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Acute leukemia

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SENIOR THESIS

A C U T E L E U K E M I A.

Presented By

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INTRODUCTION.

The term "leukemia" has been applied to certain hematological conditions which are characterized by the persistence of an abnormal type of leucocytosis associated with leucosis (an idiopathic proliferation of leucocytopoietic tissue). Leukemia means "white blood" therefore scientifically speaking it is not a suitable term, for the essential feature of the disease is the alteration in the qualitative composition of the blood rather than the increase in the number of leucocytes. The classification[46] should be based on changes occurring in the hematopoietic tissues rather than upom the alterations in the circulating blood which are purely symptomatic.

Leucosis,[46] a character which is common to all forms of these maladies, is the morphological basis of leukemia. The leucosis involving the bone marrow might well be called "myelosis" and that which manifests itself in the lymphatic tissue, "lymphadenosis". This terminology is correct but is far from being in universal usage. Perhaps, when more is known about the disease, the chapters will be rewritten under the heading of leucosis rather than leukemia.

HISTORY.

Clinicians of the early part of the nineteenth century observed and commented upon cases in which the blood in gross had a purulent character. They interpreted this as an obscure suppurative "hematitis". Bennett, in October of 1845 recorded a case of "suppuration of the blood" a great and persistent increase in the number of colorless corpuscles associated with massive enlargement of the spleen and liver. He noted at autopsy that the condition was not associated with any acute inflammation of the blood vessels or blood forming

organs. He called the disease "leucocythemia".

A month later Rudolf Virchow described a similar condition of "white blood" to which he gave the name, "Weisses Blut" or "Leukemia". Later on he noted that the cases fell into two clinical groups, one in which glandular enlargement was the marked feature, while the other was characterized by splenomegaly. Neither one distinguished any qualitative change in the white blood cells from those of sepsis. Undoubtedly the cases of both observers were those of the chronic variety.

The first case of acute leukemia was recognized and reported by Von Friedrick in 1857. The patient died shortly after the onset. In 1870 Neumann noted and determined the importance of changes in bone marrow in the recognition of the disease. Ebstein in 1889 described the clinical picture and Frankel in 1895 drew special attention to pathological changes of the blood.

Up[21] until about 1904 most observers maintained that there was no such thing as myeloid leukemia and that the conditions were all lymphemias. This was due to the fact that blood stained films gave impressions that the specimens were composed of large lymphocytes. By a method of differential staining of leucocytes (granular and non-granular) Ehrlich was able to classify the varieties of the disease according to the type of the cell instead of on a clinical basis which was formerly used. It is upon this basis that the dualistic theory of the origin of blood cells was founded.

According to the Ehrlich dualistic theory which is the basis for myeloid and lymphoid leukemia,[42] all leucocytes are divided into two main groups, the granulocytic and the non-granulocytic. The cells of the former have their origin in bone marrow of the latter in the lymphoid tissue. If the cells thus determining the diagnosis

of leukemia are of the young or immature granulocytic type, the leukemia is classed as myelogenous and if they are of the young non-granulocytic it is classed as lymphoid.

Schilling recognizes a triple origin of leucocytes. He adds a third group the reticulo endothelial system from which arises the monocyte. He also recognizes a third variety of leukemia, the monocytic, hence matters are made more complicated. Hematologists will not be able to differentiate monocytic leukemia until the origin of the monocyte has been settled plus a certain means for the identification of this type of cell.

According to Pappenheim[42] who is the chief exponent of the unitarian theory of the origin of leucocytes, all leucocytes have their common origin in one cell--the large lymphocyte and by a process of special differentiation we get the two main classes of cells, granulocytes and non-granulocytes. Pappenheim calls attention to the fact that in some of the lower invertibrates which possess neither bone marrow nor lymph glands--agranulocytes and granulocytes are still found in the blood. If one studies the mature cells he will be more liable to accept the dualistic theory of the origin of leucocytes, but if he is given more to the study of the immature or more embryonal type, he is more likely to favor the unitarian theory.

ETIOLOGY

There are no predisposing factors to the disease that are known. Hereditary influences must be disregarded because there are only a few instances of family occurrence reported and these are so imperfectly described that they are of no value. The etiology of the disease is not definitely known but several theories have been advanced which are well worth giving consideration.

