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Prognosis of chronic granulocytic leukemia as determined by peripheral blood findings, bone marrow and physical findings

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THE PROGNOSIS OF CHRONIC GRANULOCYTIC LEUKEMIA AS DETERMINED BY PERIPHERAL BLOOD FINDINGS, BONE MARROW AND PHYSICAL FINDINGS

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INTRODUCTION

It is the purpose of this study to determine the relationship, if any, of various parameters to the prognosis and ultimate survival of patients with chronic granulocytic leukemia. Prognosis is used here with reference to length of survival of the patient. Survival refers to the period from time of onset of the disease to the time of death unless otherwise stated. This study includes some patients with chronic granulocytic leukemia who are still living.

The incidence of chronic granulocytic leukemia was determined with regard to age, sex, and race. Each patient was then studied as to presenting complaints and the time elapsed between onset of these complaints and the time of consult. If death of the patient had occured, the time from the first symptoms to death was determined as well as the time from diagnosis of the disease to death. If death had not occured, duration to the time of the writing of this paper was determined. In all cases the time of the first diagnostic bone marrow was taken as the time of diagnosis.

The patients were also studied as to the presence

or absence of hepatomegaly and splenomegaly at the time of diagnosis. Peripheral blood studies were limited to review of the hemoglobin, white blood cell count, numbers of basophils and monocytes, the reticulocyte count, and the platelet count at the time of diagnosis. In all cases used in the peripheral blood study, no treatment had been given prior to the study. Special cases where some form of treatment had been given prior to the peripheral blood examination were excluded from this part of the study. The white blood cell count was then also tabulated in regard to the highest and lowest counts throughout the duration of the disease regardless of treatment or absence thereof.

Finally, the various types of treatment used in each patient and a brief resume of the bone marrow findings in regards to cellularity, red blood cell to white blood cell ratio and an estimate of megakaryocyte numbers were recorded.

For this study, 46 cases of chronic granulocytic leukemia were reviewed covering a period from 1950 to 1965. All cases were obtained from the hematology records of the University of Nebraska Hospital and from private records of Peyton T. Pratt, M.D. A

total of 26 patients were reviewed from the University records and a total of 20 were private patients (Dr. Pratt).

INCIDENCE AND SURVIVAL

In all 46 cases the ages at diagnosis were ascertained and recorded. The mean age, irrespective of sex, at the time of diagnosis was 51.9 years. Obviously, the age of onset of the disease would be somewhat lower since most of the patients had some symptoms prior to diagnosis. The age at diagnosis in years was known in all cases, however, the birthdate was not always available. Therefore, the age at the time of onset could not be accurately determined. The difference in time between the survival from diagnosis and the survival from onset of symptoms represents the period of time the disease was present before diagnosis. By subtracting this period of time from the average age at diagnosis the approximate age at the onset of the disease could be determined.

The average age of 26 patients who were followed at the University Hospital was 59 years contrasted to an average age of 42.6 years in the private patients. The youngest University Hospital patient was 20 years

of age at the time of diagnosis and the oldest was 77 years. The youngest private patient was eight months of age and the oldest was 76 years at the time of diagnosis.

Of all 46 cases, 22 were males and 24 were females. The average age at diagnosis of the males was 51.9 years and the average age of the women was also 51.9 years. Forty four patients were white and two were Negro, both females.

By distributing the ages at diagnosis by decades it was found that 28.3 per cent of all the patients were diagnosed while in their seventh decade of life. This was the highest for any one decade. However, it

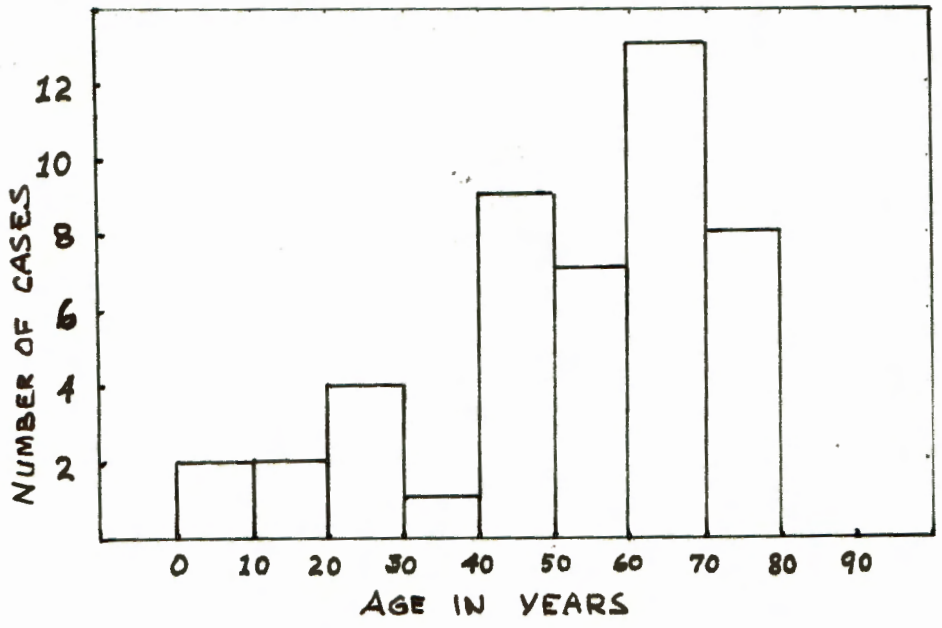


Fig. 1 Age at Diagnosis of Chronic Granulocytic Leukemia in 46 Cases.

was found that 80.4 per cent of the patients were diagnosed as having chronic granulocytic leukemia between the ages of 40 years and 79 years which covers four decades. The distribution by decades is depicted in Figure 1.

In five patients the records were incomplete as to the date of onset of symptoms. In six other cases the disease was diagnosed incidentally when the patients were hospitalized for some apparently unrelated reason or on routine examination. For example, one patient was referred to the University of Nebraska Hospital because of cholecystitis and was found to have chronic granulocytic leukemia. Another patient was found to have the disease while being treated for a squamous cell carcinoma of the neck. Still another was diagnosed while being treated for a prolapsed uterus.

To date, 10 of the 46 patients are still living and 36 have died. In four of the patients who died the diagnosis was incidental and in two others the records were incomplete. The average survival of 29 patients who died and in whom the date of onset of symptoms was known was 32.1 months. The minimum survival time of the four patients in whom the diagnosis

was incidental was obtained by counting the date of diagnosis as the time of onset. By adding these four patients to the 29 patients mentioned above the minimum survival time was found to be 32.0 months.

Of the 10 patients still living, the date of onset of symptoms was known in six cases and the average survival was found to be 38.1 months. By taking the date of diagnosis as the date of onset in the remaining four patients in whom the date of onset of symptoms was not known and including them in the tabulations, the minimum survival of all 10 living patients was found to be 42.0 months.

The overall survival of 35 patients (living and dead) in whom records were complete and who had symptoms before the diagnosis was made, was found to be 32.9 months. Including those whose diagnoses were incidental the overall survival was 33.3 months.

