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## Chronic leukemia

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Senior Thesis

Kenneth D. McShane

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## CHRONIC LEUKEMIAS

### Introduction

Leukemia is a striking example of the fact that when the specific cause of a disease is unknown, it is usually impossible to clearly define its limits, and to arrange our observations in orderly sequence. In support of this view is the vast amount of literature written on Leukemias, a great part of which seems to contain endless hypotheses and speculations as to the cause of leukemia and as to its relation to other diseases particularly the infections and tumors.<sup>29</sup>

Leukemia as understood at the present time includes numerous atypical cases and related conditions. From the various changes which may take place in the blood during the course of the process conditions such as subleukemic or aleukemic myeloses and lymphoses resembling pernicious anemia arise. The conception of leukemia is also often broadened to include such tumors as chloroma and various lymphomata;<sup>55</sup> it is difficult in some instances to distinguish from the granulomata as Hodgkins disease.<sup>57</sup>

It may be inferred from what has been stated that there is a great variety of conditions characterized by all degrees of changes in the blood and blood forming organs such as the bone marrow, spleen, lymph nodes and tissues generally. Some of these conditions have a fairly definite and characteristic clinical picture while many are atypical and variable; a study of which has helped to fill many of the gaps in our knowledge of the leukemias.

The general conception of leukemia is that it is a disease of the blood forming tissues which produce leukocytes and manifests itself by a hyperplasia of these tissues.<sup>50</sup> When fully developed in its clinical form it is characterized by a remarkable increase of the white blood cells in

the circulation and an accompanying glandular or splenic enlargement of varying degree. The white cells of leukemic blood vary from those of normal blood in that they are of an embryonal nature and represent an early stage in the development of the normal leukocyte. There are cases on record in which the blood picture was that of leukemia but at autopsy showed no evidence of leukemia and was probably a leukemoid reaction obscured by the primary malady.<sup>26</sup> These cases probably represent an abnormal response of the bone marrow to infection. On the other hand cases are seen in which the blood picture is either subleukemic or aleukemic but which at autopsy reveal the characteristic tissue changes of a leukemia.<sup>59</sup>

The essential point in the diagnosis of leukemia therefore is a hyperplasia of the leukocyte forming tissue, which may vary as to location but has the same general characteristics.

#### History

<sup>and 2</sup> Bennett in 1845 first called attention to the peculiar white appearance of the blood at autopsy but made no distinction from an ordinary leucocytosis. This he called leukemia and later (1853) distinguished a splenic and lymphatic type. In 1870 Neumann discovered changes in the bone marrow and contributed a third type or myelogenous leukemia.

The first step in the pathology of leukemias was made by Ehrlich in 1891 when he made possible the classification of the disease according to the presence or absence of granules in the white cell by the oxidase stain. This removed the arbitrary line of 50,000 wbx per cu mm to distinguish from a leucocytosis and classified the disease according to the type of cell present rather than of the gland enlarged.

At this period Ehrlich distinguished (1) a myelogenous leukemia with hyperplasia of the white cells (granulocytes) in the bone marrow

and (2) a lymphatic leukemia with a hyperplasia of the lymphocytic tissues (agranulocytes). The splenic type was shown to be accompanied by bone marrow changes therefore a myelogenous or spleno-myelogenous type of the disease. It was also shown that a lymphatic type may ultimately show a lymphoid proliferation in the marrow. Ehrlich regarded the disease as a metastatic starting either in the bone marrow or lymph glands and this founded the dualistic theory of the origin of blood cells.<sup>17</sup>

#### Incidence

Leukemia occurs in the animal kingdom more frequently than is ordinarily suspected. It has even been artificially produced in the fowl.<sup>52</sup>

In man leukemia occurs at all age periods tho the acute states have a higher incidence below 25 years of age the highest incidence being the first 5 years tho a second rise occurs between the ages of 15 and 20 years. Chronic myelogenous leukemia has the highest incidence between 25 and 45 years while chronic lymphatic leukemia shows the majority of cases to occur between the ages of 45 and 60 years.<sup>3</sup>

Some few cases of leukemia have been seen during pregnancy which were more of an acute stage.

#### Etiology

While various authors have enumerated many exciting and predisposing causes of leukemia as yet the etiology is unknown.