The first theory and the one that seems to be favored by most authorities is that of "Infection". The infectious theory of leukemia is supported by the fact, that the acute type of the disease runs a course strongly suggestive of an acute infection, high fever, prostration, tendency to hemorrhage and fatal termination also because it is so frequently associated with dental and tonsillar infection, ulcerative and necrotic changes in the mucous membranes of the mouth and pharynx. The increase of leucocytes and the abnormal forms that are found in circulation may represent the response of the hematopoietic organs to infection. A number of organisms have been found in association with this disease, streptococci, staphlococci, diphtheria, diphtheroids, typhoid-colon group and Vincent's organisms. It is generally accepted though, that no known microorganism is responsible for the disease. Vincent's organisms are the most common of those found in the oral cavities of acute leukemic patients especially if there is any necrosis of the mucous membranes, but these organisms may be found in any condition of the mouth where sloughing is taking place. It is evident therefore that if acute leukemia is due to an infection, either the causative organism has not been found or the disease represents an unusual and abnormal reaction on the part of the bone marrow which may be induced by a variety of microorganisms. The view that leukemia is due to an infection has been strongly supported by Ellerman and Bang[42] who have performed a number of experiments on animals. Leukemia is not as uncommon in the dog, cow, horse, and fowl as it is in the human. These two investigators found that they were able to transmit the disease from bird to bird not only by the injection of whole blood but also by using cell free serum. It is doubtful whether the disease transmitted in the fowls is true leukemia for Schupfer injected the blood of human leukemia into four patients suffering from cancer who lived for varying lengths

of time without developing leukemia.

Gordon[44] noted in normal human beings and in cases of septic infection that the administration of a leucocyte stimulant such as sodium cinnamate or nucleinic acid, is followed by a polynuclear leucocytosis without primitive forms. This does not occur in leukemia. Similarly, the injection of T.A.B. vaccine gives rise to an increase in the antibody titre to these organisms, in leukemia this is absent. Primitive granular cells do not appear to be phagocytic or to be capable of forming antibodies. Thus the explanation of the sloughing throat and other septic manifestations of leukemia appear to be due to the fact that the bactericidal properties of the blood are so markedly diminished that streptococci and other strains of bacteria gain an easy foothold on the patient. Sepsis would thus seem to be the result rather than the cause.

The second theory as to the etiology of acute leukemia is that it is a malignancy of the hematopoietic system. There is an unrestrained growth of certain cells differing from the ordinary neoplasm in that it has no local origin but arises from all the tissues belonging to a certain system. There is usually hyperplasia of the bone marrow, splenic pulp, lymphoid tissue and the reticulo-endothelial system throughout the body. This hyperplasia and to some extent metaplasia that occurs in leukemia may be the primary conditions caused by the same possible agents that are responsible for malignant growths or "cancer" in other tissues. When malignant cells have multiplied in great enough numbers to poison the blood stream, a state of cachexia supervenes, there is a marked lowering of the resistance of the tissues to infection so that most any organism might act as a secondary invader.

Transitions to localized tumors do occur, as chloromata are not

infrequently associated with leukemic blood pictures. Myelomata may be made up of myeloblasts and myelocytes but their blood picture is not always characteristic and their new growing tissue is circumscribed rather than generalized. In an analogous relation to the acute lymphatic leukemia stand the lymphosarcomata. The theory that acute leukemia is a malignancy is very logical except for one thing, and that is the clinical history, the patient's health has usually been good up until the sudden onset, which is severe and stormy. This is not characteristic of cancerous conditions. If the disease is a true neoplasm it surely represents one that is very malignant.

A third possible theory is that leukemias are due not to malignancy nor to specific infection, but to a special condition precipitated by an infection or by an abnormal metabolic state. The sloughing of mucous membranes of the mouth associated with the disease would suggest the possibility that necrotic mucous membranes may contain toxic substances which are the causative agents.

Trauma associated with infection is also mentioned by some authors as a possible etiological factor. Simon[14] reports a case of a leukemic blood picture following bone trauma. His theory is that extensive destruction of red marrow plus infection might lead to the stimulation of bone marrow at large with a resultant functional hyperactivity and mechanical discharge of bone marrow elements into the circulation.

Occurrence.

Acute leukemia occurs more frequent than older statistics would indicate, due in part to the fact that there is a greater frequency with which blood examinations are being made so that fewer cases are passed up unrecognized. Very often however patients are first seen in the terminal stages of chronic leukemia when the clinical picture

is that of an acute leukemia and the diagnosis is thus erroneously recorded. Cabot[41] says that the disease is about five times as rare as pernicious anemia and about as rare as myxedema.

The disease occurs more frequently in the young males than in the females. They predominate in a ratio of about 3 to 1 throughout. But at the menopause age the ratio is reversed, with three females to one male, thus showing that the disease has a predilection for females at the menopause.

Stafford Warren,[21] in the study of the age incidence of 113 cases reported in literature since 1917, reveals that the disease is particularly apt to occur at three different periods in life, namely from birth up to 10 years of age, between 25 and 35, and 45 and 56 years of age. The lymphatic type occurs more frequently in children and infrequently in adults, while the myeloblastic type has its greatest incidence in adults.

