IT IS TRULY gratifying to review the progress that has been made in the therapy of the acute leukemias since the introduction of aminopterin by Farber and coworkers in the late 1940s. This progress can be measured by the increasing proportion of patients who have achieved complete remission, the increasing duration of their survival, and the increasing evidence that for some portion of patients with acute leukemia cure is a realistic goal.

As these improvements in patient care have accrued, there has been an equally important improvement in our knowledge about the acute leukemias and the application of that knowledge to treatment strategies. Clinical therapeutic research in the treatment of acute leukemia has provided an important experience in the design and conduct of clinical trials in which therapeutic regimens were tested and compared. Knowledge acquired about the treatment of acute leukemia has had an important bearing on the treatment of other forms of disseminated cancer. The study of therapy for the acute leukemias, therefore, has general interest for the physician treating patients with cancer.

It has also been evident that the question being asked in clinical studies and the answers being obtained have undergone a continuing evolution. Initially, the important question was simply the method by which a complete remission could be most frequently and quickly obtained. As effective combination chemotherapy regimens for remission induction were designed, the emphasis shifted to a consideration of the problems involved in maintaining that remission. New solutions brought new problems and it is the purpose of this review to outline the current status for therapy of the acute leukemias and, in particular, what current questions are in need of answers.

ACUTE LYMPHOCYTIC LEUKEMIA

At the beginning of the 1970s, many physicians appeared to feel that the problem of acute lymphocytic leukemia (ALL) was near solution. Enormous strides had occurred during the 1960s and it seemed that it was only a matter of “fine tuning” the then current treatment protocols until all patients with ALL could be successfully treated. The ensuing years have indicated how poorly justified that sense of complacency was and, in fact, we seem to have just entered upon a new era of clinical therapeutic research for this disease. While it is too early to see if this activity will result in a significant improvement of our current results, at least we have formulated our current questions in a much clearer and more rationally based manner.

Classification

Perhaps one of the most compelling reasons for the new activity of clinical therapeutic research in ALL has been the development of a classification scheme that has important clinical implications. It became evident during the 1960s that not all patients with ALL behaved in a similar fashion and not all patients could be expected to respond equally well to treatment. Certain clinical features became established as having significant correlation with treatment outcome. These clinical features at diagnosis that tend to be associated with poor prognosis are a high white blood count, age under 2 or over 10 yr., the finding of a mediastinal mass on chest roentgenogram, early central nervous system (CNS) leukemia, black race, and male sex. Not all of these features are equally

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important and combinations of these features, such as a high white blood count, mediastinal mass, and early CNS leukemia, are frequently found in the same patient. It must be remembered that the most important prognostic factor of all is treatment, but these clinical features continue to bear a significant relationship to outcome with current regimens.

An inkling of the biologic meaning of these clinical features became evident when it was found that certain of them also were associated with the presence of leukemic blast cells that formed rosettes with sheep erythrocytes (E' blasts). The presence of E' blasts in patients has a strong correlation with the clinical high-risk features of high white blood count, mediastinal mass, and early central nervous system disease. Since then, many other biologic markers have been described that have allowed for a classification of subgroups of acute lymphocytic leukemia, as shown in Table 1. Also shown in that table is an assessment of the risk for treatment failure.

With the use of multiple cell markers, it is possible to further subdivide ALL patients by cell type, but at this time, the four groups shown in Table 1 define the important clinical relationships. With additional markers becoming available, however, other cell types associated with specific clinical features may emerge.

Another system of classification proposed for ALL is the French-American-British (FAB) scheme based on cell morphology. With further study, this system may also be useful in assigning prognosis, but its relationship to the biologic classification and clinical assessment of risk factors is yet to be clearly defined.

At this time, the problem of therapy must be approached with the concept of standard and high-risk leukemia in mind. The problems to be solved for these two groups of patients are different and the treatment programs necessarily divergent.