The average overall survival from the time of diagnosis, including patients who had died and those still living, was 27.4 months. The average of those who had died was found to be 24.0 months and, of the 10 still living, 39.0 months.

The longest single survival of patients who died was that of a 40 year old female who lived

8.4 years after the onset of her disease. The disease was diagnosed two months after the onset of her symptoms. The shortest single survival from the onset of symptoms in patients who had died was eight months. This patient lived five months after diagnosis. However, the shortest survival after diagnosis was in a 65 year old male who lived only six days after the bone marrow diagnosis of chronic granulocytic

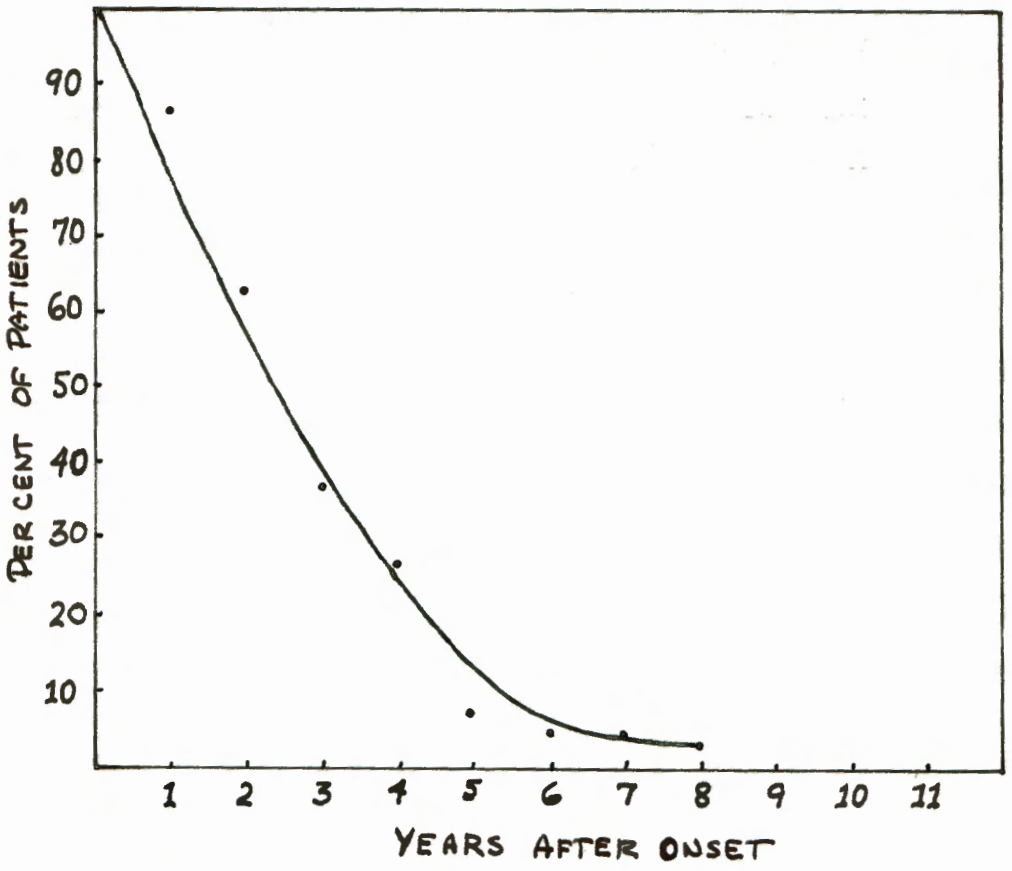


Fig. 2 Duration of illness in 46 patients with chronic granulocytic leukimia from the onset of clinical symptoms.

leukemia was made. The onset of symptoms occured 10 months prior to his death. Cause of death in this patient was massive gastrointestinal bleeding.

The longest survival from onset among patients still living has been 5.0 years. The shortest period of survival in a living patient has been five months. Figure 2 is a graphic illustration of survival indicating the number of patients in per cent living at yearly intervals.

There was considerable variation among the patients as to the elapsed time between onset of symptoms and their first medical consult. In six patients the diagnosis was incidental and thus there was no time factor involved between apparent onset and diagnosis. However, in patients who did have symptoms attributable to the disease the shortest period from onset of symptoms to medical consult was one week. The longest was in a 65 year old male who complained of fatigue, weakness, and weight loss over a period of four years prior to consult. This patient lived only six months after his first medical consultation at which time he was found to have chronic granulocytic leukemia.

In determining the prognosis and effects on

prognosis of various factors the mean survival time from onset of 33.3 years will be used. Since this includes 10 living patients it represents a minimum survival time. The final magnitude of this number is dependent upon how long each patient lives.

PERIPHERAL BLOOD FINDINGS

The peripheral blood findings studied included the hemoglobin, white blood cell count, differential with reference to monocytes and basophils, reticulocyte count, and platelet count. For purposes of comparison the foregoing studies will only be used in patients who received no treatment prior to the studies and in whom the studies were performed at or near the time of diagnosis. Three patients were found to have received treatment prior to the recording of laboratory data. In two cases the records were incomplete and laboratory data were not available. Highest and lowest white blood cell counts during the course of the disease were recorded irrespective of treatment.

In five cases no hemoglobin was recorded. In 38 patients the hemoglobin ranged from a low of 6.0 grams per cent to a high of 15.5 grams per cent. The following scattergram (Figure 3) is an attempt

to demonstrate the correlation, if any, between the magnitude of the hemoglobin and the survival after diagnosis of 38 patients with chronic granulocytic leukemia.