There is no evidence of heredity being a factor in the leukemias of man but Slye has shown that in mice leukemia occurs only in those strains that have tumors.<sup>56</sup> However familial tendency of leukemia has been pointed out by some writers.<sup>4-5-37</sup>

#### Classification

The leukemias are commonly divided into the myeloid and lymphoid types and each type is subdivided into an acute and a chronic form. The subdivision, is, in the myeloid form, both clinical and histological,

since the acute and chronic forms are associated with different blood pictures. Acute myeloid leukemia may arise as such or less commonly as a terminal phase in chronic myeloid leukemia, but in either event both the clinical picture and the blood picture are entirely different in the two conditions.

#### Definition

By chronic leukemia is meant a chronic process of several months or years duration, associated with enlargements of the lymph glands, or of the spleen or of both accompanied by an anemia and a considerable increase of the white cells.<sup>48</sup>

#### Chronic Myelogenous Leukemia

Clinical picture<sup>7</sup> - The onset is as a rule insidious the patient complaining of gastric distress, sense of weight in the abdomen, and pain especially in the left side which is produced by an enlarged spleen probably associated with a perisplenitis. In some instances the patients themselves discover an enlargement of the abdomen, while others complain of numerous vague disturbances such as weakness, loss of weight, pallor, vertigo, dyspnoea and secondary symptoms of a mildly progressive secondary anemia.<sup>9</sup> At some time the usually in the later stages hemorrhages from the bowel and nose occurs. Occasionally slight sweating with irregular fever is observed.<sup>12</sup> Increased tolerance for low temperatures is attributed to the increased metabolism which accompanies the disease.<sup>8</sup>

Examination at this early stage may reveal nothing other than a little pallor and an enlarged spleen often reaching down into the pelvis. No lymph gland enlargement being manifest. The patient may continue in this condition for a year or so but the usual course is progressively downward. In spite of the remissions, spontaneous or induced, progressive increase in symptoms of secondary anemia

occur such as increasing weakness, dyspnoea, myocardial failure with anasarca rising temperature and death from myocardial failure or intercurrent infection or occasionally from hemorrhages from nose, bowels or into the brain.

Physical examination -

Appearance- Pallor especially of the mucous membranes from the anemia and prominent abdomen due to the enlarged spleen.<sup>11</sup>

Eyes- Rarely impaired tho peripheral retinal changes may be noted by Ophthalmoscopy. The lesions are small white flecks with irregular border and represent collections of leukocytes and degenerated nerve elements surrounded by traces of hemorrhage.<sup>20</sup>

Cabot reports two cases of unilateral exophthalmos.

Ears- In late stages hemorrhage into the labyrinth may occur giving rise to Menieres syndrome of tinnitus and vertigo or to deafness.<sup>21</sup>

Nose- Epistaxis is frequent and may be severe.<sup>70</sup>

Mouth- Loosened teeth with swollen, spongy and bleeding gums may occur but is very rare in the chronic leukemias.<sup>14</sup>

Throat- As a rule the tonsils and lymphatic tissue of the pharynx may show some hypertrophy.<sup>25</sup> Necrosis is usually limited to the acute processes. Leukemic infiltration of the larynx may cause dyspnoea tho it is usually caused by myocardial weakness or abdominal distension.

Glands- In the great majority of cases glandular enlargement is either absent or only very slight and near the terminus of the disease.<sup>15</sup>

This in contradistinction to a lymphatic leukemia.

Lungs- Pneumonia and pleurisy are often seen as complications of a chronic diffuse bronchitis.<sup>51</sup> The dyspnoea is due to myocardial weakness together with the abdominal distension and splenic enlargement. A chronic and troublesome cough may arise from the basal edema.



Heart- Cardiac findings are tachycardia, palpitation, systolic murmurs and some dilatation due to the secondary anemia.

Spleen- Usually appears as a massive tumor filling more than half of the abdomen. The general contour of the spleen is fairly well preserved such that one or more notches can often be felt.

Pain and sensitiveness to pressure if present is probably due to an accompanying perisplenitis. Peritoneal friction may result in a reflex splinting of the abdominal muscles.<sup>15</sup>

Liver- As a rule there is varying degrees of general enlargement tho not complicated with jaundice unless some disease of gall bladder and ducts is present.

Digestive organs- While numerous gastrointestinal symptoms are present at the onset the only symptoms directly due to the leukocytic infiltration of the intestinal wall are probably hemorrhage and diarrhoea both of which tend to occur late in the disease.<sup>18</sup> Ascites is frequently observed the fluid containing many cells in some instances myelocytes, esinophiles and basophiles.