A large proportion (at least half) of patients with standard risk ALL, whether defined by clinical or laboratory features, will achieve long-term disease-free survival and are probably curable. For these patients, the goals are to maintain the effectiveness of treatment while attempting to reduce its late consequences. It also must be recognized that a significant proportion of these patients still will exhibit treatment failure by disease relapse. We are currently in need of additional clinical and laboratory measures by which these standard risk patients by current criteria can be identified as being likely to fail therapy.

On the other hand, only about 20% of patients with high-risk features can be expected to achieve long-term disease-free survival. A comparison of the risk of relapse for the standard and high-risk groups as a function of time from diagnosis is shown in Fig. 1. It is of interest that all of the risk differences are expressed within the first 2 yr of treatment. Thereafter, the risk rates for relapse in the standard and high-risk group are identical. It would seem that the goal for these patients then is to prevent relapse during these first 2 yr of treatment. Certainly, the worst prognostic feature of all is disease relapse during therapy. Virtually none of those patients achieve a significant duration of subsequent disease-free survival. Unfortunately, for the high-risk group, the problems of late consequences of treatment have not yet emerged.

**Therapy Phases**

Perhaps one of the more important observations about the treatment of ALL has been the identification of therapy phases and their independent contributions to the overall outcome. In this section, the current status of our understanding of remission induction, CNS prophylaxis, and continuation therapy will be discussed for both the standard and high-risk groups.

**Remission Induction**

One of the early contributions of clinical therapeutic research in ALL was the observation that a complete remission was required in order to provide

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**Table 1. Biologic Classification of ALL**

<table>
<thead>
<tr>
<th>Leukemic Blast Cell Type</th>
<th>Approximate Percent of Patients</th>
<th>Usual Cell Characteristics</th>
<th>Risk Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common ALL</td>
<td>65</td>
<td>Common ALL antigen, 1a-like antigen, cytoplasmic corticosteroid binding, nuclear TdT activity</td>
<td>Standard</td>
</tr>
<tr>
<td>Pre-B-cell ALL*</td>
<td></td>
<td>Above characteristics with cytoplasmic IgM</td>
<td></td>
</tr>
<tr>
<td>T-cell ALL</td>
<td>20</td>
<td>T-cell antigen, 50% have E' blasts, reduced cytoplasmic corticosteroid binding, nuclear TdT activity, acid phosphatase positive</td>
<td>High</td>
</tr>
<tr>
<td>B-cell ALL</td>
<td>&lt;5</td>
<td>Surface Ig positive, 1a-like antigen</td>
<td>High</td>
</tr>
<tr>
<td>Undifferentiated†</td>
<td>10</td>
<td>May have 1a-like antigen</td>
<td>Variable</td>
</tr>
</tbody>
</table>

*Approximately 20% of ALL patients have blast cells with cytoplasmic IgM demonstrable by immunofluorescence. Studies to date indicate no clinical differences from patients with common ALL not having this feature (Crist and coworkers, Blood 54 (Suppl: 183a, 1979).
†This group currently cannot be identified by defined cell marker systems. It is probably heterogenous and the clinical outcome is variable.
significant prolongation of survival.\textsuperscript{14} It is now evident that this observation is equally applicable to other forms of disseminated cancer. Another important early observation was the finding that a greater proportion of patients achieved remission if agents were combined rather than used singly.\textsuperscript{14} Combination chemotherapy is now standard practice.

Remission in from 85% to 95% of the patients with ALL can be achieved by a combination of prednisone and vincristine.\textsuperscript{15-17} The addition of a third or more agents contributes little to an increased frequency of remission.\textsuperscript{15-18} The addition of a third or fourth agent, however, may cause additional toxicity and even early death.\textsuperscript{6,17} Expected early death rates, usually from fatal sepsis, should be no greater than 2.5%-5.0%.\textsuperscript{15,16}