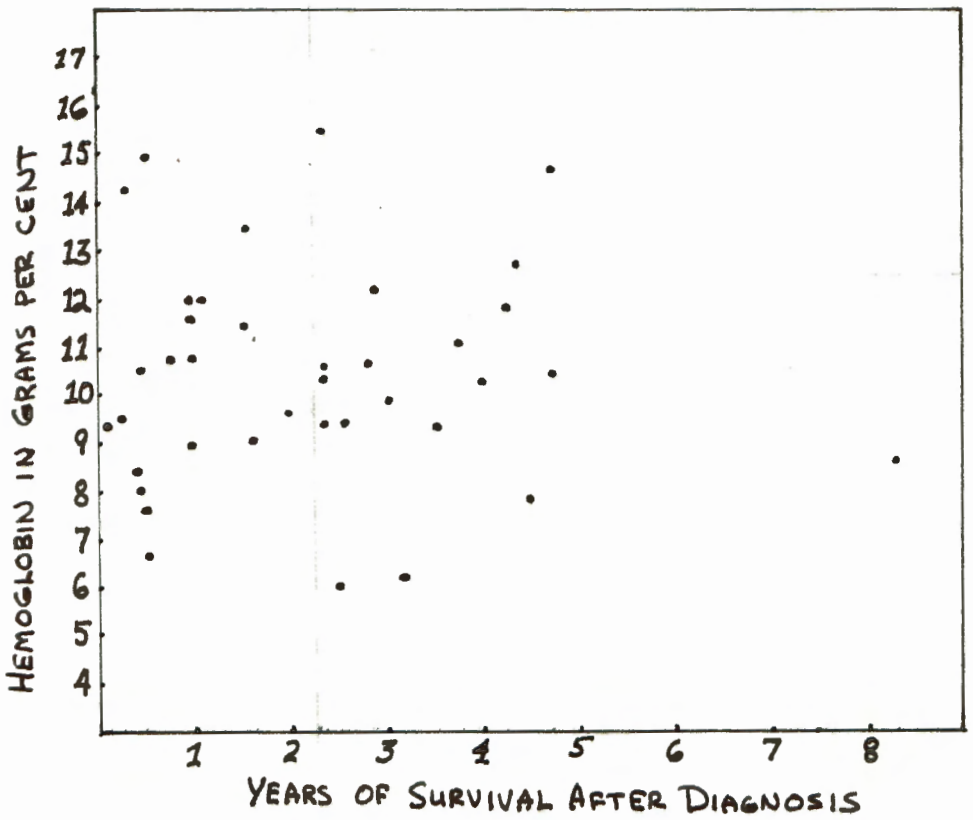


Fig. 3 The grams per cent of hemoglobin in 38 patients with chronic granulocytic leukemia relative to the length of survival after diagnosis.

In order to determine the erythropoietic activity in these patients the reticulocyte count was used as an approximate index. Reticulocyte counts were available only in 30 patients. The highest reported reticulocyte count was 7.0 per cent and the lowest was 0.4 per cent.

The white blood cell count in the patient with the highest reticulocyte count was 32,000 per cu. mm. at the time of diagnosis whereas in the patient with the lowest reticulocyte count the white blood cell count was 476,000 per cu. mm. The purpose of Figure 4 is to show the relationship between the reticulocyte response and the peripheral white blood cell count, if such a relationship exists.

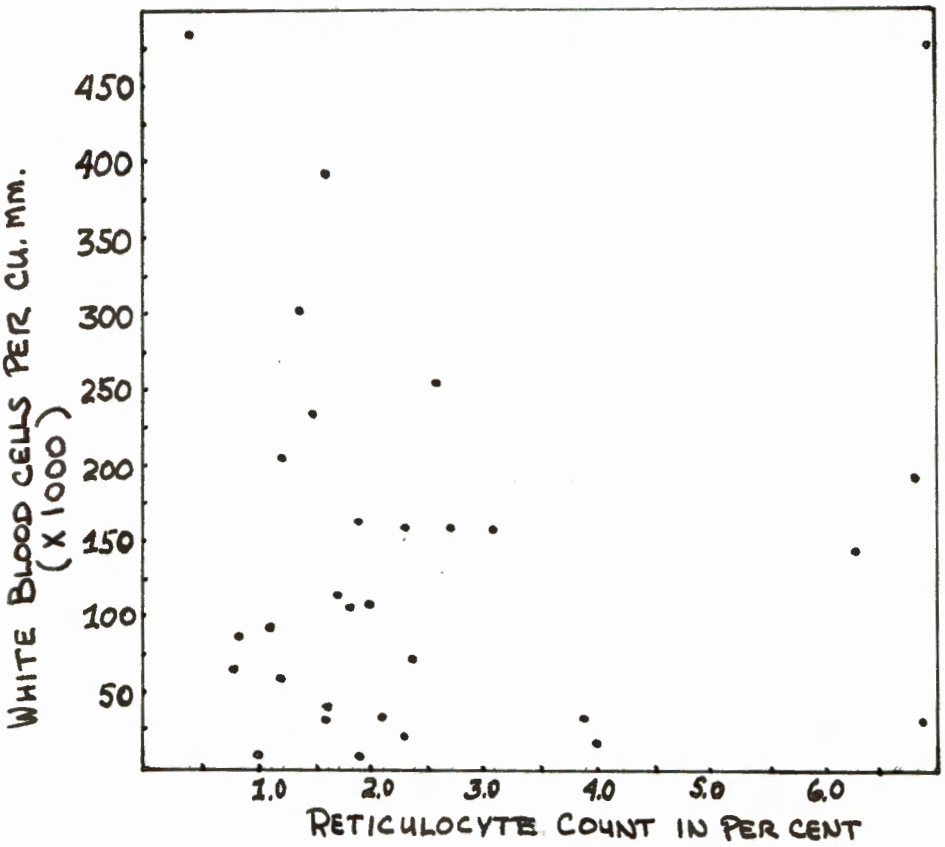


Fig. 4 White blood cell counts in 30 patients with chronic granulocytic leukemia as compared to the reticulocyte count.

The normal reticulocyte count in peripheral blood was considered to be 0.5 per cent to 1.5 per cent. The average or mean reticulocyte count in this series was found to be 2.5 per cent. The per cent of reticulocytes relative to duration of life after diagnosis of chronic granulocytic leukemia is shown in Figure 5.

