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tion of prognostic factors are important for the induction of a hematological remission. While patients in complete hematological remission are free of evidence of disease they still have residual leukemic cells, but in our present state of knowledge and with available techniques, we are unable to detect these. For this reason it is important to treat patients while in a remission. The importance of dosage schedule for remission maintenance chemotherapy is stressed.

In patients studied to date, regardless of the treatment used, the disease has recurred eventually. Available therapeutic agents are highly effective and highly selective, but they still fall short of providing ideal control of the disease. The continuing search for new chemotherapeutic agents is aided by the knowledge gained and techniques developed with current agents.

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The Influence of Morphology on Prognosis in Acute Leukemia

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The presence of definite cytoplasmic granulation in at least some of the malignant cells was used as the sole criterion to separate 156 patients with acute leukemia into two groups: 110 with myeloblastic (AML), and 46 with lymphoblastic or stem cell leukemia (ALL). The median survival from the onset of symptoms in patients with AML was 20 weeks, and those with ALL 37 weeks. The difference in survival in these two groups is much greater for patients under the age of 25 than for those over the age of 25.

La présence d'une nette granulation cytoplasmique dans au moins certaines des cellules malignes a été le seul critère employé pour répartir en deux groupes 156 malades atteints de leucémie aiguë: 110 souffraient de leucémie myéloïde aiguë (LMA) et 46 de leucémie lymphoïde aiguë (LLA). La survie moyenne, à partir du début des symptômes, a été de 20 semaines pour les malades atteints de LMA et de 37 semaines pour ceux atteints de LLA. La différence de survie entre ces deux groupes est beaucoup plus grande pour les malades âgés de moins de 25 ans que pour les malades ayant dépassé 25 ans.

THE 156 patients described in this paper were seen at three hospitals, the Toronto East General Hospital, the Toronto General Hospital, and The Princess Margaret Hospital, with almost equal numbers at each. They include all those in whom there were sufficient clinical and laboratory data for review—since 1958 at the Toronto East General Hospital, and since 1960 at the Toronto General and Princess Margaret Hospitals. In each patient blood films and/or bone marrow specimens were reviewed; the earliest available blood film was used for classification when no marrows were available. In a small number of patients only peripheral blood films were available for review and these were included only if the films showed sufficient numbers of blast cells. Because all three hospitals have a considerable proportion of their cases referred to them, some of the patients had previously been treated and had relapsed before being seen for the first time in these hospitals. In these patients the cells may have been altered by previous therapy. All doubtful films were examined by all the authors without the associated clinical history and agreement was reached; in very few cases was this not unanimous. Undoubtedly there is a high degree of preselection before these patients are admitted to these three hospitals, particularly in respect of age, because many children with leukemia in the Toronto area have their entire care in The Hospital for Sick Children.

The morphological criteria generally accepted for the differentiation of malignant lymphoblasts from malignant myeloblasts will not be described

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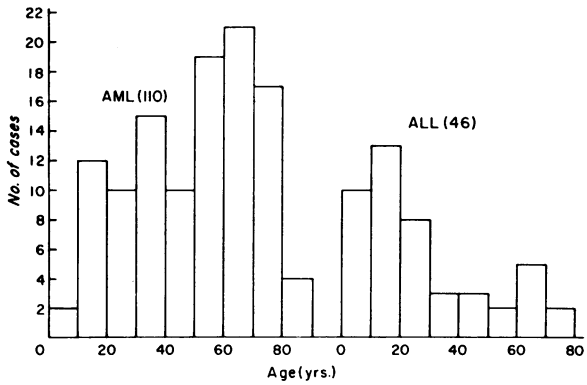

Fig. 1.—The age distribution of 156 patients with acute leukemia.

in detail.[2, 5-7] Many of the features suggested are relative—larger or smaller nuclei, more or less cytoplasm, greater or lesser degrees of nuclear folding, finer or coarser chromatin, etc. Differentiation based on these features has the disadvantage that cells which are borderline cannot readily be placed in one or the other group. In the study described in this communication, therefore, a qualitative criterion has been chosen—the presence or absence of definite cytoplasmic granulation in at least some of the cells of the malignant line as seen with Romanowski stains. This is interpreted as indicating differentiation towards a promyelocyte and therefore indicating that the involved cell line is the myeloblast. The group classified as "acute myeloblastic leukemia" (AML) also includes cases that some hematologists would label "acute myelomonoblastic leukemia" or "acute monocytic leukemia". There is no comparable criterion which will identify lymphoblasts. The term "acute lymphoblastic leukemia" (ALL) therefore includes all cases lacking cytoplasmic granulation. Some hematologists, however, might prefer terms such as "acute undifferentiated blast-cell leukemia" or "acute stem-cell leukemia" for these cases.

