The Biology of Human Leukemia

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Introduction

This past decade has seen an explosive growth of information about the biology of human cancer. In large part, this growth has occurred because of technical advances that have made possible a whole new generation of observations. Just as important, however, has been the development of the conceptual framework in which we think about the phenomena of malignancy. Much of this activity has involved studies of human leukemia, for several reasons. The most obvious advantage of the study of leukemia has been the ease with which cells can be obtained and analyzed. Less obvious but equally important has been the fact that much is known about the normal blood cell which provides a norm against which the deviations (or similarities) of the malignant cell can be measured. Moreover, leukemia patients are frequently treated according to clinical protocols, and careful assessments of outcome and clinical course therefore are available for possible correlation with specific biologic features. For these reasons, the studies of leukemia serve as excellent models for the human cancers. This book is designed to draw together studies of human leukemia, both clinical and biologic, in such a manner that it may serve as a useful basis for consideration of human cancer of all types.

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Clinical Features of Human Leukemia

Alvin M. Mauer, M.D.

Human leukemia is a heterogeneous group of disorders characterized by the malignant expansion of a clone derived from a cell of a lineage that normally populates the blood and marrow. The variety of leukemias corresponds to the functional and morphologic variety of the cells normally found in bone marrow and blood. Furthermore, blood cells are themselves derived from pluripotent bone marrow stem cells that have the capacity to progressively limit their expression of differentiation to a single cell lineage. In this process, they go through a progressive maturation characterized by distinct stages, each with its own associated morphologic and functional features. A schematic drawing of the stem cell hierarchy is shown in Figure 1.1. Thus, the clinical features associated with leukemia would be expected to reflect the level in the stem cell hierarchy at which the transformation leading to clonal expansion took place and the degree of capacity for differentiation that can be expressed by the clone. Moreover, since the malignant transformation may be associated with variable degrees of genetic instability, clonal evolution, with the possibility of altered clinical features, may be expected during the course of the disease.

Although the term *leukemia* indicates a disease of "white blood," not all patients with leukemic disorders have large numbers of abnormal blood cells. The blood counts at diagnosis can range from extremely low concentrations (profound pancytopenia) to more than 1000×10^9 leukemic cells per liter. A consistent feature, however, is the disturbance of normal hematopoiesis, with a failure of production of functioning normal blood cells. In fact, most of the significant clinical consequences of leukemia are derived from the reduction in circulating normal blood cells.

Just as the various leukemias have different features, they also show a characteristic distribution of incidence as a function of age. Some forms of leukemia occur with greatest frequency in children, while others are characteristically seen in older patients. There is also considerable variability in the frequency with which the different types of leukemia are seen in different populations. The available evidence gives no indication as to whether the latter differences are associated with environmental factors, genetic factors, or possibly an interrelationship of both. Some leukemias are characteristically derived from specific etiologic factors such as irradiation or