CLASSIFICATION

The acute leukemias are to be separated from the chronic forms by reason of their stormy onset, rapid course, peculiar blood picture and their resemblance to an infectious disease. The dividing line between the two is not always a sharp one for subacute cases occur thus bridging the gap between those cases that are typically acute or chronic. The blood picture, clinical findings and course differ perceptibly in the two chronic varieties, but in the acute leukemias there is often no appreciable difference either in the clinical or laboratory findings. Hematologically, there are two types of acute leukemia, "Myelogenous" and "Lymphatic", clinically, there is one, for the two are identical--same symptoms, course and fatal termination. The differentiation of the two acute forms rests entirely on the blood picture and even then a differential diagnosis

can not always be made with certainty.

CLINICAL HISTORY AND SYMPTOMATOLOGY

The following data on the clinical history and symptomatology includes that which may be encountered either in the acute myelogenous or acute lymphatic leukemia, being just as much characteristic of one form as the other.

In acute leukemia there may be a prodromal period during which many apparently unrelated symptoms are noted. In general however, the onset is quite sudden following some infection such as an abscessed tooth, tonsilitis, stomatitis or a furuncle. Not infrequently there is a history of a respiratory infection, sometimes classified as a "cold", La Grippe or bronchitis which fails to respond to treatment and is recorded as "hanging on". There is usually more prostration than there is reason to expect and the severity of the symptoms usually remain unexplained until the leukemia is recognized.

Prostration is usually extreme associated with, high fever, headache and general malaise. The patients may complain, of swollen, spongy gums showing a marked tendency to bleed, or of tonsilitis. The tonsils are enlarged and very often necrotic or gangrenous. This necrosis or gangrenous area may be either generalized or localized in the mouth. The regional glands of the jaw and neck become rapidly enlarged. The general picture of the patient is similar to that of an acute infection hence a reason that the true nature of the process is so often unrecognized and the glands are incised for drainage. Frequently a patient consults a throat specialist because of sore throat and tonsilitis. If the leukemia is unrecognized the tonsils may be removed and following this there is a severe prolonged hemorrhage because of the marked decrease in blood platelets. The same disaster is occasionally met with following dental extraction. Pallor,

swollen gums and pyorrhea should always arouse a suspicion of a leukemic process and suggest a differential blood count.

The symptomatology is not typical in every case. Some of the various types that are most frequently met with, are as follows:

(1) Severe ulcerative or gangrenous processes in the mouth with but little tendency to hemorrhage and with little or no lymph gland or splenic enlargement.

(2) Cases in which the most striking feature is the hemorrhagic diathesis suggesting the symptom complex, purpura hemorrhagica, morbus maculosus Werlhofii (with hemorrhage into the skin and mucous membranes of nose, stomach, rectum and vagina).

(3) Less severe cases where lymph gland and splenic enlargement are the salient features.

(4) Rarer cases where there is evidence of only a high fever and a high degree of anemia without any of the foregoing symptoms.

Physical Examination--General appearance is that of extreme toxemia--ghastly pallor with blanched lips and conjunctiva, the skin often being mottled with livid discolorations.

Eye--Ophtalmoscopic examination may reveal retinitis. Retinitis associated with leukemia may not present characteristic appearances. When changes are present both retinae are usually involved. The important ophthalmoscopic findings are slight swelling of the papilla, pallor of its surface, veiling of its edges and some opacity of the retina especially along the lines of the vessels--hemorrhagic retinitis, the latter is often quite characteristic. The veins are broad, distended and rose red in color in contrast to the arteries which are narrow and orange yellow substituting the ordinary fiery red tint. In the region of the macula lutea and near the equator prominent lesions are often noted in the form of white spots with red borders

varying in size and elevation. These white spots are due to leukemic infiltrations or the collecting of lymph corpuscles, the red border to an extravasation of red blood cells. These lesions may simulate those produced by albuminuria. In leukemia, albumin is always very apt to be found in the urine, but the true nature of the disease can be revealed only by a blood examination.

Ear--Deafness is not common in the acute form of the disease, when present it is associated with Ménière syndrome--hemorrhage into the labyrinth. Veasy[37] says that texts lay stress upon leukemic involvement of the labyrinth or the auditory nerve and barely mention or even omit middle ear deafness. He reports a case of lymphatic leukemia with bilateral deafness, there was an increase in bone conduction and greater impairment for low tones with no Eustachian involvement. The cause in this case was due to cellular infiltration in the middle ear.

