ceptor gene chains, cytoplasmic CD3 expression, ultrastructural myeloperoxidase staining, and c-*fms* oncogene expression were absent from the leukemic cells. Cytomorphologically, the cells could not be assigned to a specific French–American–British category.

Although generally considered an early T-cell marker,[2,3] CD7 has also been identified on undifferentiated nonlymphoid precursor cells, both physiologic and neoplastic.[3,4] $CD7^+$ leukemic cells have also been found to respond in vitro by the full complement of lympho/hematopoietic progeny to the appropriate stimuli.[5] The possibility, therefore, exists that the CD7 molecule may not be T-cell specific, but rather be a marker of pluripotent undifferentiated stem cells.

During embryonic ontogeny, the earliest hematopoietic progenitor cells identifiable in the human yolk sac and liver at 5–6 gestational weeks (GW) are $CD7^+$ and negative for CD2, cCD3, CD4, CD8, and TdT.[6,7] The cells initiating T-cell ontogeny in the liver at 7 GW and those seeding the thymic rudiment from yolk sac, liver, and para-aortic hematopoietic foci of the neck and upper thoracic regions between 7 and 9.5 GW express cCD3 in addition to CD7, but are negative for all other common T-cell markers.[6–8] Cytoplasmic CD3 was absent from the leukemic cells of the patients reported by Bassan et al.[1] Although the exact time of first appearance of the CD13 membrane antigen in myeloid cell ontogeny has not yet been established, biphenotypic $CD13^+$ $CD19^+$ myeloid–lymphoid progenitor cells have been reported in fetal liver and bone marrow from 15 GW.[9]

I want to suggest that the identification of the exact time of the initiating leukemogenic event[10] during a patient's life could possibly contribute to an understanding of the cytogenetic molecular lesions leading to different forms of leukemia. For example, the first step in leukemogenesis could have occured during the early stages of hemato/lymphopoietic development, perhaps at a time when the respective phenotypes make their first appearance in physiologic ontogeny.[11] In the form of leukemia reported by Bassan et al.,[1] this could have been as early as during the fifth to sixth GW. This period of development is characterized not only by rapid clonal stem cell expansion, but also by the absence of cellular immunesurveillance systems. The concept of a preleukemic phase extending back to early ontogeny postulates long latency periods before a second event triggers an expansive proliferation of the neoplastic cell clone.[10] Preleukemic latency periods with a mean of 3–4 years are conceivable in pediatric patients (who have a peak incidence at that age) and could be possibly likened to minimal residual disease of leukemic remission. In the adult patients reported by Bassan et al.,[1] we would have to postulate latency periods extending over decades. The unusual clinical features of these patients and their resistance to drug therapy are compatible with the concept of an early embryonic origin of at least some forms of leukemia.

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Use of Aspiration Cytology and Frozen Section Examination for Management of Benign and Malignant Thyroid Nodules

We read with great interest the report by Layfield et al.[1] concerning their results using cytology after fine-needle aspiration (FNA) and frozen section (FS) examination for menagement of benign and malignant thyroid nodules. They suggested thyroid lobectomy and isthmectomy when cytology diagnosis of follicular neoplasm or papillary carcinoma was made and, "if frozen section confirms the diagnosis of carcinoma, total thyroidectomy is done." In their series of 56 patients whose aspiration cytology results were positive for malignancy, only 5 were benign (8.9% false-positive). However, FS was negative for malignancy in 24 of 79 patients who had carcinoma (30.4% false-negative).

We have studied 206 patients who underwent thyroidectomy with intraoperative FS consultation after FNA of a thyroid nodule. FNA was positive for malignancy in 26 cases and suspicious in 13 (total carcinoma, 45). Four patients whose results were positive for malignancy had benign conditions (15.4% false-positive). However, FS was negative for malignancy in 18 cases (40% false-negative).

We suggest another strategy, in accordance with Hamburger et al.,[2,3] proposing FS only in patients with unsatisfactory or suspected malignancy because FNA diagnoses of definitive malignancy are seldom correctly contradicted by FS.

In view of the high risk of malignancy when the FNA diagnosis is suspicious for cancer and the low sensitivity of FS in confirming cancer in these patients, we consider it prudent to advise total or near total thyroidectomy on the basis of FNA results. This treatment would be performed in 5 of 166 patients without cancer in the Layfield series (3.1%) and in 4 of 206 patients in our series (1.9%). Reoperation will be unnecessary in a significant number of patients.

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Reply to Aguilar

We agree with Dr. Aguilar that fine-needle aspiration (FNA) represents a highly accurate method for the diagnosis of thyroid nodules. His point is well taken and, as we note in our article, FNA is more sensitive than frozen section for the diagnosis of malignancy in the thyroid. However, FNA is less specific for malignancy than frozen section evaluation. Dr. Aguilar did not supply paired data (FNA and frozen section results) for the evaluation of the clinical situation seen by the operating surgeon. Intraoperably, the surgeon must decide the extent of operation based on the operative findings, FNA diagnosis, and frozen section interpretation (if performed). We address the situation where these findings are discordant. As Dr. Aguilar pointed out, when FNA is positive for malignancy (usually papillary carcinoma), frozen section will correctly indicate a benign lesion in the minority of cases. This occurred in three of eight discordant pairs (38%) in our data. FNA correctly indicated a malignancy in 62% of these discordant pairs. However, this represents a minority of the discordance subsets in which FNA was positive or suspicious for malignancy and frozen section was negative for malignancy. In the cases where FNA was positive for a follicular neoplasm (suspicious for malignancy), frozen section correctly established the lesion to be benign in 26 of 30 cases (87%). Using the recommendation of Dr. Aguilar for the 38 cases in which FNA was positive or suspicious, 29 of 38 patients would have received more extensive surgery than necessary (total thyroidectomy). Total thyroidectomy is major surgery and exposes the patient to the hazards of hypoparathyroidism and paralysis of the recurrent laryngeal nerve. Because many of these patients are young, avoidance of such complications is highly desirable. We continue to recommend interoperative frozen section for the confirmation of positive and suspicious FNA diagnoses. When FNA and frozen section are discordant, we take a conservative approach. In healthy patients in whom reoperation does not represent a significant risk, we restrict the operation to lobectomy and isthmectomy if FNA is positive but frozen section definitively diagnoses a benign lesion. The risk of underoperation after this approach is small in our series, with only 9 of 161 patients needing reoperation. When the patient with a thyroid nodule is a poor risk for reoperation, we agree with Dr. Aguilar and find it most prudent to perform total thyroidectomy or near total thyroidectomy on the basis of a positive FNA.

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