.5	
Reticulocytes	1	-	-	2.0%	
Platelets	3	150,000	12,600	97,533	

* All cases were under the age of 8 years.

Summary of average values for blood findings in the entire U. of M. Hospitals series.

Blood Analysis	No. of Cases	Lymphatic Leukemia 35 Cases	Myelogenous Leukemia 6 Cases	Reticulo-endotheliosis 2 Cases	Atypical 2 Cases	Grand Average
Hemoglobin	45	36.8%	47%	66%	83.5	41.56%
Erythrocytes	41	1,741,212	2,320,000	2,750,000	-	1,880,000
Leucocytes	45	61,426	158,983	7,600	6,525	69,601
Polymorphonuclears	44	17.8%	39.6%	30%	41.8%	21.84%
Lymphocytes	43	78.7%	29.3%	71.5%	38.0%	70.49%
Monocytes	43	1.4%	1.0%	2.0%	-	1.22%
Myelocytes	43	0.3%	13.7%	-	-	2.09%
Promyelocytes	43	-	7.5%	-	-	1.0%
Metamyelocytes	43	-	5.3%	1.0%		0.76%
Immature or atypical cells	29	24.7%	14.5%	Present	Present	22.62%
Stem cells	43	-	3.5%	-	-	0.53%
Reticulocytes	15	2.9%	2.0%	-	-	2.93%
Platelets	30	101,768	97,533	81,500	-	99,993

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b. X-ray.

Diagnostic x-ray procedures were used in 36 cases (80%) of the group. In no instance were x-ray findings refuted by autopsy examination. Only negative x-ray findings were reported in 8 (22%) cases. Of these 8 with negative findings, 5 received no confirmatory autopsy examination; 2 had only very limited roentgenography; and 1, subjected to autopsy, showed no gross findings which might have been visualized by x-ray films. Changes demonstrable by x-ray which were considered to be consistent with leukemic disease were reported in 23 cases (51%).

The following table presents these findings.

X-ray Interpretation	No. of Cases in which reported	Autopsy Confirmation	Autopsy not Performed
Bony rarefaction	7*	4	1
Splenomegaly	6	4	2
Leukemic infiltration - bone	5	2	3
Leukemic infiltration - lungs	3	3	-
Mediastinal nodes	3	2	1
Hepatomegaly	3	2	1
Enlarged kidneys	3	3	-
Abdominal ascites	3	2	1
Increased mediastinal shadow	2	1	1
Thymic enlargement	1	-	1

* Examination of the bones was not reported in 2 autopsied cases.

X-ray changes which might or might not have been on a leukemic basis were reported in 5 cases. These are tabulated as follows:

X-ray Interpretation	No. of Cases in which reported	Autopsy Confirmation	Autopsy not Performed
Sinusitis	4*	-	2
Pneumonia	3	2	1
Lung congestion	1	1	-
Bronchiectasis	1	-	1
Bronchitis	1	-	1
Pleurisy	1	1	-
Thickened pleura	1	1	-
Osteosarcoma	1	1	-

* Examination of the sinuses was not reported in 2 autopsied cases.

In summary, considering all x-ray procedures with positive findings, 57% of the findings received autopsy confirmation and in 32% of the remainder post mortem examination was not made.

c. Biopsy Studies

Biopsy studies were made on 10 cases - 12 biopsy specimens being obtained. All of the cases having biopsy studies subsequently died with the exception of one in which the axillary node biopsy gave no positive diagnostic information. The following table presents the character of biopsy and its value as a diagnostic procedure.

Type of Biopsy	No. of Biopsies	Interpretation	
		Diagnostic*	Not Diagnostic
Lymph nodes			
a. Cervical	2	2	
b. Axillary	4	3	1
c. Inguinal	2		2
Bone marrow	1		1
Pleural fluid	1		1
Skull tumor	1	1	
Leg tumor - aspiration	1		1
TOTAL	12	6	6

* Of the six cases with diagnostic findings, five were verified by autopsy findings.

Seven of the 10 cases subjected to biopsy study later received autopsy verification of the diagnosis.

Course of the Disease

The following table represents the mortality and duration of the disease from the onset of the first manifestation to death in those cases.

Type of Leukemia	Deaths		Days Duration		
	No.	%	Maximum	Minimum	Average
Lymphatic (LYMPHOCYTIC)	27	79	273	20	109.7
Myelogenous (NEUTROPHILIC)	3	9			
a. Acute	2		135	48	91.5
b. Chronic	1		-	-	489
Reticulo-endotheliosis (MONOCYTIC)	2	6			
a. Reticulosarcoma	1		64	-	64
b. Leukemic Reticuloendotheliosis	1		-	12	12
Atypical	2	6	171	18	
Entire Series	34	76	272	12	114.7

As stated above 4 cases of chronic myelogenous leukemia (NEUTROPHILIC) were observed. Of these, 2 are being followed regularly in the Outpatient Department, receiving deep x-ray therapy as indicated, and showing satisfactory progress. In each of these the period from onset of the first manifestation to date is over 2 years. One case of Acute Lymphatic Leukemia of only 2 months' duration was discharged from the hospital April 29, 1938, being given a hopeless prognosis. The 8 remaining cases which were also discharged from the hospital with a hopeless prognosis have not returned and the duration of their course is not known.