Kidneys- Histological examination may show marked cellular infiltration without the appearance of albumen or casts in the urine. The majority of cases show both albumen and casts in the urine<sup>18</sup> which however does not signify the existence of chronic nephritis. large quantities of uric acid are found in the urine tho the presence of renal calculi and the occurrence of gout is rare!<sup>0</sup>

Sexual organs- Women manifest menstrual irregularities.<sup>68</sup> In the male priapism occurs tho the percentage is small. The cause is a myelocytic thrombosis or infiltration of the corpora cavernosa. The duration may be for weeks or months and is frequently accompanied by dull pain in the lower abdomen. According to Ruh<sup>18</sup>

no case has been reported in literature which has been due to lymphatic leukemia. Micturition may be difficult and require catheterization.

Brain and spinal cord- Symptoms referable to brain and spinal cord involvement are exceedingly rare and when present are due to small hemorrhages or leukemic infiltration of the nervous tissue.<sup>38</sup> Rarely is death caused by cerebral hemorrhage tho cases have been reported of cranial nerve involvement such as facial palsy or eighth nerve deafness.<sup>16</sup>

Skin- Petechial and purpuric hemorrhages beneath the skin are frequent toward the end of a chronic myelogenous leukemia tho skin involvements is more the case in a chronic lymphatic leukemia.

Temperature- Is not characteristic tho various changes may manifest themselves.

#### Blood Picture -

Grossly the blood does not appear any differently than normal blood as it flows from a puncture wound tho some skilled technicians are able to identify or suspect a leukemia from the sticky nature of the blood when pulling a cover slip from a slide of the blood. In the early stages the hemoglobin content of the blood is not appreciably diminished but progresses with the disease. At the beginning a lowered red count is present ( two or three million) and a low color index of a secondary anemia. The blood smear will show a variation in size with probably a greater variation in shape of the red cells and variation in staining reaction. Polychromatophilia and basophilic staining are consistently present. Normoblasts predominate tho megaloblasts are also present in some blood smears. The blood platelets are as a rule increased.

The outstanding feature of the disease however is the tremendous increase in the white blood cells ranging from a few hundred to one million. The diagnosis is made from the presence of myeloid cells rather than from the number of white cells present. Most of the cases reported in the literature of submyeloid values of white counts have to do with cases in which the white count was primarily high but had been reduced by X-ray or some infection.

The characteristics of a blood smear are: Polymorphonuclear neutrophilic increase the percentage varying from 30 to 80 per cent the absolute number being greatly increased.

Eosinophilia may vary from five tenths to five per cent with nearly always a marked absolute increase.

Basophiles vary from three to twenty per cent giving both relative and marked absolute increase.<sup>19</sup>

Large mononuclear transitional cells may be absolutely increased. When many myeloblasts are present it may be very difficult to identify this type of cell.

Neutrophilic myelocytes never present in normal blood, may appear in small percentages at first but later reach thirty to forty per cent or higher.

Eosinophilic myelocytes are also numerous.<sup>19</sup>

Basophilic myelocytes are usually present.

Myeloblasts are infrequent in the typical picture but are variable. They occur in great numbers in acute exacerbations of a chronic myelogenous leukemia.

Lymphocytes are greatly reduced on a percentage bases but almost always the total number is increased.

To summarize the most characteristic features of the blood pict-

ure are the large total numbers of myelocytes, esinophils, and mast cells, plus the presence of nucleated reds.

Repeated examination of the blood from the same patient at different intervals frequently show contradictory results in the myelocytic count. The mast cells and esinophiles are subject to the same variation. The significance of the mast (basophiles) cells is unknown tho a rise in the mast cell count often accompanies improvement or follows Xray treatment. Another point of interest is the unusual increase in myeloblasts just before terminus, sometimes almost wholly replacing the myelocytes and may represent a complete exhaustion of bone marrow which pours out the most early type of cell. Some times difficulty arises in distinguishing myeloblasts from lymphocytes but on close ~~examination~~ examination and staining oxidase granules can usually be found in the myeloblasts.

#### Pathology

Post-mortem findings are confined to the blood and blood forming organs. The body tissues microscopically show the effects of a severe anemia viz pallor and excess deposit of fat.

The spleen shows a remarkable enlargement often extending well into the pelvis. The consistency is firm from the increase in fibrous tissue and trabeculae. The surface is grayish from the thickened capsule and may show areas of peri-splenitis with resulting adhesions. On section the malphigian bodies are not visible and infarcts are not frequently found.