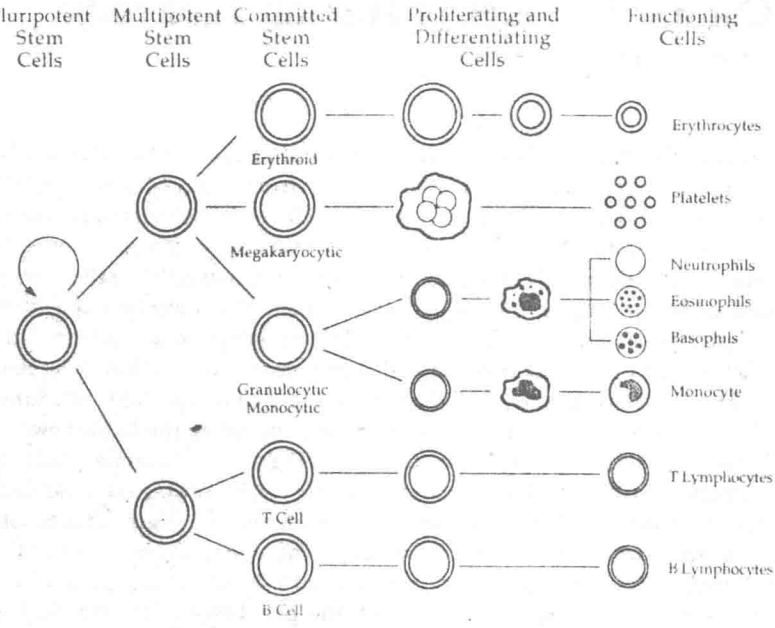

Figure 1.1 The scheme for blood cell differentiation and proliferation. All of the functional blood cells are derived from a common pluripotent stem cell pool. The *circular arrow* designates the capacity of this cell pool for self-renewal. At each step of the way, going from left to right, there is a progressive restriction of differentiation capacities until a specific commitment to a cell line has been made. Malignant transformation can involve any level of proliferating stem cells. The representation of cell lineages in the transformed cell population depends on the level of precursor cell involved in the process of malignant transformation. It is also possible from the stem cell scheme to see how, in some acute leukemias, mixed lineage characteristics can be detected. It is also possible to see in malignancies of the pluripotent stem cell such as chronic myelocytic leukemia that a blast transformation can result in leukemia blast cells having either myeloid or lymphoid characteristics.

exposure to carcinogenic drugs and chemicals. Some genetically determined predisposing conditions such as Fanconi's anemia or Bloom's syndrome are associated with specific types of leukemia, but children with Down's syndrome, also associated with increased risk, show the same distribution of leukemia types as do children without that disorder. From all of these observations, it seems clear that the different types of leukemia will eventually be found to have different etiologies and pathogenetic factors. It is therefore necessary, in epidemiologic studies, to define carefully the types of leukemia discussed. The purpose of this book is to describe the biologic basis for the heterogeneity of human leukemia. The purpose of

this chapter is to provide background information concerning the significance of this heterogeneity and to define in clinical terms what the other chapters will define on a biologic basis.

Initially, leukemias were classified as being either acute or chronic, depending on the duration of survival after diagnosis (1). Before the availability of effective antileukemic therapy, patients with acute leukemia survived an average of 3-4 months, while those with chronic leukemia survived an average of 2-3 years. While acute leukemia occurs in all age groups, it is the predominant form in children. Chronic leukemias, on the other hand, are characteristic of older patients. Leukemias of the acute and chronic type were both further defined, initially, by the morphologic appearance of the leukemic cells, according to which they were classified as being of either lymphoid or myeloid lineage. The leukemic cells of the chronic forms are morphologically more differentiated than those of the acute leukemias.

The introduction of an effective therapy for one type of leukemia in 1948 (2) led to an intensified interest in the classification of the leukemias. It became necessary to distinguish the responsive form—acute lymphocytic leukemia (ALL)—from the other leukemias, for which therapy was ineffective. With the introduction of other effective drugs and the development of combination chemotherapy regimens, progressive improvements in survival for children with acute lymphocytic leukemia were seen. The improved clinical response in some children uncovered a heterogeneity in this form of leukemia which had not been appreciated before. A particular effort was made to identify the clinical factors associated with a greater likelihood of treatment failure. Indeed, such simple clinical features as age and initial white blood cell count at diagnosis were found to be strongly correlated with prognosis (3). By that time, it had been appreciated that normal lymphocytes could be divided by their functional characteristics into B- and T-cell types. It was found that the leukemic blast cells of ALL could also be identified as being derived from a T- or B-cell lineage (4,5). This delineation was also found to have clinical significance (6). Improvements in cytogenetic methodology allowed for the study of karyotypic patterns in the blasts from patients with ALL. The cytogenetic classification has proven to be the most powerful tool yet described for determining prognosis (7).

ALL has truly been a model system of human leukemia with respect to the development of our understanding of its biology. The two critical factors in the development of our understanding were the motivation provided by effective therapy and the technological developments that provided the tools. Similar studies, which may provide information of both clinical and biologic importance, are now under way in all forms of leukemia. It can be anticipated that the biologic studies will provide a better understanding of

Table 1.1. Classification of Human Leukemia

- I. Acute
  - A. Lymphocytic
  - B. Nonlymphocytic
- II. Chronic
  - A. Lymphocytic
  - B. Myeloproliferative disorders
    1. Chronic myelocytic leukemia
    2. Polycythemia rubra vera
    3. Essential thrombocythemia
- III. Myelodysplastic syndromes
- IV. Miscellaneous chronic leukemias
  - A. Hairy cell leukemia
  - B. Adult T-cell leukemia
  - C. Sézary syndrome
  - D. Tγ-cell leukemia

the clinical features of the leukemias. They should also provide information of value in designing better therapeutic approaches.