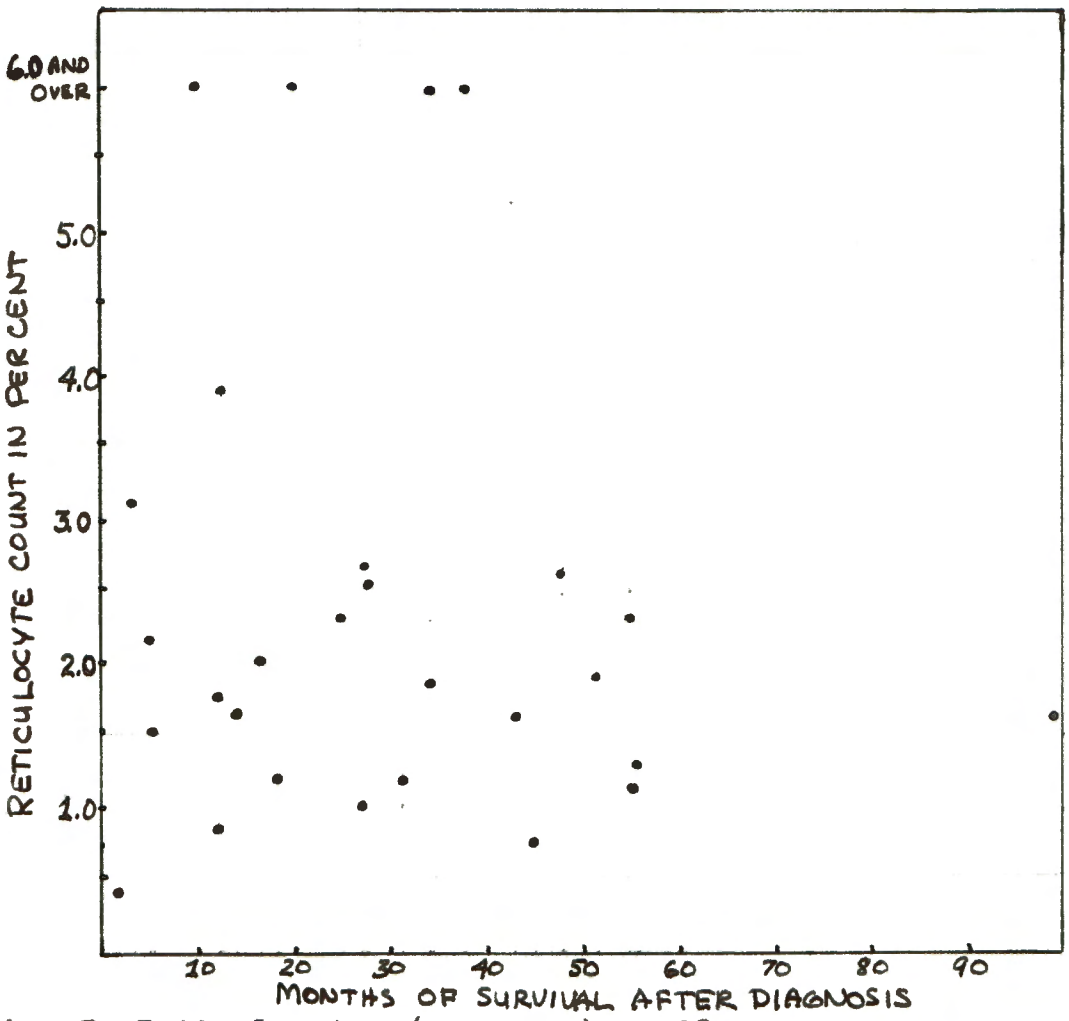


Fig. 5 Reticulocytes (per cent) in 28 patients with chronic granulocytic leukemia as compared to survival.

The white blood cell count (WBC) prior to treatment was available in 41 of the 46 patients. In two patients the initial count was missing and in three patients treatment had been given prior to recording of the WBC. The WBC ranged from a low of 4,200 per cu. mm. to a high of 562,000 per cu. mm. The mean WBC was found to be 169,400 per cu. mm. It was interesting to note that the patient with the lowest WBC was admitted for cholecystitis and gave a history of bleeding with a tooth extraction five months earlier. A blood count revealed anemia (hemoglobin 10.6 grams per cent), mild leukopenia, a moderate shift to the left in the granulocytic series, and a moncyte count of 21 per cent. On the basis of this peripheral blood picture and the history of bleeding, a bone marrow examination was performed which revealed the existence of chronic granulocytic leukemia. Figure 6 was constructed in an effort to show the effect on survival, if any, of the initial WBC.

The highest and lowest white blood cell counts were recorded whenever possible and whenever a sufficient number of determinations were recorded (30 patients). All patients received some form of treatment, therefore,

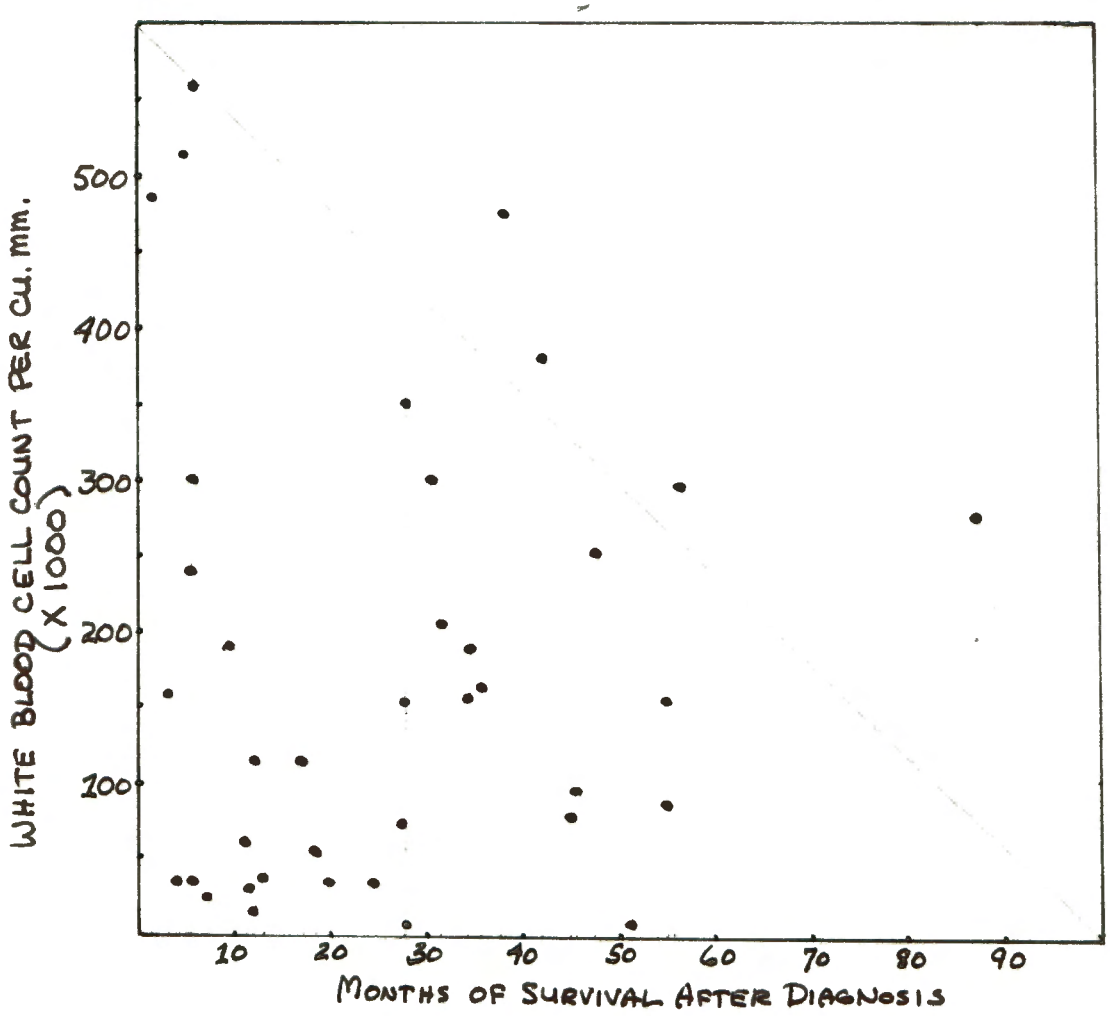


Fig. 6 White blood cell counts in 39 patients with chronic granulocytic leukemia as compared to the months of survival after diagnosis.

these counts were recorded regardless of the type or amount of anti-leukemic therapy. The highest count recorded was 670,500 per cubic mm. and the lowest was 200 per cu. mm. The average high count was 233,700 per cu. mm. and the average low count

was 22,500 per cu. mm. In eight cases the highest count recorded was the count at the time of diagnosis before therapy had begun. In only two cases was the initial WBC found to be the lowest through the course of the disease. Both were felt to be in the early stages of chronic granulocytic leukemia at the time of diagnosis.