Cranial Nerves--There may or may not be any cranial nerve palsies. If present they are usually due to leukemic infiltrations of the nerves, and are present in the cases that run less acute courses. Cerebral hemorrhage is a rare complication, occurring for the most part in young males in the very acute cases. The spinal fluid[29] is usually normal except in acute cases of hemorrhage and in cases showing neurological signs from leukemic infiltrations of nerves and cord. If immature cells such as myeloblasts and myelocytes are found in the spinal fluid, it is almost diagnostic for leukemic paraplegia.

Mouth--The fetid, dirty, sloughing, gangrenous ulcerations in the mouth and throat constitute one of the terrible features of the disease. This necrotic slough is very foul smelling. The necrosis may extend deep producing noma with subsequent severe hemorrhages. One case is reported in literature where necrosis and erosion involved

the carotid artery with subsequent death from hemorrhage. The adenoid tissue of the tongue and pharynx are involved with great regularity. The regional glands of the neck are practically always enlarged when there is any involvement in the mouth. The glands are usually quite tender. There are of course exceptions where there is no oral involvement.

Lungs--May show signs of passive congestion or bloody pleural effusion from myocardial weakening.

Heart--Presents the findings of secondary anemia--hemic murmurs. Pericaridal effusion and even pericarditis is not uncommon.

Liver and Spleen--may or may not be much enlarged and massive enlargement is very rare in contrast to that of the chronic leukemias.

Gastro-Intestinal tract--Bowel hemorrhages occur with frequency. The entire tract may be involved or the hemorrhage may be more localized in the upper intestinal tract - in the stomach or in the lower bowel and rectum. The hemorrhage is usually from the smaller vessels in the mucosa, the bleeding is slow, in the form of a constant ooze. Vomiting and severe diarrhea are often very troublesome.

Genito Urinary tract--Of all symptoms and findings in acute leukemia in the male, priapism is the most uncommon in contrast with the chronic forms where it occurs frequently. When it does occur it may be an expression of paraplegia or myelocytic and lymphocytic infiltration of the corpus cavernosum of the penis. In the female bleeding from the uterus and vagina may occur with or unassociated with menstruation. Gwyn[23] reports a case in a girl aged twenty where acute renal pain and hematuria were the beginning symptoms, shortly followed by persistent vaginal bleeding. The girl died on the tenth day.

Acute leukemia in pregnancy[47] does not exert any direct effect upon gestation, though the association of the two conditions may seriously affect the mother. In several instances premature labor has been reported. Examination of the foetal blood indicates that the characteristic leucocytes are not transmitted to the foetus. Ward[17] reports, in the study of a series of fifteen cases of leukemia in pregnancy, that none of the children were leukemic except for one, a chronic case where the whole family was leukemic.

Bones and Joints--The bone may be sensitive to pressure. Tenderness over the sternum is observed frequently. This is probably due to extensive mediastinal glandular involvement. Seward[33] reports a case of leukemia with the unusual symptoms of severe pain in the joints. Physical examination and laboratory findings at autopsy confirmed the diagnosis of leukemia. The pains were very irregular and varied from one joint to the other. The hemorrhagic tendency was marked with petechiae, epistaxis and bleeding from the gums. The cause of joint pains was undertermined. Possible causes were: (1) Lymphocytic infiltration in the heads of the long bones--not probable; (2) Effusion of blood into synovial membranes or joint cavities. But the pain subsided quicker than one would expect in effusion of blood into the joints--the autopsy did not reveal this. The bone marrow was packed with lymphocytic tissue, grayish yellow in color. The synovial membranes of the joints were normal.

Skin--In the acute leukemias the skin manifestations are variable and not characteristic probably because of the short duration of the disease before death takes place. The skin may show occasionally, petechial hemorrhages, occasionally leukemic nodules and rarely actual areas of necrosis. In a review of sixteen cases of acute or subacute leukemia cutis, Hazen[16] found that the cutaneous manifestations con-

sisted of petechiae, nodules, vesicles, bullae, papules, maculopapules, pustules, hematomas and tumors.

LABORATORY AND SPECIAL TESTS.

Basal Metabolism--The basal metabolism is increased in both the myeloid and lymphoid type often approaching the high mark of severe types of thyroid disease. Gunderson,[43] Boothby and Sandiford in the study of thirty-five cases reported the B.M.R. ranged between 6 to 80 percent above the average normal. A general tendency was noted for the highest B.M.R. to be associated with the highest leucocytosis although many high B.M.R's were noted with low white counts. The basal metabolism seemed a truer indicator of the severity of the process than the blood count. In some cases a rise in the B.M.R. foretold an approaching increase in white blood cells. The increase in metabolism may be due to some toxic substance not yet discovered or to some internal secretion of the hematopoietic system. It is quite possible that there may be some specific effect on the thyroid gland. Minot and Means in a recent analysis of the pulse rate in leukemia have proved that the increase in heart rate in the blood disease for a given increase in the metabolic rate is just the same as in exophthalmic goitre. In other words a leukemic patient with a B.M.R. of a +50% has about the same pulse rate as a Basedow patient with a B.M.R. of +50%.