A classification of the leukemias is shown in Table 1.1. In subsequent chapters, this classification will be further expanded according to morphologic and biologic features. In this chapter, a description of the typical clinical features of the leukemias will be given to provide a background for an understanding of the significance of the associated biologic features. For further information concerning details of diagnosis, clinical course, and therapy, standard textbooks of hematology may be consulted.

Acute Leukemias

Acute Lymphocytic Leukemia (ALL)

Acute lymphocytic leukemia is the most common malignancy of childhood (8), with a peak incidence between the ages of 3 and 7 years (1). ALL also occurs in adolescents and adults, with a slight secondary rise in incidence during the 6th and 7th decades (1). As mentioned above, the phenotypic features of ALL can indicate derivation from either the T- or B-cell lineage (6). It is of interest that the peak in total incidence between the ages of 3 and 7 years observed in Europe and the United States is due entirely to a peak in the incidence of ALL of the B-cell lineage. Leukemia of the T-cell lineage represents a greater proportion of the cases during adolescence and adulthood than during childhood. The significance of the specific phenotypic features will be discussed in later chapters.

In both types of ALL, the leukemic cell represents a phenotype with limited differentiation features. The major clinical consequences of ALL are derived from a replacement of normally functioning hematopoietic tissue in the bone marrow by proliferating and accumulating leukemic blast cells. As a consequence, production of normal granulocytes, erythrocytes, and platelets decreases markedly, with a progressive pancytopenia being reflected in blood cell counts. The concentration of leukemic blast cells in blood is variable and can range at diagnosis from less than 1 to more than 200×10^9/liter. Higher leukemic blast cell counts are more typical of T-cell than B-cell ALL.

The duration of signs and symptoms prior to diagnosis is usually brief, averaging 6 weeks (9,10). The development of anemia is associated with the finding of pallor and the onset of weakness and easy fatigability. With the reduction of blood granulocytes, there is a predisposition to infection, and fever occurs in most patients, with or without a demonstrable focus of infection. The blood platelets are reduced in almost all patients; in about two-thirds, they are sufficiently reduced to be associated with signs of bleeding such as petechiae, easy bruisability, or mucous membrane bleeding, which is usually from the nasal pharynx. For most patients, it is the combination of fever and bleeding which leads to the diagnostic studies.

In addition to blood and bone marrow, extramedullary sites may also be involved by leukemic blast cell infiltration. This is most frequently evidenced on physical examination by enlargement of the liver, spleen, and lymph nodes. The most important site of extramedullary involvement is the central nervous system, beginning early with meningeal involvement. In a small fraction of patients ($< 5\%$), this meningeal infiltration may be symptomatic at diagnosis, with signs of increased intracranial pressure. In most patients, when it is present, it is presymptomatic. The clinical importance of this site is due to its role as a relative sanctuary for leukemic cells from the effects of orally and parenterally administered chemotherapeutic agents (11).

The diagnosis of ALL is generally simple, being suspected from the clinical presentation and easily confirmed by an examination of blood and bone marrow specimens. However, it is important that each patient be studied for a variety of biologic features because of their importance in establishing prognosis (12). In addition to routine blood cell counts and bone marrow examination, a minimal set of laboratory studies should include cytogenetics (or a determination of ploidy by DNA index as determined from flow cytometric studies), immunophenotype, and cell morphology. The combination of these studies can be most useful in anticipating a patient's likelihood of treatment failure. Age at diagnosis is also another important prognostic factor, with treatment failure being more

Table 1.2 Risk Factors for Patients with Acute Lymphocytic Leukemia

Factor (At Diagnosis)	Influence	
	Favorable	Unfavorable
Age (years)		
< 1		X
1–10	X	
> 10		X
White blood cell count		
Low	X	
High		X
Immunophenotype		
B cell		
CALLA-positive (CD10-positive)	X	
CALLA-negative (CD10-negative)		X
T cell		X
Cytogenetics		
Hyperdiploidy (> 50)	X	
Chromosomal translocations		X

likely under the age of 1 year or over the age of 10 years. On inspection of patients between 1 and 10 years of age, it is also evident that they are more likely to present with a cluster of clinical and biologic features associated with a reduced likelihood of treatment failure. A schematic representation of the effect of these clinical and biologic features on prognosis is shown in Table 1.2.

