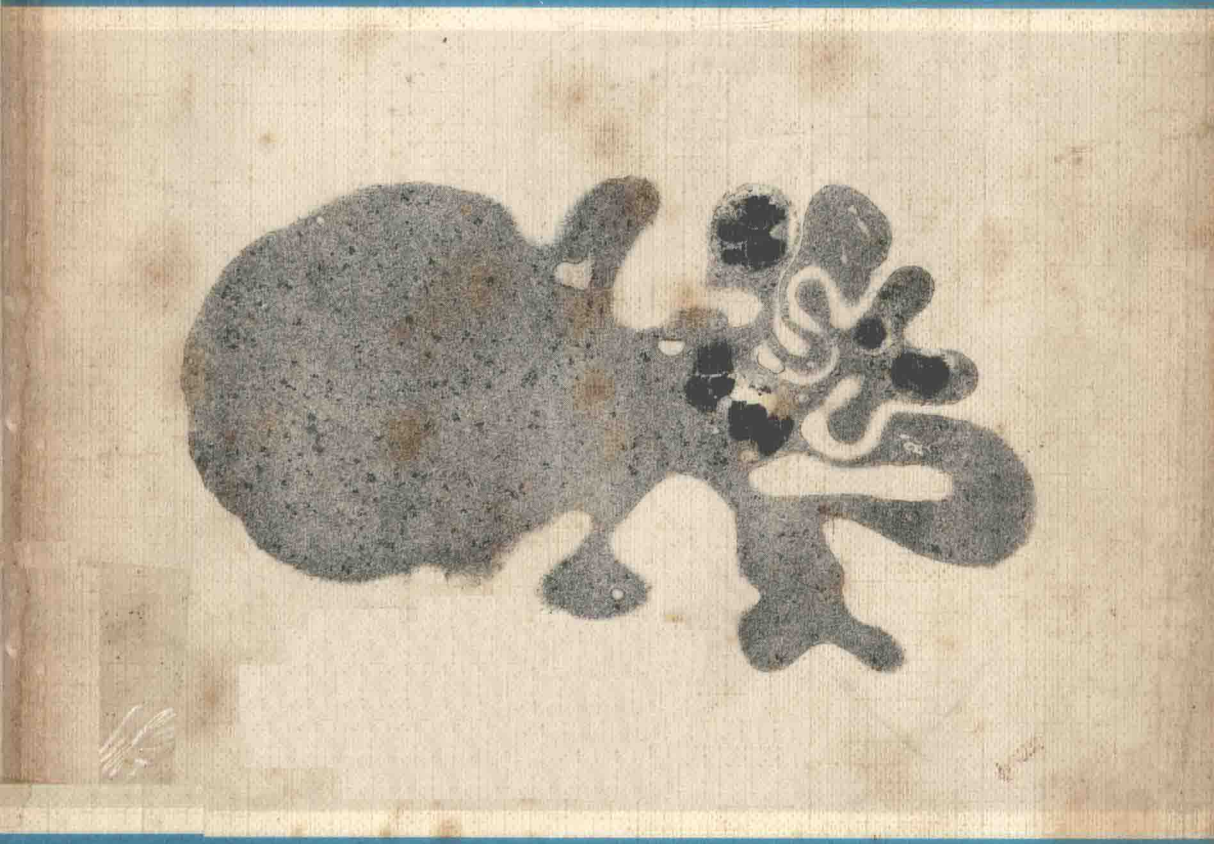
Hemopoietic Dysplasias (Preleukemic States)

Editors: Marcel Bessis and George Brecher



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Preleukemic States

Jean BERNARD*

I

Preleukemic states may be prototypes, forerunners or incomplete manifestations of leukemia, or unrelated diseases bearing superficial resemblances to leukemia. By definition, a preleukemia does not allow the diagnosis of acute leukemia and yet develops into leukemia. However, in our present state of ignorance, we cannot predict the leukemic outcome. Hence, if we are to diagnose preleukemia other than retrospectively, we will inevitably include in the diagnosis other entities which dot not develop into leukemia, but resemble the preleukemic states morphologically and clinically. It is this uncertainty of prospective diagnosis which has caused the great interest in the subject.

The preleukemic states proper, i.e. those that will develop into leukemias can conceptually be of 2 types: early subclinical stages of leukemia and clinical states which are merely conducive to the development of leukemia. It is not clear how these 2 states can be distinguished from each other or from those only apparently preleukemic states that do not carry with them the eventual leukemic outcome.