The two-drug combination, while less toxic, is inferior with respect to subsequent remission continuation.\textsuperscript{12} The addition of a third induction agent, either an anthracycline or L-asparaginase, provides an advantage with respect to the proportion of patients continuing in remission. The inferiority of a prednisone-vincristine induction regimen can be partially corrected by "pulses" of this induction regimen throughout the period of subsequent remission continuation. No advantage has been found to the addition of a fourth agent to the induction regimen or the application of an intensification phase following remission induction if a three-drug regimen has been used.\textsuperscript{19}

Most patients will have achieved remission within a 4-wk period. An early achievement of remission is a favorable prognostic sign,\textsuperscript{20} and patients who have not achieved remission by 4 wk are at high risk for subsequent disease relapse if a remission is finally achieved.\textsuperscript{3} Recently, it has been found that patients failing the initial remission induction of prednisone, vincristine, and an anthracycline may achieve remission with a combination of the epipodophyllotoxin VM26 and cytosine arabinoside with improved subsequent remission duration.\textsuperscript{21}

In summary, the treatment results in this phase have been highly successful. With a three-drug regimen incorporating vincristine, prednisone, and either L-asparaginase or an anthracycline almost all patients will achieve complete remission. Less than 3% should fail induction because of death due to fatal infections and less than 5% should prove refractory to all induction regimens.

**CNS Prophylaxis**

As a greater number of patients experienced longer bone marrow remissions with improved induction and continuation therapy regimens, proliferation of leukemic blast cells in the central nervous system emerged as the major limiting factor for disease control.\textsuperscript{22,23} More than 50% of the patients experienced their first relapse in that site.\textsuperscript{23} Ineffective drug levels are achieved in the cerebrospinal fluid and, thus, the CNS behaves as a sanctuary site, protecting the leukemic blast cells present there until drug resistance is achieved followed by a CNS and a bone marrow relapse. It was demonstrated that the risk of relapse in CNS could be markedly reduced by treatment with 2400-rad irradiation to the craniospinal axis or 2400 rad to the cranium with 5 doses of methotrexate given intrathecally.\textsuperscript{24-27} Furthermore, treatment of the sanctuary area also reduced the frequency of subsequent bone marrow relapse and increased the proportion of patients remaining in continuous complete remission. This CNS phase of the treatment regimen is usually administered immediately following completion of the induction regimen.

In recent years, it has become apparent that this form of CNS prophylaxis, while effective, carries some risk of CNS damage. The most clearly demonstrated...
risk has been that associated with the alterations of vascular permeability to methotrexate, which follows irradiation. A demyelinating leukoencephalopathy has resulted from the administration of parenteral methotrexate in large doses to patients who have had previous cranial irradiation.\(^{28,29}\) Exact dose relationships are incompletely documented but the risk seems greatest in those patients who have had more than 2000-rad irradiation and who receive methotrexate intravenously in doses greater than 40 mg/sq m. Insufficient information is available to determine risks for the development of leukoencephalopathy at lesser dose levels.

Another apparent consequence of cranial irradiation is a mineralizing vasculopathy.\(^{30}\) Other risk factors, such as the occurrence of CNS leukemia, appear to increase the likelihood of this irradiation-induced change. The functional consequences associated with this vascular alteration are not known. Additional alterations of the brain have been demonstrated by studies with computerized tomography.\(^{31,32}\) In addition to mineralization, dilation of the ventricles and decreased attenuation of brain substance have been described. The relationship of these changes to brain function has not been clearly established. In all of these studies, it is impossible to determine the exact risk for a patient receiving cranial irradiation because the studies have been retrospective in nature, relied on autopsy findings, or represented small and possibly unrepresentative groups of children treated for ALL. Furthermore, it is hard to discern from these studies what other factors of disease and treatment might contribute to the risk of the irradiation-related changes.

