Canad. Med. Ass. J.
June 24, 1967, vol. 96

FREIREICH: LEUKEMIA 1605

51. ENGEL, E. et al.: New Eng. J. Med., 273: 738, 1965.
52. ADAMS, A., FITZGERALD, P. H. AND GUNZ, F. W.: Brit. Med. J., 2: 1474, 1961.
53. GOH, K., SWISHER, S. N. AND TROUP, S. B.: Arch. Intern. Med. (Chicago), 114: 439, 1964.
54. HOUSTON, E. W., LEVIN, W. C. AND RITZMANN, S. E.: Ann. Intern. Med., 61: 696, 1964.
55. PEDERSEN, B.: Acta Path. Microbiol. Scand., 61: 497, 1964.
56. PEDERSEN, B. AND VIDEBAEK, A.: Scand. J. Haemat., 1: 129, 1964.
57. SANCHEZ CASCOS, A. AND BARREIRO, E.: Rev. Clin. Esp., 94: 10, 1964.
58. LEVAN, A., NICHOLS, W. W. AND NORDEN, A.: Hereditas (Lund.), 49: 433, 1963.
59. REISMAN, L. E., MITANI, M. AND ZUELZER, W. W.: New Eng. J. Med., 270: 591, 1964.
60. FITZGERALD, P. H., ADAMS, A. AND GUNZ, F. W.: J. Nat. Cancer Inst., 32: 395, 1964.
61. SANDBERG, A. A. et al.: Ann. N.Y. Acad. Sci., 113: 663, 1964.
62. PYATKIN, E.: Probl. Gemat., 11: 14, 1965.

63. BAIKIE, A. G. et al.: Lancet, 2: 425, 1959.
64. ATKIN, N. B. AND BAKER, M. C.: J. Nat. Cancer Inst., 36: 539, 1966.
65. MAKINO, S., SASAKI, M. S. AND FUKUSCHIMA, T.: Proceedings of the Japan Academy, 39: 54, 1963.
66. SANDBERG, A. A., ISHIHARA, T. AND CROSSWHITE, L. H.: Blood, 24: 716, 1964.
67. ROWLEY, J. D., BLAISDELL, R. K. AND JACOBSON, L. O.: Ibid., 27: 782, 1966.
68. KIOSSOGLOU, K. A., MITUS, W. J. AND DAMESHEK, W.: Ibid., 28: 241, 1966.
69. McCLURE, P. D., THALER, M. M. AND CONEN, P. E.: Arch. Intern. Med. (Chicago), 115: 697, 1965.
70. SAWITSKY, A., BLOOM, D. AND GERMAN, J.: Ann. Intern. Med., 65: 487, 1966.
71. HECHT, F. et al.: Lancet, 2: 1193, 1966.
72. GARRIGA, S. AND CROSBY, W. H.: Blood, 14: 1008, 1959.
73. SWIFT, M. R. AND HIRSCHHORN, K.: Ann. Intern. Med., 65: 496, 1966.
74. BLOOM, G. E. et al.: New Eng. J. Med., 274: 8, 1966.
75. GROUCHY, J. DE: Ann. Intern. Med., 65: 603, 1966.
76. NICHOLS, W. W.: Hereditas (Lund), 50: 53, 1963.

The Management of Acute Leukemia

EMIL J. FREIREICH, M.D., Houston, Texas, U.S.A.

The therapy of acute leukemia has improved rapidly in the last two decades. Using available therapeutic agents, complete clinical and hematological remission can be achieved regularly in children with acute lymphocytic leukemia. The choice of chemotherapeutic agent, management of complications of hemorrhage and infection, and recognition 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 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.

Le traitement de la leucémie aiguë s'est grandement amélioré au cours des deux dernières décennies. Grâce aux agents thérapeutiques existants, il est possible de réaliser régulièrement une rémission clinique et hématologique complète chez des enfants souffrant de leucémie lymphoïde aiguë. Le choix de l'agent chimiothérapique, le traitement des complications hémorragiques et infectieuses et la reconnaissance des facteurs pronostiques ont beaucoup d'importance pour le déclenchement de la rémission hématologique. Même si les leucémiques qui sont en phase de rémission hématologique complète ne présentent aucun signe pathologique, ils hébergent néanmoins encore des cellules leucémiques résiduelles que, malheureusement, dans l'état actuel de nos connaissances et faute de la technique appropriée, nous sommes incapables de déceler. C'est pourquoi il est capital de traiter les malades en phase de rémission. L'auteur attire l'attention sur l'importance de l'horaire posologique de la chimiothérapie d'entretien en phase de rémission.