For current treatment strategies, children with ALL are assigned to risk groups depending on initial clinical and biologic features that predict a standard or high likelihood of treatment failure. The features used by different investigators for risk assignment vary (13), and thus the results of reported therapeutic studies are difficult to compare because the patient populations may vary considerably in composition. Current therapeutic strategies begin with intensive combinations of chemotherapy in association with central nervous system sanctuary prophylaxis (10,13). Following this early intensive phase, there is a period of continued combination chemotherapy, generally for a period of 2–3 years from diagnosis. Similar approaches are being used in adults (14), but since all patients over the age of 10 years are considered to be in a high-risk group, there is generally no stratification according to initial clinical or laboratory features.

The goal of therapy is the rapid eradication of leukemic blast cells with systemic chemotherapy and the elimination of residual central nervous system disease by sanctuary therapy. Normal hematopoiesis returns to the bone marrow, and the blood cell counts become normal except for

the results of chemotherapy-induced myelosuppression. Sixty to eighty percent of children with ALL can anticipate continuous complete remission for 4 to 5 years (10,13). In adults, the results are not as good, with 25–40 percent achieving 5 years of continuous complete remission (14). Infants do the least well, with only 25 percent achieving a long-duration remission. In those patients in whom therapy fails, the most frequent cause is recurrent disease, usually in the blood and bone marrow, although isolated central nervous system or, in males, testicular relapse may be the initial harbinger of failure. The earlier the relapse occurs, the more likely the patient is to have disease that will be resistant to further therapy. If, on the other hand, relapse occurs months or years after elective cessation of therapy, a subsequent long-term continuous complete remission may be reinduced (15). In patients who are in continuous complete remission several years after elective cessation of therapy, it is likely that a cure has been achieved (16).

Acute Myeloid Leukemia (AML)

This group of leukemias has also been described as acute nonlymphocytic leukemia (ANLL). This designation by a name that indicates what they are not is obviously unsatisfactory. This group of leukemias is also called *acute myeloblastic* or *myelogenous leukemia* (AML), but the heterogeneity expressed within the group makes that single designation also inadequate. The group includes all acute leukemias with nonlymphoid lineage features. The morphologic and, to a degree, the clinical features are determined by the predominant expression of specific lineage features and the degree of differentiation achieved. In some cases, the leukemic clone expresses the features of a single lineage; in other patients, all nonlymphoid cells are derived from the leukemic stem cells. There is also a much greater degree of heterogeneity expressed with respect to degree differentiation than is found in ALL. The bone marrow appearance can therefore be much less uniform.

AML is seen at all ages, but there is some increase in incidence beginning in the 6th and 7th decades (1). It is the type of leukemia that is associated with irradiation and chemical exposure (17) and is seen following treatment for other malignancies (18). In most patients with AML, no history of antecedent exposure can be elicited. In AML as in ALL, the leukemic cell population represents a phenotype with limited differentiation features. The degree and type of differentiation have been used by the French, American, and British (FAB) Cooperative Group (19) to develop a classification scheme. This morphologically based system will be discussed in greater detail in chapter 2. For the purposes of this description of the clinical features of AML, a simplified description of the designations will

suffice. The FAB classification for AML uses the designation *M* followed by the numbers 1 through 7. *M1* represents morphologically undifferentiated myeloblasts; *M2*, myeloblasts with some cells having cytoplasmic granules; *M3*, blast cells resembling promyelocytes; *M4*, a mixture of cells having myeloid and monocytoid features; *M5*, cells with purely monocytoid features; *M6*, blast cells with features of erythroid precursors; and *M7*, megakaryoblast-like cells. Although the pathophysiologic feature of these leukemias is an accumulation of cells derived from the leukemic clone in the early stages of differentiation, it is possible in some patients to see mature neutrophilic or eosinophilic granulocytes representative of the leukemic cell population. As in ALL, most of the major clinical consequences are derived from a loss of normally functioning hematopoietic tissue. At diagnosis, the bone marrow is usually found to be replaced by leukemic cells. The loss of normal hematopoiesis is reflected in the blood by decreased concentrations of erythrocytes and normal granulocytes. Leukemic cells are usually present in the blood, with the white blood cell count being increased, sometimes to concentrations greater than 200×10^9/liter.