A study of neuropsychologic functioning of children after CNS prophylaxis with 2400-rad cranial irradiation reported no evident disability. However, the follow-up period was less than 2 yr in the prospective portion of that study.\(^{33}\) Similarly, an assessment of neurologic status and school performance in a group of 22 children 5 yr after 2400-rad cranial irradiation failed to indicate significant alteration of function.\(^{34}\) In other studies of children given psychometric testing after cessation of therapy for ALL, it was found that children receiving CNS prophylactic irradiation under the age of 5 yr had reduced IQ scores.\(^{35,36}\) Other studies have indicated the presence of gross neurologic abnormalities and apparent learning disabilities in some long-term survivors of ALL who had had 2400-rad cranial irradiation.\(^{37}\) Clearly, a carefully controlled prospective study is needed to establish the risk of the form of CNS prophylaxis and assess the possible contributing roles of other aspects of the disease and its treatment.

In light of all of these observations, attention has turned to methods of providing for CNS prophylaxis that will be as effective as CNS irradiation in the doses mentioned above and yet carry a much diminished or negligible risk of immediate and late consequences. Intrathecal methotrexate by itself at the time of remission induction provides ineffective prophylaxis.\(^{38}\) An intensive multidrug induction and continuation therapy regimen in association with intrathecal methotrexate has provided a frequency of first relapse in the CNS equivalent to the standard irradiation regimen.\(^{39}\) Recently, studies have been done in which the dose of irradiation has been reduced to 1800 rad.\(^{40,41}\) The risk of CNS relapse is equivalent to that of 2400 rad for the standard risk patient but may be inadequate for those patients with high-risk features. The studies to determine the consequences of 1800 rad with respect to CNS alterations have not yet been reported. Another proposal for CNS prophylaxis has been the combined use of methotrexate intrathecally and intravenously.\(^{42}\) The methotrexate is given intravenously in large enough doses over a sufficient period of time so that effective levels of methotrexate are achieved in the cerebrospinal fluid. Full evaluation of this method must await a longer period of follow-up. The final tests of any method for CNS prophylaxis must be the likelihood of disease relapse (not only during continuation therapy but also after therapy has been stopped) and the consequences with respect to CNS damage.

For the standard risk patient, some form of CNS prophylaxis is essential. At this time, it is impossible to determine which standard risk patients are likely to develop CNS relapse. Current studies, therefore, are designed to determine the most effective method for preventing CNS leukemia in all of these patients, while reducing to a minimum the risk of late consequences of that therapy.

For the high-risk patient, however, CNS relapse continues to be a significant problem. For these patients, 2400-rad cranial irradiation with concurrent doses of intrathecal methotrexate have proved effective in preventing CNS relapse. Unfortunately, as will be discussed in the following section, the advantage of effective control of disease in this sanctuary area is lost because of the great likelihood of early relapse in the bone marrow.

**Continuation Therapy**

After remission and induction and CNS prophylaxis, some period of continued therapy is necessary, otherwise almost all patients will undergo bone marrow relapse.\(^{14,43}\) Continued use of the agents so effective in remission induction is not possible because
of dose-limiting side effects. Combinations of drugs not used in the induction regimen are most effective in maintaining the remission. Of the available agents 6-mercaptopurine and methotrexate are the most effective.\textsuperscript{44} Both agents can be given orally with 6-mercaptopurine taken daily and the methotrexate intermittently, usually at intervals of 1 wk. In a study designed to evaluate the effectiveness of continuation regimens, it was found that the addition of a third or fourth drug (cyclophosphamide and cytosine arabinoside, respectively) to the continuation regimen of 6-mercaptopurine and methotrexate did not provide any advantage for disease control and was associated with increased risk of those infections related to immunosuppression.\textsuperscript{44}

In some studies, “pulses” of the induction regimen drugs\textsuperscript{45} or other combinations\textsuperscript{46} have been given periodically throughout the continuation phase. In some regimens, these “pulses” have increased the duration of remission and also the proportion of patients achieving long-term disease-free remission. In comparative studies, however, the results have indicated that with an adequate induction regimen and effective continuation therapy, “pulses” do not make a significant contribution to the overall results.\textsuperscript{12,26}

Another approach to the design of a superior continuation regimen has been the use of intermittent combination chemotherapy.\textsuperscript{20} The regimen provides for a 5-day intensive chemotherapy period every 3 wk, thus allowing an interval for recovery of marrow and immune function. The results appear comparable to other current multidrug programs.