Graf in 1911 cites the importance of the young blood cells as chief factors causing an increase in metabolism because of an increased oxygen consumption of the blood itself.

Urine--The urinary findings are not constant. Very often the urine is bloody, casts and albumin are usually present in the majority of cases.

Blood Culture--In acute leukemia the blood is usually sterile, later on however it may show the presence of a secondary invader.

Blood Chemistry--Owing to abnormal quantities of myeloid or lymphoid cells which are being formed and broken down in leukemia, there is an increased liberation of the products of nucleiproteid destruction, purins uric acid and xanthine. Proteoses and amino acids are produced by the enzymes present in the granulocytes hence more abundant in the myeloid than the lymphoid form. Since there is an exceedingly high protein metabolism the N.P.N. and uric acid are very apt to run quite high.

BLOOD PICTURE.

The blood picture of the acute myelogenous and acute lymphatic leukemia is not always characteristic of that specific type for not infrequently one type is apparently superimposed on the other or they are inseparable.

From a review of literature and case histories on blood findings in acute leukemia, it is clear in the majority of the cases, that there are the two hematological varieties, myeloid and lymphoid distinguishable only by the leukocytes.

Myelogenous Leukemia.

The red blood cells as a rule show a marked anemia. There is a rapid and progressive fall of the total red cell count and hemoglobin. Anicytosis, poikylocytosis and polychromatophilia are variable. In the very acute cases basophilic granulations, normablasts and megaloblasts may be present. At the very beginning and even during the course of the disease, there is often a resemblance to pernicious anemia, that is of course, during the subleukemic phase. The platelets are reduced early in the disease and toward the end greatly diminished, thus accounting for the hemorrhagic diathesis.

Leucocytes--Coincident with the onset of the symptoms there is a subleukemic phase in which the count is only several thousand. This subleukemic phase may be a result of a spontaneous change or a complicating infection. Following this, the white blood count rapidly rises in the course of a few days often to two or three hundred thousand, even as high as one million per cu. mm., though usually not as high as in the chronic type. In the myeloid variety, the predominate cells are the myeloblasts, premyelocytes and myelocytes. The stained blood film often is misleading in that the specimen may seem to be composed of large lymphocytes thus a case of acute lymphatic leukemia is suspected and until quite recently most all of the acute leukemias were thought to be lymphatic.

By careful study of the various immature cells many may be found to contain variable amounts of fine neutrophilic granulations--these represent the transition stages between the myeloblast and the myelocyte. Mature adult neutrophiles are quite scarce. Neutrophilic granulations are poorly developed and even absent in many of the cells. The frequent absence of eosinophiles and basophiles and the abnormal indentations in the nuclei of the myeloblast (so called Rieder cells) are other evidences of rapid atypical cell growth. The myeloblast and lymphoblast are so similar that one is often mistaken for the other.

Some hematologists attempt to differentiate the two on certain fine morphological characteristics of the nucleus, for example, the myeloblast is a large mononuclear cell with basophilic protoplasm, with a light azure staining nucleus containing four or five nucleoli. The lymphoblast differs from the cell in that the protoplasm is less basophilic and the nucleus is darker containing three to four nucleoli. This method is not always reliable, because there are so many cellular variations and bizarre forms that it is often impossible to distinguish

one type of cell from another.

Changes[21] in the appearance and number of the white blood cells during the course of the disease may cause confusion in the diagnosis, for in many of the cases at the onset of the disease, the blood smears have shown large numbers of granular myelocytes and a few large atypical non-granular mononuclears. Later on the situation reverses until finally, the myelocytes have almost disappeared and the large non-granular forms have predominated. Myeloblasts cannot readily be distinguished from immature lymphoid cells except by some differential staining method like that used by Sabin-Supra-Vital Staining.

Various criteria,[27] such as the structure of nuclear chromatin, the number of nucleoli, the intensity of staining of nucleus and cytoplasm, have been laid down, but the application of these standards to an isolated mono-nuclear cell is usually unsatisfactory. In many cases the presence of more mature cells of the particular series enables one to decide as to the identity of the more primitive and less differentiated cell. But there are certain diseases of the blood forming tissues, such as glandular fever and acute myeloid leukemia, in which there is only one type of mono-nuclear cell present, and it is in these cases that supra-vital staining is of most value.