Microscopically the spleen shows the normal picture to be replaced by infiltrating hordes of neutrophilic and esinophilic myelocytes also large numbers of neutrophilic, esinophilic and basophilic leucocytes

together with myeloblasts, nucleated reds and often a few megalocaryocytes. The malphigian bodies are obliterated and fibrous tissue increase is noted along the walls and sinuses of the capillaries which may show hyaline changes.

The bone marrow shows a replacement of the normal bright yellow marrow by a more gray and firm tissue in some instances approaching the green seen in chloroma.

Microscopically the bone marrow presents a picture closely resembling that seen in the spleen. Predominance of neutrophilic or eosinophilic myelocytes with basophilic myelocytes, all kinds of leucocytes, myeloblasts and a few normoblasts with small numbers of megalocaryocytes. A general suppression of erythroblastic tissue noted.

Lymph glands do not as a rule show any changes in contradistinction to lymphatic leukemia. However when present is of a mild degree and localized which on sectioning presents a picture very similar to that seen in the spleen.

The liver shows a firm symmetrical enlargement much less in proportion to that of the spleen. Microscopically the capillaries are seen to be distended with myeloid cells and varying degrees of periportal tissue infiltration.

The other organs show only capillary filling of myeloid cells if any change has taken place.

#### Treatment

Given for both Myelogenous and Lymphatic leukemia at the end of the paper.

### Chronic Lymphatic Leukemia

Physical examination usually reveals a general lymphatic enlargement, palpable spleen, liver enlarged to a less degree than in chronic myelogenous leukemia and pallor from the anemia.

General appearance- Pallor of skin and mucous membranes.

Eyes- Disturbance of vision is rare but may result from retinal hemorrhages. The fundus may show a "retinitis leukemica" small white flecks with a red border. Infiltration of the eyelids is rarely seen. A case has been reported of lymphatic leukemia involving the sclera. Symmetrical tumors were removed from the sclera with diagnosis of lymphoma. Lymphocytes 33% and physical examination negative. One year later recurrence and removed again with 55% lymphocytes and negative physical examination. Four years later a general lymphatic enlargement occurred with rise to 95% lymphocytes and a 2,000,000 white count.

Ears- Rarely deafness occurs as a result of lymphomatous involvement of the labyrinth.

Mouth- Swelling and bleeding of gums with gangrenous processes of mouth are limited more to the acute leukemias.

Tonsils- Considerable enlargement sometimes leads to removal before the true condition is recognized and may lead to hemorrhage and death.<sup>55</sup>

Glands- The most characteristic picture of the disease is seen in the glandular enlargement especially cervical, axillary and inguinal. As these glands are practically never the seat of primary infection, they exist in chains separately, freely movable and not attached to the overlying integument. If breaking down or matting together occurs it is due to secondary infection. The glands are firm,

painless and not tender to pressure. Mediastinal gland enlargement may be seen by Xray. A thorough examination reveals a generalized enlargement of the lymph glands tho cases have been reported without the adenopathy.<sup>26</sup>

Heart- Myocardial insufficiency develops from the anemia and may be accompanied by systolic murmurs, palpitation, tachycardia and the signs of a secondary anemia.

Lungs- Well after the onset of the disease pleural effusion may occur, possible the result of mediastinal gland enlargement. In the terminal stage edema of the lung with broncho-pneumonia is not uncommon.

Liver- The jaundice does not occur a smooth enlargement of the liver often extends two to four fingers breadth below the costal margin. On the average splenic enlargement tends to exceed hepatic.

Spleen- Enlargement is present in practically every case. The average size is smaller than that found in chronic myelogenous leukemia.

Digestive organs- As in chronic myelogenous leukemia disturbances may occur but there are no characteristic clinical findings. Varying grades of anorexia, flatulence, vomiting, melena, diarrhoea or constipation may be present. The presence of changed blood in the stool either macroscopic or microscopic points to leukemic infiltration of the intestinal wall.

Kidneys- Palpable enlargement of the kidneys in chronic lymphatic leukemia does not occur. Albumen, casts and red blood cells are frequently found in the urine. There is also an increase in the uric acid of the urine, tho not as marked as in myelogenous leukemia. Bence-Jones proteinuria has been reported by several authors.<sup>42</sup> It would seem that Bence-Jones proteinuria is not essentially dependent

upon one disease but is a manifestation of bone marrow disturbance.