For the standard risk patients, there still are about a third or more who will fail during continuation therapy because of the emergence of drug-resistant leukemic blasts. Regimens are needed that will prevent the emergence of these resistant cells while not jeopardizing the remaining patients for whom current therapy is quite adequate and minimally productive of early or late serious consequences. It is possible that clinical and laboratory features can be identified that will accurately predict which among the standard risk patients by current definition are most likely to fail therapy. For these patients then, regimens might be designed to prevent the emergence of drug-resistant leukemic cells. At the present time, efforts must be directed toward increasing the proportion of patients achieving long-term and possibly permanent disease control without increasing the hazards to patients who will do well with current therapy.

For the high-risk patient, disease relapse occurs in about 80\% with a median remission time of about 1 yr.\textsuperscript{47} Clearly, the major impediment to disease control is the emergence of drug-resistant leukemic cells. To prevent this occurrence, three approaches might be considered. In the first approach a more intensive or prolonged remission induction regimen might be tried with a greater number of non-cross-resistant drugs. If the total number of leukemic cells present at diagnosis probably containing leukemic cells of variable drug sensitivity can be reduced to the minimal number possible, subsequent continuation therapy might be more effective in controlling the residual cells.

A second approach might be the method initially proposed by Zuelzer\textsuperscript{48} for “cyclic” therapy during the continuation phase. As initially proposed, the cycles were designed to rotate single drugs with different modes of action throughout the period of initial remission to avoid the prolonged exposure to a single agent that might enhance acquired drug resistance. Unfortunately, single drug cycles proved ineffective but with today’s understanding of multidrug, non-cross-reactive regimens, this approach might be tried again with the same basic rationale. As indicated by the data illustrated in Fig. I, if disease control could be maintained in these high-risk patients for a period of 2 yr, perhaps the subsequent risk of relapse might approach that of standard risk patients.

The third approach to solving the problem of the high-risk failure rate is to increase our knowledge of the mechanisms by which drug resistance is acquired by a leukemic cell population. Leads to methods of preventing the acquisition of resistance might then be forthcoming. While the high-risk ALL patients currently present a real challenge, they also represent an unequaled opportunity to study one of the most pressing problems in cancer therapy—acquired drug resistance.

It should be noted that with respect to prognosis, adults with ALL should be considered in this high-risk category. They have a higher frequency of CNS leukemia and early relapse.\textsuperscript{49,50}

Therapy for Relapse

There are three major sites of relapse in acute lymphocytic leukemia—the bone marrow, the central nervous system, and, for boys, the testes. The current most frequent site of relapse and one that carries the most ominous outlook is the bone marrow. An important consideration for the patient in whom the relapse has occurred is whether it has been during therapy or follows cessation of therapy. Relapse during therapy, especially in the bone marrow, almost inevitably means the end to any hope for long-term disease control.\textsuperscript{51} For some patients in whom the relapse has occurred following cessation of therapy, however, disease control can be reestablished and be maintained for long periods.\textsuperscript{52,53} Although disease relapse is now
the greatest impediment to cure in leukemia, relatively little attention has been paid to this aspect of therapy.

When disease relapse occurs during therapy, remission reinduction can be obtained by a variety of combination regimens in about 80% of patients. As in the initial remission induction regimen, three drugs in combination appear preferable. The role of subsequent intensification or consolidation by further drugs is yet to be established but may offer an advantage to some patients. The greatest problem in relapse therapy is the lack of effective drugs for the continuation period. In most patients, the most effective agents have been used for the primary treatment program and resistance to these agents is already evident, as demonstrated by regrowth of the leukemic cell population during treatment. It must be remembered that relapse in the bone marrow reintroduces the risk of CNS seeding. At the present time, CNS relapse is not a major factor in disease control for these patients because of the relatively short duration of marrow remissions obtained. Other combinations that are useful in patients refractory to reinduction with standard regimens are L-asparaginase and cytosine arabinoside, cytosine arabinoside and 6-thioguanine, and cytosine arabinoside and VM26.