By supra-vital staining is meant the application of certain dyes, notably neutral red and Janus green, to living blood cells. The dye which is so diluted as not to impair the vitality of the cell, is taken up in a characteristic way. The Janus green stains the mito-chondria which are present in the cytoplasm as small rod and coccus like bodies. The mito-chondria which are present in the cytoplasm are particularly in evidence in growing cells and are characteristic in certain cells with regard to number, distribution and arrangement.

Myeloblasts can be discriminated in Sabin's supra-vital technique

by the great numbers of tiny mitochondria in the cytoplasm and the absence of any other vitally stainable substance.

Sabin[20] has demonstrated by the supra-vital staining method that the lack of ameboid activity of the myeloblast and myelocyte is an important point in discriminating them from leucocytes. By this method the three stages in the maturation of myelocytes can be correlated. It is interesting also to note that Sabin points out that there is a variation in the size of the myeloblasts, from a cell whose diameter is more than twice that of a red blood cell to one even smaller.

The myeloid nature of the white cells is also revealed by the "Oxidase Test" which was perfected by Graham Sato and Yoshimatsu. In short the principle of the test is as follows: When an aqueous solution of alphanaphthol and dimethylparaphenylendiamine come in contact with an oxidizing agent, a blue substance--indolphenol is formed. Thus when these solutions are applied to a cell of the myeloid type the oxidizing "ferment" or enzyme in these cells sets free the reaction, and indolphenol is formed in the cells containing the oxidase, in the form of blue granules. Lymphoid cells or tissue are not endowed with these properties. In the large lymphoid like cells in acute leukemia where a diagnosis cannot be made morphologically it is a very conclusive test if positive. If the oxidase test is negative it is not at all conclusive and is of little value, because the more embryonal the myelocytes are, the more they tend to react oxidase negative.

Lymphatic Leukemia.

The blood picture will very often simulate that of an acute myelogenous leukemia. The red blood count and the hemoglobin will show the same progressive anemia. The platelets will be diminished in proportion to the severity of the disease.

The white blood count may be subleukemic at first, then followed by a marked increase in the total number of cells paralleling the myeloid variety. The differential will show an increase in the percentage of lymphocytes which may vary from 50-99%. The immature and abnormal forms of lymphocytes are characteristic. The lymphocytes are usually large, having pale staining nuclei and indented Rieder cells. The cytoplasm is agranular. Neutrophiles and eosinophiles are greatly reduced. Myelocytes are seen rarely. The oxidase stain is always negative but a diagnosis could not be made from this test because certain myeloid forms show a negative oxidase reaction.

The differential diagnosis of the acute myeloid from the acute lymphoid leukemia is of little clinical importance, for they are almost identical clinically. It is to the hematologist and scientific observers that they are of a great deal of interest. Differentiation of the two when possible, is made only by a blood examination. In the myeloblastic type, the stained smears, as mentioned previously, show a predominence of myelocytes, premyelocytes and myeloblasts. The acute lymphatic variety on the other hand shows a predominence of lymphocytes, large and small transitionals with but few if any myelocytes and myeloblasts. In the cases of the acute lymphoid leukemia where every cell may be a myeloblast or lymphoblast it is often only possible to make a positive diagnosis at autopsy by a final histological study of the tissues. Primitive myeloblasts in the myeloid variety may not show any reaction to the oxidase test, because this "ferment" fluctuates with the maturity or immaturity of the cell, so a negative test is of little value. The differentiation by nuclear morphology is also uncertain and not convincing.

DIAGNOSIS.

The diagnosis is very often difficult to make because of the

rarety of the disease and because of the misleading symptomatology.

Definite proof of acute leukemia[49] is made by demonstrating or proving the following postulates:

(1) An aleukemic or subleukemic stage which is demonstratable only very early in the disease.

(2) Characteristic blood pictures with embryonal white cells, large mononuclears with various transitional forms.

(3) An acute downward course with death ensuing in several weeks to four months.

(4) Typical gross and histological findings in bone marrow, spleen, liver and lymph glands at autopsy.

(5) Myeloid and lymphoid nature of the cells as determined by aid of the oxidase test and supra-vital staining.

A criticism of this is that there are only a few cases on record that would pass a censorship so strict as that outlined above. I believe that there are only about seven cases authentic in literature up to 1903 that fulfill the postulates.

In many excellently studied cases of acute leukemia, conclusive proof is lacking because of the failure of making a complete autopsy with histological study of the liver, spleen and bone marrow. Marked definite myeloid or lymphoid changes in these organs must be demonstrated microscopically in order to prove the identity of the disease. Slight changes are not sufficient because in ordinary severe anemias there are often small amounts of proliferative changes.

Herz admits that acute leukemia is invariably a fatal malady but he does not think that the diagnosis should rest solely on the fact whether the patient recovers or dies, for there is that possibility that a patient might accidently recover.