Fig. 1 shows the age distribution of patients in the two groups. The median age of the 110 patients with acute myeloblastic leukemia was 57 years, but significant numbers of cases were seen in all decades of life except the first. The median age of 46 patients with acute lymphoblastic leukemia was 20 years, and there is clearly a decreased proportion of these cases after the third decade of life. The difference between the behaviour of acute leukemia in children and adults is confirmed in the data presented here. The age of 25 has arbitrarily been taken to separate childhood leukemia from adult acute leukemia.

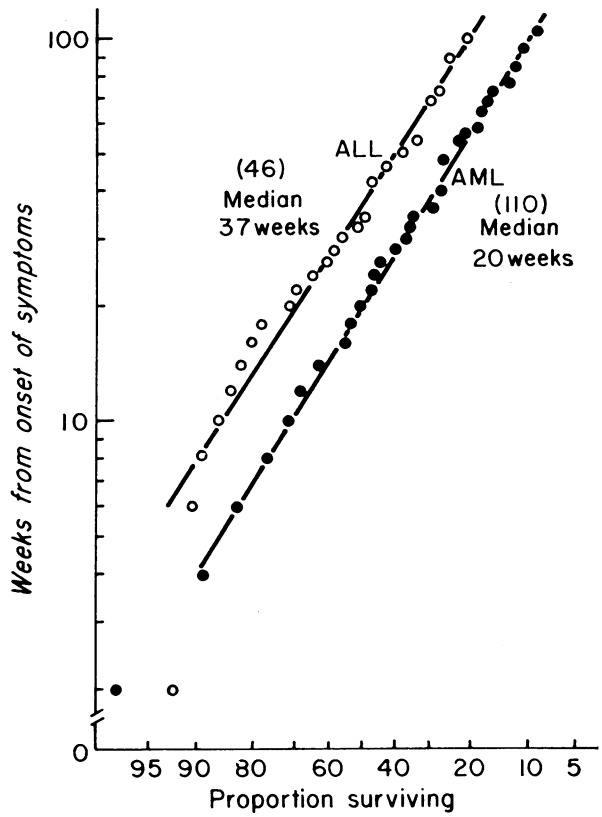

Fig. 2.—Survival of all patients from onset of symptoms to death. Log probability scale.

Survival statistics have been graphed on log-probability paper. The ordinate shows the number of weeks elapsed from the onset of symptoms to death, or in those still living, to the time of the study; the abscissa shows the proportion of patients still living at that time. The duration of disease to the time of the study in patients still living has been used to calculate these ratios. Fig. 2 includes all patients from onset of symptoms. The median survival in acute myeloblastic leukemia was 20 weeks, and in acute lymphoblastic leukemia 37 weeks.

Because of the difficulties in fixing the onset of symptoms, the same cases were analyzed from the date on which the diagnosis was made (Fig. 3). The better survival of patients with acute lymphoblastic leukemia as compared to those with acute myeloblastic leukemia is confirmed here: the median survival of acute lymphoblastic leukemia is 25 weeks, and of acute myeloblastic leukemia seven weeks. Note that the time from onset of symptoms to diagnosis, 12 to 13 weeks, is not significantly different in the two groups.

To what extent is age responsible for the difference in median survivals in the two morphological groups? If the patients are divided into "childhood" and "adult" acute leukemia, separating them at age 25, the results must be treated