It become crucial to define the onset of leukemia. It is almost trivial to note that the diagnosis requires not only the presence on an increased number of mature and immature cells in the peripheral blood, but alteration of the hemopoietic tissues which must be widespread and significant in the individual sites. The difficulty arises when one attempts to define how many different areas of hemopoietic tissues must be involved to distinguish preleukemia from leukemia. What must the rate of cell division be to characterize the onset of leukemia? There is not set of criteria that can claim general acceptance. Meanwhile, we must continue our semantic efforts to define leukemia and preleukemia and related conditions such as dyserythropoiesis and refractory anemia. Perhaps these terms can be eliminated as irrational. Perhaps we need to consider new terms such as the recently proposed term "stem cell disorder". At any rate, to explore the limits of our knowledge and our nomenclature should be one of the objects of the symposium.

Two tasks confront us. First, how to distinguish the different types of preleukemia from each other and from similar conditions which do not lead to leukemia, and from the onset of early leukemia. Secondly, how to exploit these forerunners or models of leukemia to get to the bottom of questions of etiology and pathogenesis of leukemia.

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Three types of leukemic states seem to offer possible approaches to the problem of etiology and pathogenesis: first, the leukemias of known origin which include viral leukemias of animals and leukemias due to radiation and chemotherapy in both experimental animals and man; secondly, certain types of leukemia of unknown origin; and thirdly, the quasi-preleukemic states of prolonged remission and apparent cure in childhood leukemia which suddenly relapse.

Viral leukemia of animals has been the subject of numerous sophisticated studies, but they have not yet answered the following important questions. Is leukemia under these given conditions inevitable? If not, what special features separate those conditions that develop into leukemia from those that do not? Is spontaneous regression possible after cellular lesions have appeared? If so, is it possible to promote this reversibility to prevent progression by timely intervention and by what sort of intervention?

A quite different set of questions arises *in leukemia* induced in man and experimental animals by *irradiation and chemicals*. Two additional factors require attention: variability and duration. The development of leukemia in this instance is certainly not inevitable. For example, a population subject to a given dose of radiation or of a chemical agent can be divided into several groups. One with persistance of normal health; a second which develops immediately an obvious leukemia; a third with appearance of various non-leukemic blood disorders; and a fourth in which a succession of non-leukemic episodes is followed by overt leukemia. Observation of the last two groups over many years may perhaps answer some of our questions. For instance, will a leukopenia or neutrophilic leukocytosis inevitably progress to leukemia? Can certain apparently leukemic states characterized by the presence of a few blasts regress? Can these anomalies be recognized and corrected? Modern methods of the study of cells in different environments have perhaps not been exploited sufficiently. It would be useful to examine the role played by a preceding illness, whether it be a non-malignant condition such as polyarthritis or a malignant one such as Hodgkin's disease in which radiation or chemotherapy triggers the appearance of leukemia.

Experimental work has shown that under certain conditions radiation may cause liberation of latent leukemogenic viruses in mice. Similar discoveries have been made in relation to various chemical agents. Perhaps by use of this model, in which the inducer is known, one could define exactly the earliest moment at which precise markers of viral expression, such as new sequences of RNA in antigenic proteins can be recognized. In addition, the study of these markers during the development of the syndrome could define the physiopathologic mechanisms of the hematologic and clinical events more precisely.

Concerning *the leukemias of unknown etiology*, the study of spontaneous preleukemia is relevant. It has gone through two stages. The initial phase consisted of simplistic and poorly organized descriptions of all the symptoms preceding the time before leukemia can be diagnosed, a second phase brought more precise distinction of syndromes such as the acute aplasia in children, and the "oligoblastic" disorders of adults. It is high time that a third phase of detailed analysis

of these disease states began. We need to compare the appearance of "blasts" which appear to be leukemic, yet regress and turn out not to be leukemic, as observed in Down's disease, with a small number of similar immature cells which appear to be non-leukemic, yet progress and turn out to leukemic after all.

Concerning *remissions in childhood leukemia*, these have become more and more prolonged recently and actual cures have been obtained. Their number is still small. In the great majority of cases, the "complete" remissions of prolonged duration are in fact incomplete and may be comparable to some of the preleukemic states. The study of these complete remissions has, in the past, been concerned with survival only. We may now begin to ask, can the eventual relapse be predicted? Can appropriate treatment prevent it? Such studies may profit from consideration of the "true" preleukemic states and in turn strengthen our knowledge of these states. Of particular interest are the prolonged remissions of 4 or 5 years duration which suddenly relapse. Have there been regular divisions of leukemic cells during the entire duration of remission? Or have truly quiescent cells suddenly been reawakened and how? It has recently been postulated minute sub-populations exist which may include these quiescent cells. Are we dealing with reactivation of a dormant virus or possibly even reinfection from an exogenous one?

The solution, or at least a suitable start toward solving these questions could shed new light on the preleukemic states. Conceivably, such studies could eventually lead to prevention and permit early and rational therapy of the leukemias themselves.