Prognosis and Clinical Course.

The course of the disease is very stormy from the onset with an increasing tendency to hemorrhage, high fever, increasing prostration and anemia with a fatal termination within a few days to three or four months. The most usual duration is from six to eight weeks. Cases in which the disease lasts as long as a half a year, pass into the category of chronic leukemia. It is not the duration so much as it is the mode of onset that determines how acute it may be.

The prognosis is always bad for death always occurs without exception. The sole factor in the prognosis is the exclusion of chronic leukemia.

Differential Diagnosis.

Because of their rapid onset, cases of acute leukemia often confuse the clinician with acute infections. Some of these diseases that acute leukemia may be mistaken for and which must always be considered in making a differential diagnosis, are: diphtheria, quinsy, sore throat, ulcerative stomatitis, scurvy, gumma of the tonsil, sepsis, acute bacterial endocarditis, chronic leukemia, tuberculous lymphadenitis, typhoid, lymphosarcoma, psuedo-leukemia, pernicious anemia, purpura hemorrhagica, chloromata, morbus maculosus Werlhofii, acute infectious mononucleosis and agranulocytic angina.

If the clinician has a fair knowledge of the usual clinical and laboratory findings met with in these various diseases, and if he thoroughly works up the cases, by obtaining careful histories, does complete physical examinations and utilizes all of the possible laboratory resources, and if he is able to correlate the clinical and laboratory findings, he should be fairly accurate in arriving at a correct diagnosis in the majority of cases.

PATHOLOGY.

The lesions of the acute resemble to a certain degree those of the chronic form except that the tendency to hemorrhage from the mucous and serous membranes and into the organs is much more pronounced in the acute form. The enlargement of the lymph glands and spleen is less and often slight, probably due to the short duration of the disease. Masses of lymphoid tissue occurring in the mediastinum retroperitoneal glands, thymus or abdominal orgams have been noted in a few cases to be so large as to suggest the presence of metastatic tumors. Massive local accumulations are not the rule however, but diffuse hyperplasia of the lymphoid or myeloid structures everywhere is always present to some extent and may produce changes in any of the organs and tissues. Hemorrhages into organs, serous cavities, brain and meninges are common. The adenoid tissue of the tongue and pharynx are involved with great regularity.

Myeloblastic Variety.

During the last few days before and at the time of death a condition simulating a lipaemia may exist, the blood serum being opaque and milky. This has been mentioned as an occasional cause of milky blood. The condition is not a lipemia but rather a pseudo-lipaemia because the substance present is not fat but a proteo-lipoid soluble in alcohol but not ether.

The spleen, liver and lymph glands usually show moderate enlargement not marked though as is the condition in the chronic form. Upon opening the glands a green tint is often noted which is evanescent in character. The bone marrow is usually red to grayish in color, rarely is a normal yellow fat marrow encountered and the small nodules occasionally seen in lymphatic leukemia are never observed.

Abnormal bone marrow activity is strongly evidenced by the varia-

tion of the white cells. A microscopic examination shows a suppression of lymphoid elements but reveals a diffuse extensive hyperplasia of the bone marrow (myeloblastic) elements in the spleen, lymph glands, bone marrow, liver, nerves or any organ that is involved. The myeloblasts and myelocytes are the predominate cells. The capillaries of the liver are distended with bone marrow cells, there is also infiltration of the periportal tissue.

Lymphoblastic Variety.

Only slight variations are noted from those of chronic lymphatic leukemia. The spleen, liver and lymph glands are enlarged. Small grayish leukemic nodules may be observed in various organs of the body. The bone marrow is increased and reddish in color, there being but little fat present. Hemorrhages may be noted in any of the serous membranes. Histologically all of the hematopoietic tissues contain large numbers of lymphoblasts or the cells predominating in the blood. The bone marrow shows aplasia of the myeloid elements. The lymphoblastic infiltration is often so marked as to suggest neoplasm.

Several cases of typical acute lymphatic leukemia have been reported at autopsy to show few or no large lymphocytes in the tissues, the cells all being of the small type as they may be in blood during life.

The thymus gland is rarely enlarged in lymphatic leukemia. The predominant tendency in this disease is in the direction of involution of the organ. Margolis[36] of the Mayo Foundation in his study of thirty-two cases, ten of which were children, of various types of lymphatic leukemia reports enlargement of the thymus in only four cases, in twenty-eight cases there was no gross or histological evidence of involution. Just what influences the thymus gland in leukemia is not

understood but the most probable factor suggested is that of altered nutrition. When thymic enlargement does occur in leukemia, it usually parallels the degree of infiltration in other organs. Such enlargement is not due to hyperplasia of the small thymic cells, but is due to lymphocytic infiltration, the process is identical with that leading to infiltrations of other non lymphoid organs. The reaction of the small thymic cells in lymphatic leukemia differs from that of the blood lymphocytes and suggests a difference in the biologic nature of the small thymic cells and the blood lymphocytes. From this, a different histogenetic source of the small thymic cells from that of the blood lymphocytes may be inferred.