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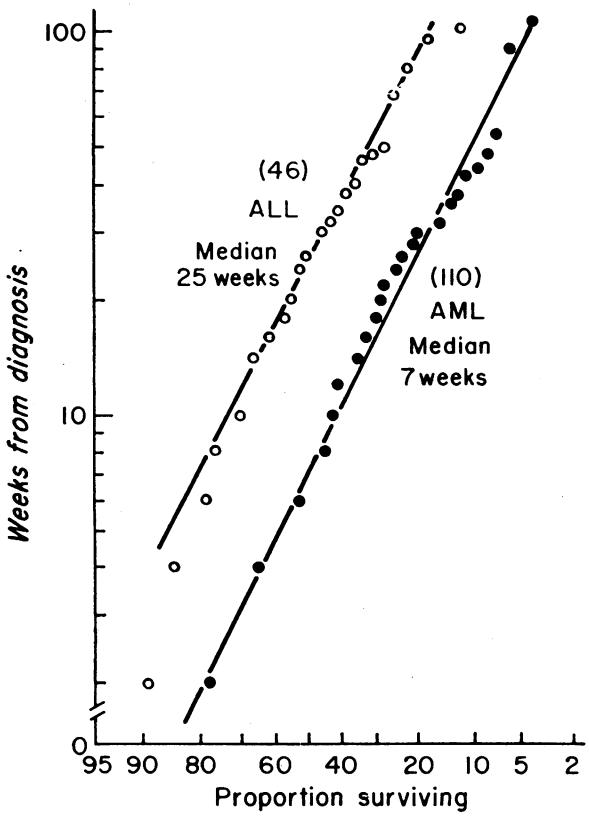

Fig. 3.—Survival of all patients from diagnosis to death. Log probability scale.

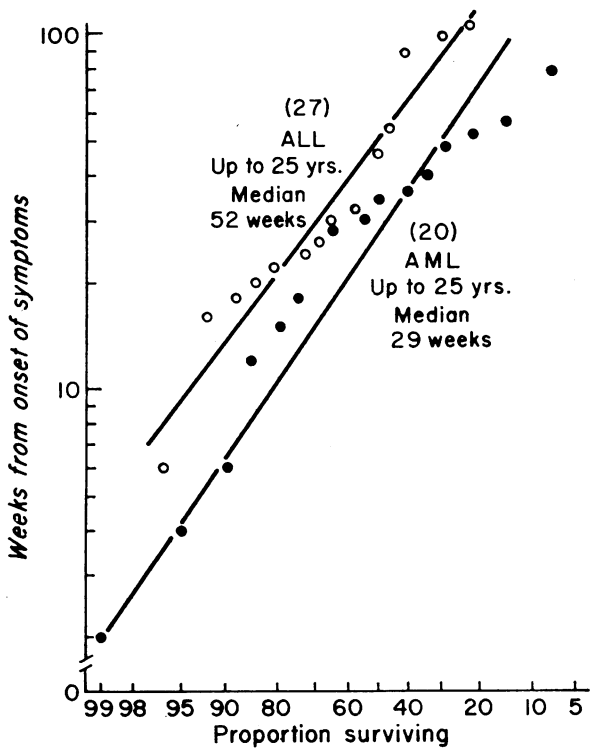

Fig. 4.—Survival of patients up to 25 years of age, onset of symptoms to death. Log probability scale.

with caution, because of the relatively small numbers in each group.

Fig. 4 shows the duration of survival of patients under 25 from the onset of symptoms. Median survival of children with acute myelogenous leukemia is still only 29 weeks, but the children with acute lymphoblastic leukemia survive a median of 52 weeks. The longest survivals among the 20 patients under 25 with acute myeloblastic leukemia were in three who lived from one to one and one-half years, including one 25-year-old woman who was still alive at 82 weeks, although acutely ill. The longest survivals among those with acute lymphoblastic leukemia in this age group were four of 27 patients who survived more than two years; one is still living at two and one-half years and the other three have died at 108, 142 and 219 weeks, respectively.

In this age group the longest median survivals and longest individual survivals were both in the acute lymphoblastic leukemia group.

When these individuals are studied from the date of diagnosis the results are not significantly altered (Fig. 5), although it is difficult to determine a satisfactory median survival for acute myeloblastic leukemia because of scatter.