Differential white cell counts were available prior to treatment in 38 patients. An observation of the numbers of basophils and the numbers of monocytes was made in each of these patients. Twenty one per cent was the highest basophil count while the lowest was zero in six cases. The average basophil count was 4.3 per cent. The highest number of monocytes recorded was 23 per cent and the lowest was zero in 12 cases. The average number of monocytes was also 4.3 per cent. Since 4.3 per cent represented the average number in both monocytic and basophil series and since in both series this represents high normal or above normal counts, Figure 7 was constructed to show the relationship in numbers between these two series of cells. Figure 8 was constructed to show the relationship between the monocyte count and survival from diagnosis. The same is shown in Figure 9 except

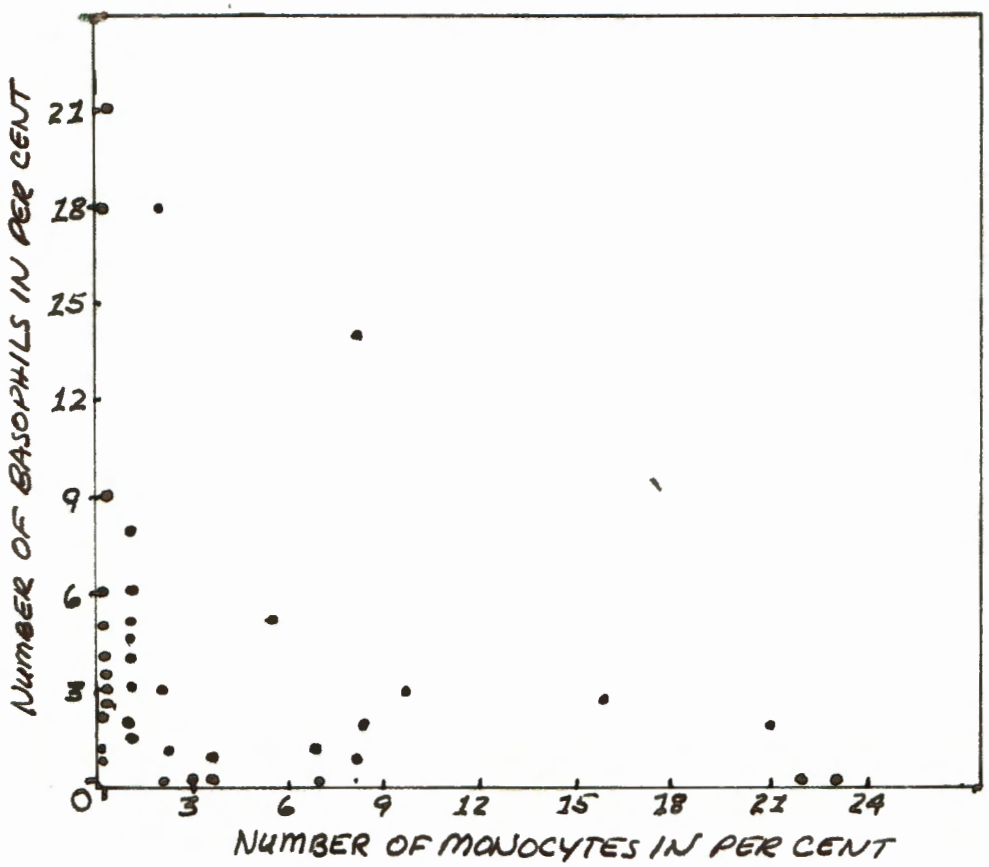


Fig. 7 The number of basophils (per cent) in 38 patients with chronic granulocytic leukemia as compared to the number of monocytes (per cent).

that the basophil count was substituted for the monocyte count.

An absolute number of platelets was given in 32 cases. In two other cases an absolute figure was given but treatment for leukemia had been initiated prior to the performance of the platelet count. In the remainder of the cases platelets were designated as decreased, normal, or increased in number. For

Fig. 8 The monocyte count in 36 patients with chronic granulocytic leukemia compared to survival.

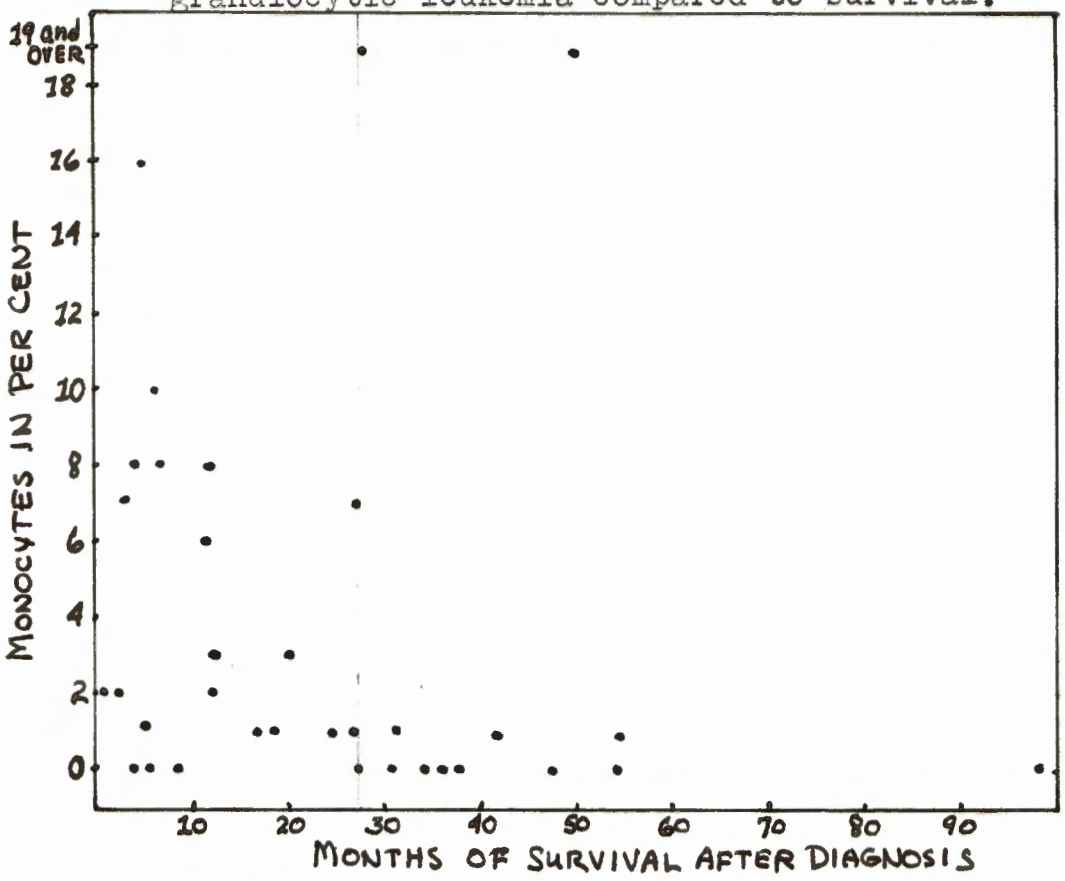
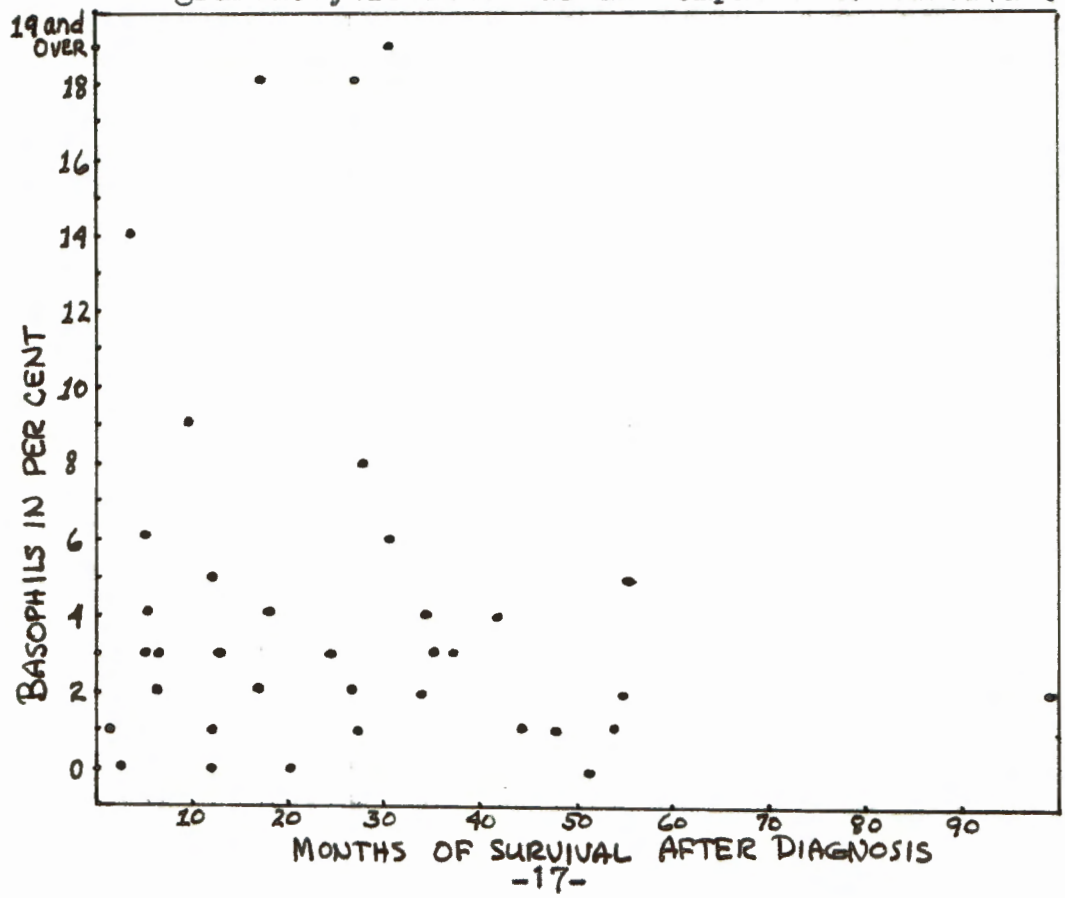