TREATMENT.

The ultimate aim of the physician in his practice in the art of healing is to make a correct diagnosis and to institute the proper treatment to the very best of his knowledge and the knowledge of others of reputable standing in the medical profession. Sadly enough there are a number of diseases, that the clinician is able to diagnose correctly, but which are absolutely refractory to therapeutic measures known to the profession. Of these various diseases, acute leukemia is a striking example. In the chronic leukemias, x-ray, radium, mesothorium, thorium-x and benzol have been used to induce remissions. "The acute forms though are apparently not influenced by any treatment."[43] It is therefor necessary to treat the disease symptomatically as much as possible, such as to combat, anemia, diarrhea, vomiting, and the necrosis and sloughing of tissues in the oral cavity, so that the patient's sufferings may be somewhat alleviated until death.

Cases of Acute Leukemia at University Hospital.

In a review of case histories at the University Hospital from 1918

to 1931, I find 18 cases of leukemia reported, 3 of which are of the acute type, the others were of the chronic, aplastic, or psuedo varieties. A brief summary of the symptoms and manifestations of these three acute cases are as follows:

Case I. Woman aged 48 years. History of pyorrhea for five years. Following a bad cold she had swelling of the gums. She consulted a dentist. Following extraction of an abscessed tooth the patient became bedridden. She had chills and high fever characteristic of a severe toxemia. The ulcerations and necrosis of the tissues in the oral cavity were the features of the disease, associated with regional adenopathy and moderate splenic enlargement. The urine contained albumen, many casts, pus cells, and red blood cells. The blood picture was typical of myeloid leukemia. Blood culture was negative. Throat and mouth cultures were positive for hemalytic streptococci, Fusiform and Vincent's organisms in large numbers. Death took place on the fifth week. The autopsy was not complete enough to warrant an absolute diagnosis of acute myelogenous leukemia, for the histo-pathological study was lacking. It is interesting to note that on the death certificate the "primary" cause of death was given as Vincent's Angina and "Septicemia" secondary. Death was attributed to the same cause in several cases of the chronic leukemias.

Case II. White girl, aged 20 was brought to the Hospital because of: prolonged and profuse menstruation of a duration of one month; generalized reddish blotchy areas; backache and weakness. Past history negative except for an abortion 8 months prior induced by an M.D. and another 2 months later induced by taking three half oz. doses of turpentine. On physical examination--reddish brown macules (subcutaneous hemorrhages) noted on covered surfaces especially the thighs. Absence of any oral involvement. Vaginal--large number of blood clots, soft

bleeding cervix one finger dilated, uterus soft and retrodisplaced; adnexia very tender on the right.

The feature of the disease was persistent vaginal and subcutaneous hemorrhage, high temperature and rapid pulse. Urine--alb. 2 +, many casts and pus cells. Clotting time--8 minutes, bleeding time--4 minutes.

Blood picture--typical of acute lymphatic leukemia, total leucocytes 102,000 with 100% lymphocytes. Death on 12th day. Autopsy confirmed diagnosis of acute lymphatic leukemia. Essential findings were (1) Bloody fluid in right chest. (2) Granular nodules in lungs, liver and spleen. (3) Petechiae in serous surfaces. (4) Large mesenteric lymph nodes with necrotic gray areas. (5) Grayish hyperplastic bone marrow.

Case III. Male child, aged 2½ years. History of prodromal period of malaise, loss of appetite and weight. Brought to the hospital because of uncontrollable hemorrhage from the nose, mouth and rectum. Hemorrhage from mucous membranes was the feature in this case. Fever high throughout 104-106.4°. Infected tonsils, cervical and axillary adenopathy, and splenic enlargement noted on examination. Blood picture--Hb.10%. R.B.C. 880,000. W.B.C. 34,000-210,000. Lymphocytes 98%. Throat culture negative. Urine--trace of albumen. Transfusions of no avail--death on the 6th day. Autopsy confirmed diagnosis of acute lymphatic leukemia.

The first case is a good example of the acute myelogenous leukemia occurring in females at the time of the menopause in which the manifest symptoms are those of ulceration and necrosis in the tissues of the oral cavity.

The second and third cases are representative of the acute lymph-

atic variety occurring in the young adult and infant in which the hemorrhagic diathesis is characteristic.

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