SECTION I

CLINICAL AND HEMATOLOGICAL DATA

The Preleukemic Syndrome: Clinical and Laboratory Features, Natural Course, and Management

James W. LINMAN and Grover C. BAGBY, Jr.

ABSTRACT. **The clinical and laboratory features of the early stages in the evolution of acute nonlymphocytic leukemia are reviewed. Based on a retrospective analysis of 34 patients who died with an acute myelomonoblastic leukemia, the "preleukemic syndrome" has been shown to display a clinical picture sufficiently specific to permit its recognition prospectively (i.e., before the development of overt leukemia). The results to date of a variety of prospective studies are reviewed, and the approach(es) to the management of these cases is considered.**

KEY WORD: **Preleukemia**

INTRODUCTION

Our interest in the early phases of evolving leukemia (i.e., the preleukemic syndrome) was intensified several years ago as the result of a retrospective study designed to evaluate the lack of morphologic homogeneity in the acute nonlymphocytic leukemias. The results of this project have been described elsewhere [1]; in brief, 132 cases of acute nonlymphocytic leukemia were analyzed, and each patient displayed morphologic evidence of involvement by more than one cell line. At the time of diagnosis of overt leukemia, there were leukemic changes in all marrow cell lines (erythrocytic, granulocytic, megakaryocytic, and monocytic) in 83 of these cases (63%); in 38 (29%) three lines were affected, and in 11 cases (8%) two cell lines appeared to be involved. It was concluded from these observations that acute nonlymphocytic leukemia(s) was basically a marrow stem cell disease and that most (if not all) of the acute nonlymphocytic leukemias were variants of one disease. We have used as a label for the leukemic phase of this myeloproliferative disorder "myelomonocytic leukemia" ("myelo-" to indicate that all myeloid – that is, marrow elements are involved, and "mono-" to emphasize the prominent monocytoid features). Because of the striking variability in courses among these 132 cases, it seemed inappropriate to attempt further subdivision into "acute" and "chronic" types. An alternative designation that is acquiring more and more appeal is "nonlym-

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phocytic leukemia" with "acute nonlymphocytic leukemia" being reserved for those patients who are clearly in the blastic phase of their disease. Attempts to apply strict morphologic criteria to the classification of the leukemias supports the suggestion that most leukemias can be divided into four groups (acute lymphocytic, chronic lymphocytic, chronic granulocytic, and nonlymphocytic) [2]; the first three types have easily recognizable clinical pictures, whereas the nonlymphocytic leukemias are characterized by variability in findings and natural courses. We currently believe that the nonlymphocytic leukemias reflect a single polyphasic disorder and that the various labels that have been used in the past most likely represent stages in the evolution of the disease and/or differing host responses (e.g., erythroleukemia, DiGuglielmo's syndrome, monocytic leukemia, granulocytic leukemia, and megakaryocytic leukemia).

In addition to clarifying the clinical manifestations of overt nonlymphocytic leukemia(s), the retrospective study described above was responsible for an additional study that has shed light on the clinical and laboratory features of the evolutionary stages in the disease prior to the development of the classical cytologic and histologic features of acute leukemia (i.e., a marrow packed with blast cells). Contrary to the widely held opinion that "preleukemia" can be diagnosed only retrospectively (i.e., after the onset of blast cell leukemia), our observations point to a rather monotonous hematologic syndrome that does permit prospective recognition.

CLINICAL AND LABORATORY FEATURES

I. Retrospective Studies

Among our 132 cases of acute nonlymphocytic leukemia, the majority (52%) gave a history of a poorly defined hematologic disorder of variable duration that preceded the onset of leukemia; in 41 cases (31%) a preleukemic phase could be documented; in 34 cases (26%) clinical and laboratory data, including blood smears and marrow specimens, were available. Retrospective analysis of these cases yielded diagnostic criteria that have since withstood prospective testing. Details of this project have been published [3, 4]; however, these observations will be summarized here, for they form the basis of our Prospective studies now in progress.

Most of these 34 patients were men (30) with a median age of 58 and a range of 16 to 80 years (68% were 50 years of age or older when their hematologic disease began). Symptoms and physical findings lacked specificity and were ordinarily attributable to too few blood cells, that is, anemia (weakness and pallor), thrombocytopenia (a hemorrhagic diathesis), and/or neutropenia (increased susceptibility to infections). Splenomegaly was present in less than 20%.

In contrast to the nondescript nature of the symptoms and physical findings, the hematologic manifestations proved to be remarkably constant and straightforward. Peripheral blood cytopenias dominated the picture with pancytopenia being commonest (Table 1). Abnormalities in red cell morphology were conspic-