Fig. 9 The basophil count in 36 patients with chronic granulocytic leukemia as compared to survival.



this study the normal platelet count was taken to be 150,000 per cu. mm. to 600,000 per cu. mm. The average platelet count was found to be 533,914 per cu. mm. The lowest was 93,100 and the highest was 3,250,000. The relationship between the platelet count and survival after diagnosis is shown in Figure 10.

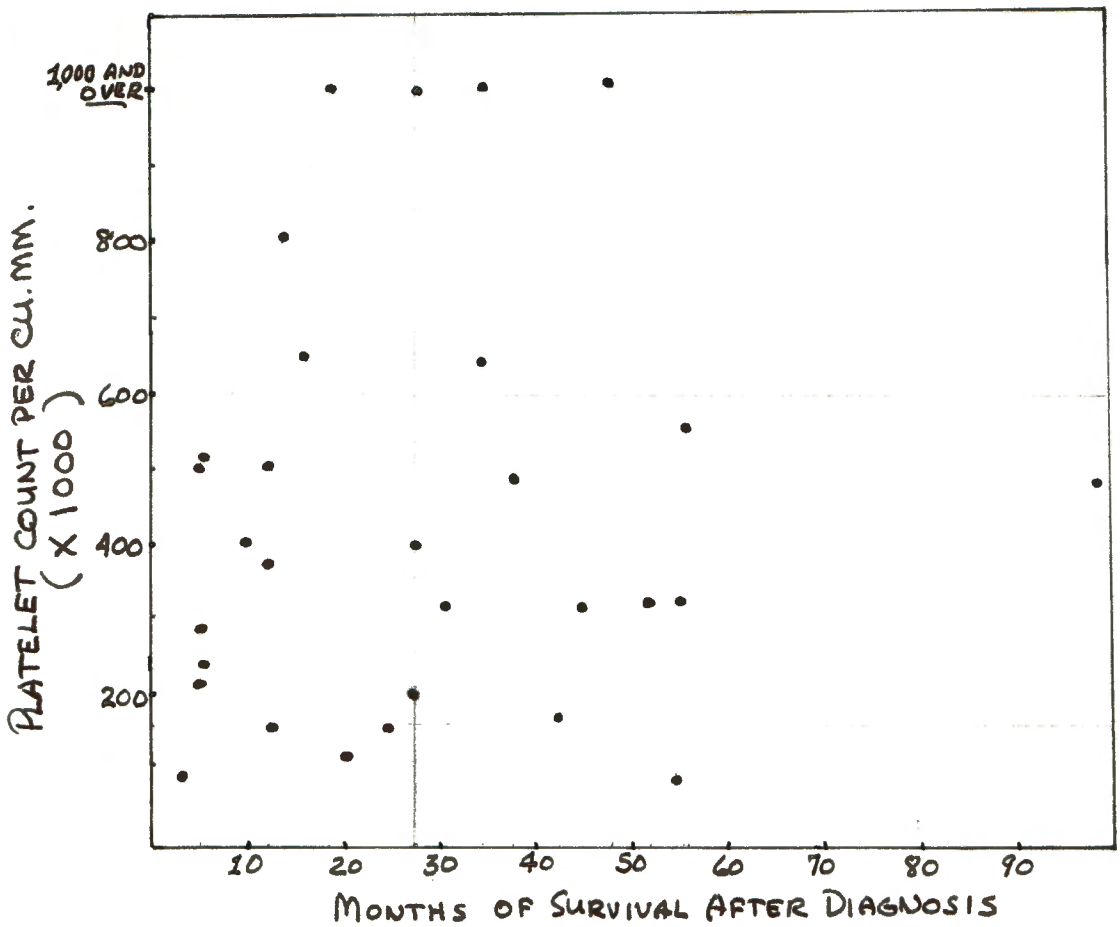


Fig. 10 The number of platelets per cu. mm. in 30 cases of chronic granulocytic leukemia as compared to the months of survival after diagnosis.