When relapse occurs following cessation of therapy, treatment programs should be carried out with a curative intent. In these patients, remissions are almost always reinduced with a three-drug regimen. The role of intensification for consolidation therapy following remission induction needs to be established. Continuation therapy, likewise, needs study for the establishment of the most effective regimen. The patients are likely to have long-term disease-free periods and, thus, are at great risk for CNS relapse as in the initial remission. The use of intrathecal chemotherapy with methotrexate and cytosine arabinoside has been found effective for prophylaxis in those patients who have had CNS irradiation as part of their primary treatment program.

Central nervous system relapse, either during or following cessation of therapy, should be treated with intrathecal chemotherapy with methotrexate or a combination of agents, including methotrexate, cytosine arabinoside, and corticosteroids. There are no studies available to indicate whether single or combination chemotherapy is more effective, although three drugs are not more effective than two. After the cerebrospinal fluid has returned to normal with chemotherapy, periodic instillation of drugs in the CSF is necessary to maintain control. For some refractory patients, the instillation of methotrexate into the ventricles by means of an Ommaya reservoir has proven effective. Whether CNS relapse occurs during therapy or after therapy, it must be assumed that there has probably been spread of leukemic cells to marrow and other sites. Concomitant with treatment of the CNS, there should be systemic chemotherapy administered in the form of an induction regimen with at least vincristine and prednisone.

The risk of testicular relapse in boys is about 15%, but as the only site of first relapse, it is less than 5%. Emphasis has been recently placed on the probability that testicular relapse may be the only clinical evidence for occult systemic relapse. If testicular relapse occurs during or following cessation of therapy, irradiation in a dose of 2400 rad should be given to both testes. As when CNS relapse occurs, systemic spread must be assumed, and therefore, a systemic chemotherapy reinduction regimen should be given followed by continuation therapy for those patients in whom this relapse has occurred after treatment has been stopped.

Cessation of Therapy

At the present time, with current treatment regimens, the majority of patients with acute lymphocytic leukemia of childhood can be expected to survive 5 yr in continuous complete remission. Because of the hazards of long-term cancer chemotherapy, consideration has to be given to the duration of time beyond which further therapy would be unnecessary. The exact duration of time has not yet clearly been defined but the usual practice is to discontinue treatment after 2.5–5 yr of continuous complete remission. It must be stressed that this practice is applicable only to those patients who have had effective treatment regimens by today's standards. If a continuous complete remission has been maintained for 2.5–3 yr, the overall frequency of relapse following cessation of treatment is about 25%. The most frequent site of relapse, when it occurs, is in the bone marrow, and it occurs most frequently during the first year after cessation of therapy. The risk of relapse is considerably less in the second and third year after treatment has been stopped, and in our experience, becomes exceedingly small and possibly negligible if there has been a period of 4 yr following cessation of therapy without relapse.

It is impossible by current standards to identify those patients who are at risk for relapse following cessation of therapy with one exception. The one exception as far as prognostic features are concerned is sex. Boys have a greater risk of relapse (about 30%) than do girls (about 20%). Some of this increased frequency is related to testicular relapse, but not all of the increased risk can be accounted for by this site. It would be important to be able to identify those patients at risk for relapse so that some intensification of consolidation regimen could be given to them prior
to cessation of therapy, or therapy could be continued for a longer period of time. From the studies that are available, in which the period of continuation therapy has been varied, there seems to be no advantage for most patients in continuing treatment beyond 2.5–3 yr. Continuing treatment beyond that period obviously puts most patients at risk from treatment unnecessarily to possibly benefit those patients who are at risk from relapse.