The duration of signs and symptoms is usually brief before diagnosis, as it is in ALL, averaging about 6 weeks. The clinical features of AML are similar in children (20) and adults (21). The clinical features are virtually identical to those already described for ALL, because the mechanisms for their development are similar. At presentation, patients with AML have the signs and symptoms of anemia, the bleeding associated with thrombocytopenia, and the fever characteristic of granulocytopenia.

Extramedullary sites may be involved by leukemic cell infiltration. Enlargement of liver, spleen, and lymph nodes reflects the more common sites of involvement. Infiltration of the gums is a finding particularly characteristic of the M4 and M5 leukemias. In some patients, localized tumor masses can be seen in regions such as the skin or the orbit. These tumor masses are referred to as chloromas because of the greenish colorations caused by the presence of verdoperoxidase. Bleeding associated with disseminated intravascular coagulation is a particular feature of the M3 leukemia because of the release of procoagulant from the leukemic blast cells. The central nervous system is less commonly a site of extramedullary involvement than it is in ALL.

The diagnosis of AML is usually suggested by the history and physical examination and is easily confirmed by blood and bone marrow examination. In AML, the use of histochemical stains including myeloperoxidase, Sudan black B, and specific and nonspecific esterase is useful in defining the cytoplasmic characteristics needed to apply the FAB classification. All patients should have cytogenetic studies (22,23).

The response to therapy is influenced by the FAB classification, cyto-

genetic pattern, and patient's age. However, because the overall response to therapy is not as favorable as it is in patients with ALL (24–26), the distinction between standard- and high-risk groups is not as definite. One of the more important risk factors is age, with patients over 60 years old having a higher failure rate. In AML, children do not form the favorable prognostic group as they do in ALL. For these reasons, patients are generally not stratified by risk groups other than age for entry into therapeutic protocols. As in ALL, the overall treatment strategy is to use intensive combination chemotherapy to induce the rapid attainment of remission. The role of continued therapy for a period of 2–3 years is not clear. Many studies have used one or two intensification periods for consolidation following the induction of remission and have not used continued therapy. The role of central nervous system prophylaxis has also not been definitively established, perhaps because the duration of the period at risk in remission is not as long. The overall prognosis is less favorable for AML than for ALL. Treatment failure can occur during the induction of remission because of either a lack of response of the leukemic cell population, or death from complications of pancytopenia. If remission is achieved, there is a likelihood of failure due to recurrence of the leukemia. Because of the high likelihood of failure on the chemotherapy regimens, allogeneic bone marrow transplantation is a treatment option when a suitable donor is available (27).

Chronic Leukemias

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is a disease of older individuals, with a median age at diagnosis of 60 years (28); it is rare under the age of 30 years. It is more frequent in men, with a male-to-female ratio of 2:1. It is the most common leukemia in Caucasians but is rare in Asians. A familial distribution has been described, but no mechanism for genetic predisposition has been proposed as yet.

In CLL, 95 percent of patients will have leukemic clones of the B-cell lineage, with the remainder having clones with T-cell characteristics. In both cases, the lymphocytes of the leukemic clone are mature in appearance and have mature differentiation features. The pathogenetic mechanism appears to be a progressive expansion of the leukemic clone through accumulation rather than rapid proliferation.

The major clinical consequences of CLL are derived from the effects of this expanding clone on normal bone marrow function, alterations in normal immune regulation, and accumulation in extramedullary sites

such as liver, spleen, and lymph nodes. CLL of T-cell lineage has a particular disposition to skin involvement.