BONE MARROW FINDINGS

In all cases where bone marrow reports were available the marrow was found to by hypercellular, ranging from slightly hypercellular to markedly hypercellular. The white blood cell to red blood cell ratio ranged from 1:5 to 1:40. Megakaryocytes were increased in number in 23 cases, normal in number in eight cases and decreased in three cases. In 11 of the 46 cases of chronic granulocytic leukemia there was bone marrow evidence in the form of increase in immature cells, of change from a chronic phase to an acute phase. In all 11 cases this was a terminal event. The mean survival from diagnosis in cases which ended in an acute phase was 25.3 months compared to 28.1 months in those which showed no evidence of conversion to an acute phase.

PHYSICAL FINDINGS

The only physical findings reviewed in this study were the presence or absence of splenomegaly and hepatomegaly. A crude estimate of the size of the spleen and liver was obtained by recording the number of centimeters the spleen or liver extended below the costal margin. In three cases there was

no indication as to whether or not the liver was palpable, the same being true in two cases were no indication of splenic palpation was given. In 33 cases both splenomegaly and hepatomegaly were reported. In four cases there was splenomegaly but no hepatomegaly. In two cases there was only hepatomegaly. In one case splenomegaly was reported with no evidence as to presence or absence of hepatomegaly.

These physical findings in all cases were present at the time of diagnosis of the disease. Figure 11 was constructed to show the relationship between the size of the spleen at the time of diagnosis and the survival time of the patient.

TREATMENT

Since more than one type of treatment was used in many of the 46 cases no accurate appraisal of the effect on the course of chronic granulocytic leukemia of any particular agent can be given. Various agents were tabulated as to the frequency of their use. Myleran was used most often, being used in 30 cases. X-Ray treatment to the spleen was used 14 times. Triethylenemelamine and 6-Mercaptopurine were used two times and Methotrexate was used one time.

All patients received at least one of the above

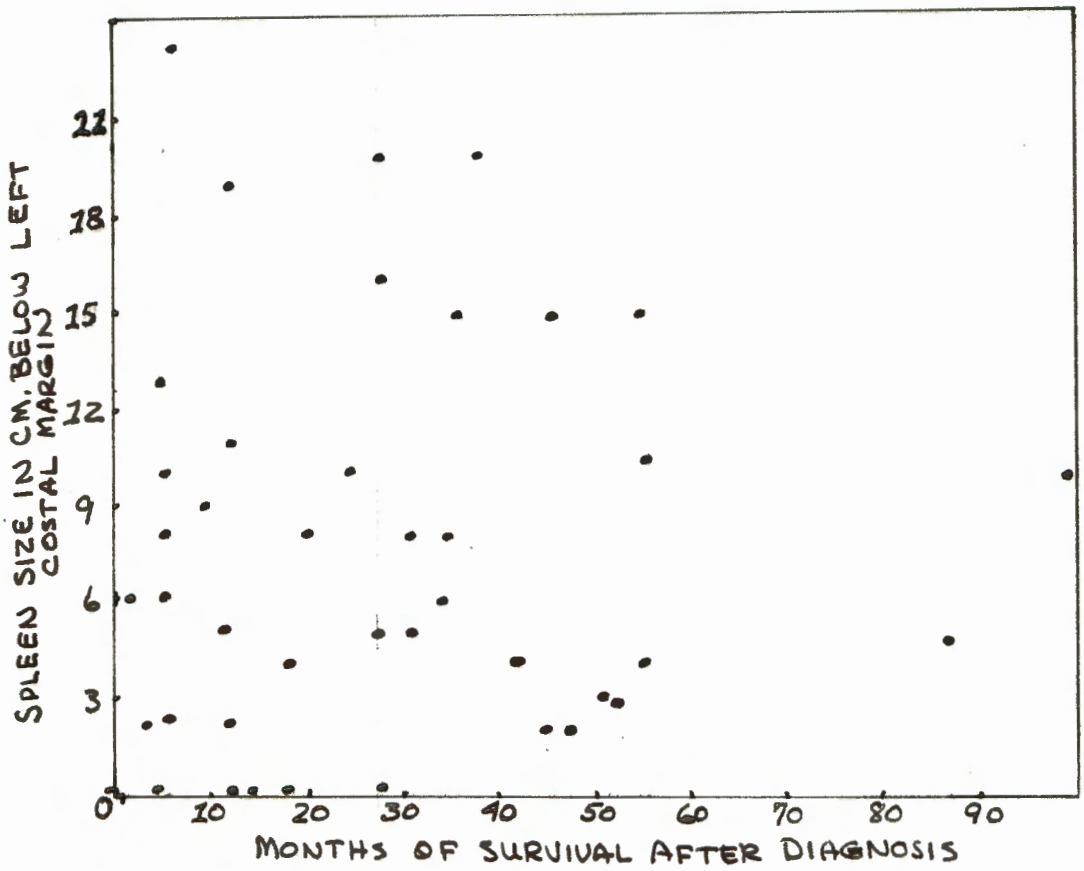


Fig. 11 Size of the spleen in 41 patients with chronic granulocytic leukemia as compared to the months of survival after diagnosis.

forms of treatment. One patient who survived 10 months from the time of onset of symptoms received Triethylenemelamine only through the last six days of life. Another patient who lived 4.25 years after the onset of the disease received Myleran only through the last 10 days of life.

DISCUSSION

The mean age at the time of diagnosis in this series of 46 patients with chronic granulocytic

leukemia was found to be 51.9 years. The average survival time after diagnosis was calculated to be 27.4 months. If this survival of 27.4 months for persons 51.9 years of age is compared to the life expectancy of 25.5 years[9] for this age group calculated by the United States Bureau of the Census, then it would appear that chronic granulocytic leukemia did indeed have a notable effect upon the survival of the patient. A proper control group would have to be studied in order to attach statistical significance to this statement.

Minot[1] who studied a series of 166 patients with chronic granulocytic leukemia reported the highest incidence of the disease between the ages of 35 and 45 years of age. In this study the highest incidence was found to be in the seventh decade (60-69 years). Feinleib[2] found the highest incidence to be in the 40 to 59 year age group. In 1952 Osgood[3] in a series of 61 patients with chronic granulocytic leukemia reported that 79 per cent of the patients studied fell in the age group between 31 and 70 years of age with a mean age of 48 years. In this study it was found that 80.4 per cent of the cases occured between the ages of 40 and 79 years.

The average age at diagnosis was 51.9 years. Shimkin,[4] who studied 212 patients with chronic granulocytic leukemia occuring in the years 1910-1948 found the age at onset to be 39.6 years before 1930 and 43.6 years after 1940 with a mean period between onset of the disease and diagnosis of 12 months.

In this series of patients 52.2 per cent were females and 47.8 per cent were males. Wintrobe[5] in a series of 39 cases reported 61.5 per cent to be males. Shimkin[4] found no significant difference in age at onset and diagnosis between the two sexes.