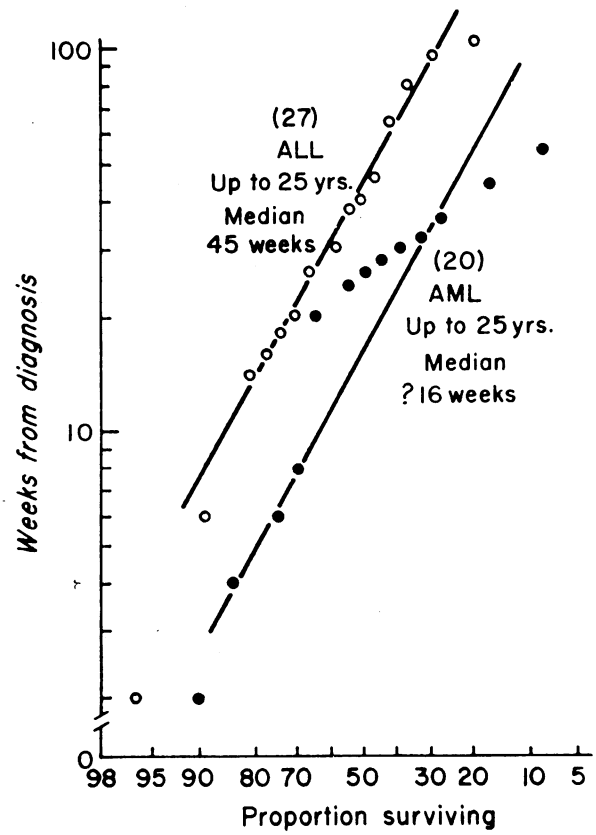

Fig. 5.—Survival of patients up to 25 years of age, diagnosis to death. Log probability scale.

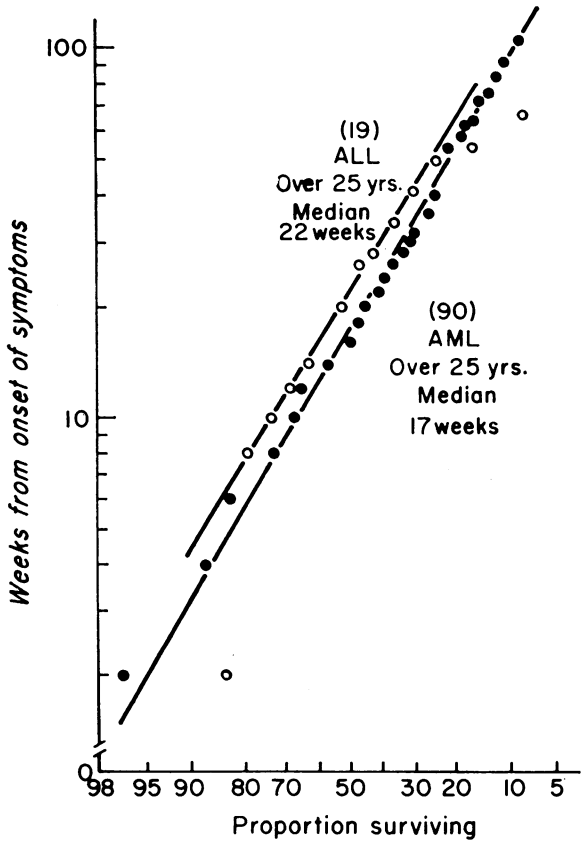

Fig. 6.—Survival of patients over 25 years of age, onset of symptoms to death. Log probability scale.

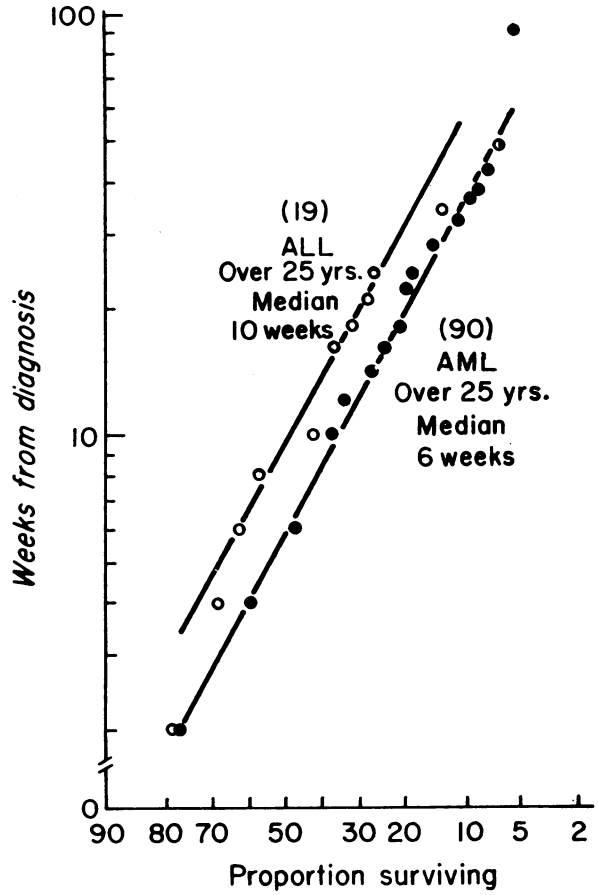

Fig. 7.—Survival of patients over 25 years of age, diagnosis to death. Log probability scale.