There tends to be a regular progression of the disease, which allows classification according to stage at diagnosis (29). In one-fourth of individuals, the progress of the disease is so slow that the patient has no signs or symptoms at diagnosis. In these individuals, the diagnosis is established by the finding of blood count abnormalities, usually when a blood count is obtained for an unrelated reason. The diagnostic abnormality is the finding of an absolute lymphocytosis, the upper limits of which have been variously set as 5 or 15 $\times$ 10^9/liter by different authors (29). The lymphocytes of the leukemic clone are rather uniform in appearance and resemble normal blood lymphocytes. The bone marrow also has an increased percentage of lymphocytes, with limits of 25–40 percent being established for diagnosis by different investigators (29). Some patients will be seen for diagnosis because of the presence of unexplained diffuse lymph node enlargement. The abnormal blood and bone marrow findings will confirm the diagnosis of CLL. With disease progression, enlargement of the liver and spleen will be found. As the infiltrating lymphocytes disrupt normal hematopoiesis, anemia and then thrombocytopenia will occur.

The disease is sometimes associated with clinical findings resulting from abnormalities of immune regulation (28). Ten to twenty percent of patients will have an immunohemolytic anemia during the course of their disease. In some patients, immunothrombocytopenia may occur. Hypogammaglobulinemia may be present and may be associated with a predisposition to bacterial infection. The likelihood of symptomatic hypogammaglobulinemia increases as the disease progresses, with more than half of the patients ultimately having this finding. Almost half of the deaths of patients with CLL are related to the consequences of infections associated with the hypogammaglobulinemia.

The diagnosis of CLL is relatively simple, and the lymphocyte lineage can be established by immunophenotyping. A cytogenetic study should be done because of its independent prognostic significance. However, the prognosis can also be determined rather simply, based on the extent of disease at the time the diagnosis is made. Age does not appear to play an important role. Several staging systems have been proposed (29,30) as guides to prognosis and therapy. The simple clinical system of Rai (29,30) is as effective as any. Stage 0 is associated with only the absolute lymphocytosis in blood and bone marrow. Rai has set an absolute blood lymphocyte count of 15 $\times$ 10^9/liter and a 40 percent infiltration of the bone marrow as the minimal criteria for diagnosis. With the addition of enlarged lymph glands, the classification becomes stage I. The addition of splenomegaly designates stage II. The findings of anemia and thrombocytopenia (not of immune origin) indicate stages III and IV, respectively. Patients who have

stage 0 or I disease at diagnosis may survive 10 years or more without therapy. Stage II patients have a life expectancy that is more limited but still has a median value of 5 years. Patients with stage III or IV disease at diagnosis have a much more limited life expectancy, with a median value of about 2 years.

The strategies of current therapy are entirely for the purpose of palliation. There are no current protocols with cure as the goal. Patients with stage 0 to II disease may not require therapy at all if they are asymptomatic. The white blood cell count is not by itself an indication for therapy, although some treating clinicians will set arbitrary limits of 50, 100, or 200 $\times 10^9$/liter as an indication for beginning treatment. Massive lymph node enlargement can result in sufficient discomfort for treatment with irradiation or alkylating agents. Immune hemolytic anemia or thrombocytopenia may respond to the administration of corticosteroids. Patients with stage III or IV disease are generally treated with alkylating agents with or without corticosteroids (30), but there is little indication that therapy has caused prolongation of survival at any stage of the disease.

Myeloproliferative Disorders

These disorders have not traditionally been considered together under the heading of leukemia. They include chronic myelocytic leukemia, polycythemia rubra vera, and essential thrombocythemia, which are characterized by an overproduction of granulocytes, erythrocytes, and platelets, respectively. For some time, however, clinical observations have led to a proposal that these three bone marrow diseases are closely related. Although the increased cell production may be predominantly of one lineage, in some patients the blood concentrations of two or all three cell lines may be increased. All three diseases may have similar clinical outcomes, such as progressive bone marrow fibrosis or terminal conversion to acute leukemia, in their later stages. With the development of an understanding of the bone marrow stem cell hierarchy and the advent of techniques for demonstrating the clonality of a cell population, it has become evident that each of these three conditions represents a clonal stem cell disorder. The precise level of stem cell commitment is not entirely certain, but in cases studied to date, the clone has been derived from a cell capable of differentiating to granulocytic, erythroid, and megakaryocytic committed stem cells. At this time, it is still unknown which feature of the malignant transformation determines which cell will be overproduced to provide the typical features of each of these three disorders. In one of the myeloproliferative syndromes, chronic myelocytic leukemia, there is a characteristic cytogenetic finding of a specific reciprocal translocation between chromosomes 9 and 22, designated t(9;22) (31). The fact that this finding is specifically associ