The average survival from the onset of 44 of the 46 patients in this series, including those in whom the diagnoses were incidental, was 33.3 months or 2.78 years. The average survival from the time of diagnosis was 27.4 months or 2.28 years and the mean time period from onset to diagnosis was 5.9 months. Shimkin[4] found the mean survival from onset of 173 patients to be 3.1 years whereas Wintrobe[5] calculated a mean survival of 2.79 years after onset with a survival time 1.68 years from diagnosis of the disease. He found the time between onset of symptoms and recognition of the disease to be 1.11 years. He, furthermore, reported five cases in which

a diagnosis of chronic granulocytic leukemia was made before the patients had any symptoms and postulated on this basis that the actual onset of the disease may be two to five years before symptoms cause the patient to obtain medical consultation. Minot[1] found the average duration of life from the first symptom to be 3.04 years and 3.5 years in untreated and irradiated patients respectively. In this series survival was not calculated with regard to amount or kind of treatment but all patients received some kind of treatment.

Tivey[6] used the maximum likelihood method using log-normal distributions for calculating survival of patients with chronic leukemias. He felt that use of arithmetic means when applied to skewed distributions as in this group of patients did not represent a true picture for life expectancy in this type of disease, in most cases too optimistic an expectation of survival being given. Feinlieb[2] used a modified maximum likelihood method in his study. More recently Green and Dixon[7] used the modified maximum likelihood method of logarithmic probability analysis and an actuarial method in calculating the survival of their patients. Although these methods were not used in this particular study it is conceded

that in most instances where the data tend to be skewed they represent a superior method over use of the arithmetic mean when it does not follow the familiar gaussian distribution.

By Figure 2 it can be seen that at one year after onset of symptoms 86 per cent of the patients were still living. Although not shown graphically it was calculated that at one year after diagnosis 79.1 per cent of the patients were living. This compares with 35 to 50 per cent living at one year after diagnosis in a study by Clemmesen[8] in which both patients from the United States and Scandinavian countries were included. In his study five to nine per cent were living after five years and in this study it was found that 4.6 per cent were living five years after diagnosis.

According to Wintrobe[10], anemia may not always be present at the time of diagnosis of chronic granulocytic leukemia, however, generally it is present and may be quite severe. At least one explanation of anemia in this disease is the active displacement of erythropoietic tissue by myeloid tissue. It would seem reasonable then, to assume that there might be some relationship between the hemoglobin at the time of diagnosis and the expected survival of the patient.

Figure 3 gives no real support to the proposal that anemia at t e time of diagnosis of chronic granulocytic leukemia carries with it a poorer prognosis than if anemia were not present. Of 32 patients whose hemoglobins were less than 12.5 grams per cent, 16 had lower survival times from the time of diagnosis than the mean of 27.4 months and 16 survived longer than the mean of 27.4 months.

Since the number of reticulocytes in the peripheral smear is an indicator of erythropoietic activity,[11] then displacement or replacement of erythropoietic tissue could result in a lowered reticulocyte count. Conversely, increased reticulocyte counts would indicate accelerated erythropoietic activity. By reviewing figure 5, it is seen that elevated reticulocyte counts at the time of diagnosis of chronec granulocytic leukemia do not appear to indicate poor prognosis in this series of patients. Twenty patients had elevated reticulocyte counts and of these, 10, or 50 per cent lived longer than the mean 27.4 months and 10, or 50 per cent did not reach the mean survival time. Only one patient had a reticulocyte count which was below the normal minimum of 0.5 percent and this carried an extremely poor prognosis. However, no valid statements concerning prognosis

an be made on the basis of one patient.

By observing figure 3 in which the white blood cell counts of 39 patients are compared to survival, it is seen that of 28 patients with white counts over 50,000 per cu. mm., 16 or 57 per cent lived longer than the mean survival time of 27.4 months and 12, or 43 per cent did not reach the average survival time after diagnosis. However, of 10 patients whose white blood cell counts were below 50,000 at the time of diagnosis, only two, or 20 per cent attained the mean survival of 27.4 months. Both of these had white counts below 10,000 per cu. mm. at the time of diagnosis. The remaining 80 per cent had elevated white cell counts but only moderately elevated in that they were all below 50,000 per cu, mm.

Monocyte and basophil counts were tabulated to see if there was any prognostic correlation between their numbers and ultimate survival of the patient. Figure 8 shows that of 10 patients with monocyte counts over four per cent, only three or 30 per cent attained the mean survival of 27.4 months. Seven, or 70 per cent, died before reaching the mean. Figure 9 deals with the relationship between the basophil count and ultimate prognosis of the patient with chronic granulocytic leukemia. Eleven patients with basophil counts

over two per cent failed to attain the average survival of 27.4 months, whereas nine patients with elevated basophil counts surpassed the mean survival time. From these limited data it would appear that elevated monocyte counts are a worse prognostic sign than elevated basophil counts, however, a larger series would have to be observed to validate this statement.

By observing the distribution of platelet counts in figure 10, it is seen that there is no apparent prognostic sign in elevated platelet counts, since, of six patients with elevated platelet counts, three each fell above and below the mean survival of 27.4 months. Of five platelet counts which were below normal, four died before attaining the mean and one surpassed the mean survival time.

The spleen is usually markedly enlarged in chronic granulocytic leukemia.[10] Figure 11 shows the relationship of splenic enlargement, on the basis of physical examination, to months of survival after diagnosis. Twenty patients who had splenomegaly survived longer than the mean of 27.4 months and 16 patients who had splenomegaly did not attain the mean survival time. Of five patients who had no splenomegaly at the time of diagnosis, four did not

attain the mean survival time and one surpassed the mean survival time of 27.4 months.

In this series of 46 patients, 11, or 24 per cent, were found to have an acute terminal exacerbation of the disease. Shimkin[4] reported that approximately one fourth of a series of patients were found to have an acute exacerbation of chronic granulocytic leukemia of established long duration.

CONCLUSION

1. Forty six cases of chronic granulocytic leukemia from the hematology records of the University of Nebraska Hospital and private records of Peyton T. Pratt, M.D. were studied in detail.
2. Thirty six patients had died and 10 patients were living.
3. Of all the patients, 22 were males and 24 were females. Two of the 46 patients were Negro females.
4. The highest incidence of chronic granulocytic leukemia was in the seventh decade (60 to 69 years), however, the average age of all patients at the time of diagnosis was 51.9 years. There was no difference between sexes as to age of onset.

5. The mean survival from onset was 33.3 years. Since this figure includes 10 patients still living, the survival time will increase as these patients continue to live. The average survival of the patients who had died was 32.0 months. The average survival to date of the 10 living patients has already been 42.0 months.

6. The average survival from the date of diagnosis was 27.4 months.

7. The hemoglobin value at the time of diagnosis gave no indication as to the ultimate prognosis of the patient. The reticulocyte count showed only minimal correlation in that patients with normal or near normal reticulocyte counts tended to live longer.

8. The initial white blood cell count showed little correlation with ultimate survival of the patient.

9. An inverse relationship between numbers of monocytes and basophils was seen.

10. Separately, both monocytes and basophils, when increased, were poor prognostic signs.

11. Spleen size at the time of diagnosis was of no value in predicting the ultimate survival of the

patient.

12. Eleven, or 24 per cent of the patients had an acute terminal exacerbation of chronic granulocytic leukemia.

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