Sexual organs- The priapism of myelogenous leukemia has not been reported in lymphatic leukemia the menstrual irregularities may occur in the female.

Central nervous system- Lymphoma of the brain or cord or leukemic infiltration of the nervous system are apparently limited to the myelogenous type of leukemia. Tumor formations are more characteristic of the acute leukemia and the closely related chloroma. White reports a case of lymphatic leukemia with combined degeneration.<sup>60</sup>

Skin- There is a remarkable tendency to a variety of skin lesions in lymphatic leukemia. These may occur in all types of the disease from the slowly progressive aleukemic variety to the acute fulminating type where the hemorrhage tendency is constant.<sup>61</sup> The most common findings are pruritis, prurigo, urticaria, bronzing, vesicles, pustules, localized infiltrations, nodules and tumors. In addition to finding these lesions in typical cases when splenic or glandular enlargement and the blood picture verify the diagnosis, leukemic changes are also found where there is little or no splenic or glandular enlargement and the blood picture is normal. Section of these lesions show a lymphocytic infiltration and are considered as instances of aleukemic leukemia. The term "leukemia cutis" is used to cover all leukemic manifestations of the skin. However the term "lymphadenosis cutis" is used by some<sup>62</sup> and is divided into three subdivisions (a) aleukemic form if the blood is normal; (b) subleukemic form if the white blood cells are only slightly increased but the percentage of lymphocytes is above normal; and (c) leukemic form where the



blood picture is that of lymphatic leukemia. The circumscribed type of leukemia cutis is the usual form the Sweitzer<sup>54</sup> reports a case of universal leukemia cutis which was aleukemic for two years.

In the diagnosis of leukemia cutis differentiation has to be made from only one condition, mycosis fungoides, which may be done by histological examination of a piece of the skin. In cases of leukemia cutis where the papules and small tumors coalesce the patient's face may take on the leonine appearance which has been described as one form of mycosis fungoides. Cases of this type are those described lymphoderma perniciosum. The leonine or pseudoleprous appearance of the face suggests the premycotic skin condition in granuloma fungoides.

Temperature- Fever of varying degree in no way diagnostic, may be encountered during the course of the disease.

#### Blood Picture

The average red cell count when the patient is first seen is about 3,000,000 which falls to a lower figure as death approaches. Remissions are marked by a rise in the red count which often approaches normal. The hemoglobin curve tends to follow the red cell curve.

The stained blood smear will show red cell changes characterizing a severe secondary anemia, nucleated reds, poikilocytes, anisocytosis, megalocytes and polychromatophilia. The appearance of white cells is of striking uniformity the majority being identical with the small lymphocyte of the blood. Careful study however will reveal certain changes such as replacement of the light blue border by only a tiny visible rim and in some cases only the naked nucleus remaining. The nucleus of the pathological cell is often more light staining showing

a much more delicate chromatin network. The blood of lymphatic leukemia does not give the guaiac or oxydase test nor does it show the presence of a peptic ferment.

#### Course of the disease

Clinical improvement manifest by subsidence of glandular swelling, splenic enlargement and change of the blood picture toward normal may occur three ways: (1) spontaneous remission (2) therapeutic remission induced by Xray, radium or benzol, (3) remission produced by an inter-current infection especially one causing aneutrophilic granulocytosis. The white count may approach normal and the percentage of lymphocytes become greatly reduced yet a relative increase persists.<sup>57</sup>

Without exception exodus occurs after varying periods of time. Occasionally a stationary period of a good many years occurs but the anemia progresses with its train of symptoms following. In the late stages the tendency to fever and hemorrhages suggest the similarity to acute lymphatic leukemia. Death may result from complications such as sepsis which the patients stand badly and is attributed to the bone marrow's inability to react properly to the invading organism.

#### Pathology

The glands in the leukemic and aleukemic forms of the disease appear to be identical in character often being more enlarged than in Hodgkins disease. They remain discrete and are globular or ovoid in shape. They are more or less soft to the feel. When sectioned the glands have a medullated appearance, often with areas of hemorrhage and necrosis. Similar changes are seen in other lymphoid organs such as the spleen and mucous membranes. Some authors even associate the changes of Mikulieze's disease as one form of the disease.