In patients over the age of 25, although the number of acute lymphoblastic leukemias is small, the difference in survival is less striking (Fig. 6). The median survivals in both morphological groups are distinctly shorter than for the children, 17 weeks in acute myeloblastic leukemia and 22 weeks in acute lymphoblastic leukemia. Three of the 19 patients with acute lymphoblastic leukemia lived more than one year, only one of them more than one and one-half years—a 36-year-old woman who had recurrent respiratory infections for five years before the diagnosis of leukemia was made—she died 32 weeks after diagnosis. Of the 90 patients with acute myeloblastic leukemia, 23 lived longer than one year, 10 longer than two years, and four longer than three years from onset of symptoms; in only one of the last four was the diagnosis established more than one year before death.

Fig. 7 shows that the analysis of survival from diagnosis to death gives data comparable to those from symptoms to death. Seven patients with acute myeloblastic leukemia lived more than one year, three more than two years, and one patient was alive more than six years from onset of acute myeloblastic leukemia, although she now shows disseminated "lymphoblastic lymphosarcoma".

Comparison of these data with other published series is difficult because of differences in the age selected as the dividing line between childhood and adult life and variations in criteria for typing. In acute myeloblastic leukemia, the median survival of seven weeks from diagnosis is somewhat less than the figure of three to four months given by Boggs, Wintrobe and Cartwright[1] from Salt Lake City and four months given by Dameshek, Necheles and Finkel[3] from Boston. In acute lymphoblastic leukemia, local experience is more closely compar-

		Did Not Receive Cortico Steroids	Responded In Alone	Responded In Combination	Total	Median Survival	Did Not Respond	Survival
ALL	<25	0	4	16	20	45 wks	7	14 wks
	>25	4	3	6	9		6	
					69%			
AML	<25	5	6	4	10	35 wks	5	13 wks
	>25	50	1	10	11		29	
					38%			

Fig. 8.—The frequency of response to corticosteroids, and the effect of response on survival.

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able to that given in the literature. Boggs' median figure for survival of children under 15 years was seven months, and for adults five months from diagnosis: our figures were 10 months and two and one-half months, respectively. However, his data are derived from an earlier period and he divided children from adults at the age of 15. Freireich[4] has obtained survivals in childhood lymphoblastic leukemia now approaching 30 months. We have no explanation for this somewhat shorter median survival in the Toronto area.

It has been suggested that the longer survival in acute lymphoblastic leukemia may be due entirely to the responsiveness of acute lymphoblastic leukemia to therapy, particularly with corticosteroids. Few patients have been treated with corticosteroids alone, so this hypothesis is difficult to evaluate. Rigid criteria were not laid down to judge response rates, partly because, for many patients, there were not enough data to evaluate the response on the basis of rigid criteria. However, Fig. 8 shows that 69% of patients with acute lymphoblastic leukemia treated with steroids showed evidence of a response and in seven of the 29 this was the only agent used as antileukemic therapy at the time. Thirty-five per cent of patients with acute myeloblastic leukemia responded to therapy and in seven of 22 cases corticosteroids only were used. On the other hand, 13 out of 44 patients with acute lymphoblastic and 34 out of 55 with acute myeloblastic leukemias who received corticosteroids alone or in combination did not respond.

SUMMARY AND CONCLUSIONS

When cytoplasmic granulation was used as the sole criterion for differentiating acute myeloblastic leukemia from acute lymphoblastic or stem-cell leukemia, the median survival from the onset of symptoms in patients with acute myeloblastic leukemia was 20 weeks, and of those with acute lymphoblastic leukemia 37 weeks. The difference in survival between these two groups is much greater for patients under the age of 25 than for those over the age of 25.

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