Autopsy Findings

Twenty-six cases (58% of total number) were subjected to post mortem examination. Anatomical changes observed at necropsy were quite similar in all types of leukemia. The essential difference was primarily one of degree and type of predominating cell found. A brief analysis of leukemic changes ap-

pearing in the autopsied cases is shown in the following table.

Pathological Changes	No. of Cases
Leukemic infiltration	
a. Liver	15
b. Kidney	13
c. Spleen	12
d. Lungs	6
e. Lymphoid tissue	5
f. Heart	2
g. Thymus*	1
h. Adrenals	1
Multiple hemorrhagic areas	15
Bone marrow involvement**	8
Generalized lymphoid hyperplasia	5
Multiple tumors	1

* 3 additional cases showed marked thymic atrophy and 1 thymic hyperplasia.

** 2 additional cases showed marked bony atrophy.

In addition to the above, 11 cases showed changes of an infectious nature. Tabulated results of these findings are as follows:

Pathological Findings	No. of Cases
Pneumonia	4
Bacteria in internal organs	2
Pericarditis	2
Miliary abscesses	1
Pleurisy	1
Otitis media	1
Perisplenitis	1
Perihepatitis	1
Septicemia	1
Multiple superficial abscesses	1

CASE REPORT

The following case is presented because of its rapid course, the questionable blood findings, the unusually high blood calcium, and the obscurity of diagnosis.

____ - Eight and one-half year old girl.

Admitted to the Pediatric Service in the Minnesota University Hospitals July 25, 1937 and expired August 23, 1937 after 29 days of hospitalization.

The girl had been perfectly well until mid-June, 1937, six weeks prior to admission, when decreased activity and increased irritability were first noted. About July 1, 1937 she developed a mild upper respiratory infection following swimming, which improved spontaneously within a few days. Anorexia was noted from that time on. At this same time backache was noted for the first time and continued to admission. Vomiting, weight loss, rheumatoid pains in the knees, painless swelling over the left tibia, and several painless subcutaneous tumors over the scalp all developed during the two weeks previous to her entry.

Past history.

She had measles at 2 years, scarlet fever at 3 years, and pneumonia at 7 years (autumn, 1936). Her general health had been good until onset of her present illness.

Family history.

No similar illness in the family. Father and mother were 58 years and 53 years respectively, and had good general health. An aunt and grandmother had died of tuberculosis.

Physical examination at the time of admission revealed a poorly nourished, irritable girl of stated age. Three subcutaneous tumor nodules varying in size from 1 cm. to 3 cm. in diameter were present over the skull. The eyes, ears, nose, mouth, neck and lungs were negative. The heart was not enlarged, but a loud systolic murmur was present, heard best in the mitral region and transmitted to all areas. Liver and spleen were not palpable. A moderately firm, nontender, soft tissue mass about 4 cm. in diameter was present over the distal portion of the left tibia. There was no general glandular enlargement.

The laboratory findings are best presented in the following table:

	7-25-37	7-26-37	7-28-37	7-29-37	8-4-37	8-6-37	8-7-37	8-11-37	8-18-37
Hemoglobin	90%			74		33			
Erythrocytes				3,500,000		2,670,000			
Leukocytes	12,200			11,000					6,100
Neutrophils	58					63			49
Lymphocytes	40					35			45
Metamyelocytes									2
Monocytes	2					2			4
Platelets	148,000					99,200			
Blood sugar		145 mg.					86 mg.		
Serum calcium		20 mg.	19.8 mg.		21.2mg.	24.6mg.	22.6mg.		
Blood phosphorous		4.5mg.			2.9mg.	2.95"	2.31"		
Plasma sodium							288.9mg.		
Plasma potassium							9.09"		
Plamsa magnesium							0.88"		
Plasma chlorides							324.4mg.		
Total Plasma protein			5.9 mg.				4.67mg.	5.0mg.	
Plasma albumin			3.2 mg.					2.8mg.	
Plasma globulin			2.3 mg.					2.2mg.	
CO_2 combining power							52.6 vol./%		
Sed.rate				80 min. in 30 min.					
Plasma N.P.N.							3.27mg.	32.7mg.	

Blood smears examined by the University Pathology and Hematology Departments were interpreted as showing no leukemic changes. The phosphatase activity was within normal limits, 3.15 units per 100 cc. of serum. Rabbit inoculations of the patient's blood gave normal parathormone reaction.

X-ray examination showed moth-eaten destructive lesions with no evidence of new bone formation involving skull, vertebrae, right humerus, right scapula and left fibula. The impression was leukemic infiltration. The upper ends of the femur were also involved. Enlarged kidneys were disclosed by intravenous pyelography. The right hilus shadow was increased. Some infiltration involving the upper lobes of both lungs was noted.

Biopsy from nodule on the scalp showed a heavy infiltration of a uniform type of monocytic cells, some of which showed mitotic figures, around spicules of bone. The conclusion was leukemic infiltration of periosteum.

In spite of repeated transfusions and other supportive measures, the patient grew progressively worse and expired with terminal bronchopneumonia. Duration from onset of first manifestation to death was 64 days.

Autopsy findings revealed multiple tumors of the skull, pancreas, vertebrae, ilium, and leg, all of similar nature. Microscopically they consisted of small hyperchromatic round cells arranged in broad sheets. A dense fibrous stroma was present. No evidence of leukemia was seen in the bone marrow, liver, or spleen. The kidneys showed extensive calcification of the tubules of both cortex and medulla. Similar calcification in areas of the lungs was present in addition to patchy areas of pneumonia.

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