Histological examination reveals a complete loss of the normal lymph gland structure accompanied by a diffuse infiltration of small lymphocytes. Scattered among the lymphocytes are endothelial cells of large size, and even mononuclear endothelial giant cells, like those in Hodgkins disease. There may be some increase in the stroma of the gland. Infiltration may be seen in the capsule and periglandular tissues.<sup>46</sup>

#### Treatment

In the rare instances in which one encounters chronic leukemia, whether myeloid or lymphatic, in the earlier stages it is perfectly justifiable to use any and all methods of treatment which have proved useful in securing remissions. The two chief therapeutic agents being roentgen radiation and benzol.

BENZOL is a powerful leucocytic poison. In favorable cases the administration of this drug is followed by slight increase in the leucocyte count and later a striking diminution chiefly affecting the polymorphonuclear cells. If favorable affects continue the pathological types of cells tend to disappear. The drug is much more valuable in the myeloid than the lymphatic leukemia. Excessive use of the drug may produce an aleukemia or an aleukemic state associated with anemia. Benzol may be administered in capsules of olive oil. The initial dose is 30 grains and maximum 75 grains daily is reached during the course of one week. The maximum daily dose of 75 grains may be continued until the leucocyte count is 30,000 per cm or under. Toxic symptoms such as headache, vertigo, bladder irritability, gastric disturbance and evidence of renal congestion should be carefully watched for.

THORIUM X may be used advantageously in many instances to supplement the action of Xray. The substance has the advantage of being relatively harmless and permitting a more exact dosage.

ARSENIC was formerly the drug of preference with the resulting appearance of many cases of poisoning. The preparation of arsenic best adapted for use in this disease is Fowlers solution. The initial daily dosage of 30 minims should be raised one drop each day until a daily dosage of 200 minims is reached. It may then be continued on this level with due precautions against chronic arsenical poisoning.

TUBERCULIN injections and the use of bacterial toxins has been recommended by some investigators but the methods have attained no prominent place in the therapy of leukemia.

SPLENECTOMY is absolutely contraindicated.

GENERAL MEASURES To a large extent symptomatic treatment is the essential course to follow.

Irradiation by roentgen rays and radium is a form of treatment that often brings relief in the treatment of chronic leukemia.<sup>65</sup> It produces more benefit in the treatment of myelogenous than of lymphatic leukemia. Minot and associates showed by study of 78 irradiated and 52 non-irradiated cases of chronic myelogenous leukemia that, though a very high percentage of the irradiated cases were distinctly and often markedly benefited, the duration of life was but little prolonged.

The only symptomatic results are obtained, and the most striking results in the myelogenic form, irradiation is a distinctly valuable form of therapy. Persons in a bedridden state are often enabled to return to a useful existence for months and even years. Minot reports definite improvement in 95 per cent of 78 cases of chronic myelogenous

leukemia and marked improvement in 50 per cent. The percentage of time of efficient life after irradiation was increased at least 30 percent on the average above that of 52 non-irradiated cases. Striking improvement is seen much less often in the chronic lymphatic form, yet continued adequate irradiation brings comfort to the patient. The degree of improvement varies with the amount of irradiation, character of irradiation, state of the patient and hemopoietic organs, as well as the basal metabolism and time in the disease when treatment is given.

The effect on efficiency is manifest by an increase in the patients sense of well being and a decrease in the most prominent symptom, abnormal fatigue. This is attributed to a decrease in the metabolic rate, a lessening of the anemia by stimulating the bone marrow function and decreasing the formation of lymphocytes and by decreasing the symptoms due to enlarged external or internal lymphatic tissue.

Irradiation induces a better production of the three formed elements of the marrow and lessen the activity of the formation of lymphocytic cells. The hemoglobin level, numbers of blood platelets, and character of the lymphocytes serve more importantly to adjudge the patients condition than the number of white cells. Little or no improvement is produced in the patient whose hemoglobin is 50 per cent or less, or when outstanding purpura with thrombopenia is present, or when there are many immature and atypical lymphocytes in the peripheral blood.

<sup>69</sup> Struma has shown from the morphological changes of the blood following radium applications in myelogenous leukemia that, the

mechanism of action of radium upon the leukemic foci is of generalized as well as of localized nature. From a localized application a generalized effect is obtained. This observation, and the fact that regardless of the place of application very similar results are obtained lends support to the view that the direct action of radiations upon the hemopoietic foci is altogether unimportant. In all cases the blood acts as a carrier of radiations,<sup>69</sup> either as such or modified, to the hemopoietic foci, where its main action takes place.

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