Cure for the patient with acute lymphocytic leukemia has been the goal of these treatment regimens. Definition of cure in this disease, however, has been difficult to establish. Complete disappearance of all measurable disease obviously cannot be considered because of the risk of subsequent relapse. Currently, there are no means by which we can measure the presence of residual leukemic cells during remission. The ability to define residual disease would be highly desirable, not only for the establishment of cure but also as a guide to the duration of therapy a specific patient might require. Without this ability, the only means for establishing a working definition of cure have been the observations of a large number of patients over a long period of time. As mentioned above, patients who have been in continuous complete remission for a period of 6.5 yr following institution of effective treatment have a small and possibly negligible risk of relapse.68 As a working definition, these patients can be considered cured of their disease. This working definition now needs to be tested by further observations.

Late Consequences of Disease and Treatment

With an increasing number of children surviving disease-free for long periods of time, and with some patients being cured of their disease, attention has been drawn to late consequences of this disease and its treatment. Already mentioned is the group of children who have neuropsychologic deficits that may be associated with difficulties in learning some subjects. Careful studies of long-term survivors now need to be done to assess the possible damage involving other organs, such as liver, lung, kidney, and endocrine function. The reproductive capacity of successfully treated individuals should be established. At this time, there is no indication of excessive risk of abnormalities in the offspring of those patients who have had children. Another important need is the determination of the risk of second malignancy and particularly to determine if there are any factors that might be predictive of such a risk. Perhaps one of the most important things is to establish in the community the concept of curability of leukemia for some patients so that there will be acceptance of these individuals into the usual activities for all people.

Immunotherapy

In 1969, Mathe and coworkers reported success in the treatment of patients with ALL by “active immunotherapy,” consisting of BCG scarification and/or vaccination from a pool of allogenic leukemic lymphoblasts.70 The number of patients was small and the study was not well controlled, however, several other studies were begun to extend these initial observations. Some of the studies were interpreted as being confirmatory of the positive effect of immunotherapy,71 while others failed to confirm a beneficial effect of immunotherapy.72,73 In spite of the decade available for study of this modality of treatment for ALL since the initial report, recent reviews of the subject74,75 have concluded that while the positive benefit of immunotherapy with BCG and/or leukemic cells has not been convincingly demonstrated, neither has sufficient evidence been presented in such a manner as to definitively conclude that it is worthless. At this time, with our better understanding of the immune system and its responses, the classification of ALL and its relationship to clinical features, the availability of better treatment regimens with an understanding of the importance of sanctuary sites, and also the availability of a wider range of agents, including the group of biological modifiers for study, perhaps in the coming decade well designed studies can be developed for further evaluation of immunotherapy in ALL.

Bone Marrow Transplantation

The early results of bone marrow transplantation for patients with ALL were disappointing. For the most part, these attempts were made in patients in relapse following various schedules of chemotherapy. Mortality from early infection, graft-versus-host disease, and leukemic relapse left only about 15% of this group having long-term leukemia control.76,77 Since the beginning of these bone marrow transplantation studies for ALL, much progress has been made in treatment for this disease and also a better understanding for the optimal conditions under which bone marrow transplantation should take place. At the present time, the group of patients with ALL for which bone marrow transplantation should be evaluated are those patients who achieve a second or subsequent remission following relapse during chemotherapy. As indicated above, the prognosis for that group of patients is almost uniformly one of no hope for long-term disease-free control by current available regimens. Bone marrow transplantation in remission can be accomplished with less risk from the procedure to the patient.78 Further study of this treatment in the high-risk patient who relapses during therapy may support its role as the best available treatment for
patients who have an appropriately matched sibling. In the future, however, better primary and relapse treatment regimens for these high-risk patients may yet yield significantly better results.

SUMMARY

Clearly, the decade since 1970 has brought about considerable change in our understanding of ALL and its treatment. We have developed a base of new knowledge that should allow the development of treatment regimens for study in the coming decade based on the need to answer the questions that have arisen and solve the problems we currently face. While the challenges for this coming decade are indeed formidable, the opportunities to learn more about ALL and other forms of disseminated cancer are proportionately great. The coming decade should prove interesting and, hopefully, exciting and gratifying as well.

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Therapy of acute lymphoblastic leukemia in childhood

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