Chez les malades observés jusqu'ici, et quel qu'ait été le traitement employé, la maladie a présenté des récidives. Les agents thérapeutiques actuels sont très efficaces et extrêmement sélectifs, mais ils sont encore loin de constituer le traitement idéal pour enrayer la pathologie. La recherche continuelle de nouveaux médicaments est grandement facilitée par les connaissances accumulées et les techniques mises au point concernant les derniers agents.

THE ability of an antimetabolite to induce a hematological remission in children with acute leukemia was discovered less than two decades ago.[1] Since that time, there has been rapid progress in our knowledge of the natural history of this disease, of the management of its complications, and of the specific chemothera-

peutic agents with proved activity against the leukemic cells.[2, 3] This increase in knowledge has provided a substantial reduction in morbidity and a prolongation of life for most of the patients with acute leukemia. Therapy is most effective for the acute lymphoblastic form of acute leukemia occurring in children. Most of the quantitative data concerning therapy of

1606 FREIREICH: LEUKEMIA

Canad. Med. Ass. J.
June 24, 1967, vol. 96

acute leukemia have come from the study of childhood acute lymphocytic leukemia. For this reason, I will concentrate on the therapy of this form of leukemia, although the principles of this therapy should also apply to acute myelocytic leukemia and acute lymphocytic leukemia of the adult.

REMISSION—INDUCTION THERAPY

The objective of the therapy program is the induction of a complete hematological remission. Because the major causes of morbidity and mortality in acute leukemia are hemorrhage and infection, which in turn are due to peripheral cytopenias, the induction of a complete hematological remission, with return of the peripheral blood to normal, virtually eliminates these complications. Moreover, since the duration of peripheral blood remission is directly related to the degree of improvement in the bone marrow, it is also important to continue therapy until the bone marrow returns to a state which is indistinguishable from the normal. The duration of remission correlates directly with the duration of survival of the patient with leukemia; thus, the induction of a complete hematological remission is a clear objective of therapy. I will discuss three aspects of the remission induction therapy: (1) the choice of chemotherapeutic agent used to induce remission, (2) the supportive therapy necessary to avoid complications resulting from both the disease and the therapy, and (3) the prognostic factors which allow prediction of the frequency and duration of remissions.

1. Choice of Chemotherapeutic Agent

The most useful drugs for remission induction are those which are highly specific for the leukemic cells and are only slightly toxic to the normal bone marrow elements. Two agents, the adrenal corticosteroids (prednisone) and vincristine (Oncovin), are capable of inducing remission in more than 50% of the children with childhood acute lymphocytic leukemia within four weeks of the start of therapy. Both agents have little toxicity when given "acutely" over a four-week period. However, toxicity does occur with prolonged use, and such therapy should be discontinued as soon as hematological remission is achieved. The antimetabolites, 6-mercaptopurine and methotrexate, are also capable of inducing complete hematological remissions but in a smaller proportion of patients, 25 to 40%. Finally, the alkylating agent, cyclophosphamide (Cytoxan), is also capable of inducing a complete remission in 15 to 30% of patients

with childhood acute lymphocytic leukemia. However, when drugs which are able to induce remission are used in combinations at full therapeutic dosage, the observed remission rate will be substantially higher than could be achieved with either of the agents used alone, and is consistent with their independent action in inducing remission. The nature of the limiting toxicity observed with each of the agents is important for the selection of the drugs for combination chemotherapy. If the limiting toxicity is different for the two agents, such as for prednisone and vincristine which have different limiting toxicities, each agent may be given in full therapeutic dosage. Such combinations offer the best therapeutic effect. For drugs that have similar toxicity, such as the antimetabolites, 6-mercaptopurine and methotrexate, a lower dosage must often be used in simultaneous administration and the full therapeutic benefit should not be anticipated. The combination of vincristine and prednisone has proved to be extremely useful because these two agents not only have independent toxicity but are highly active against the disease, and in neither is myelosuppression an important side effect. In recent large group-studies of childhood acute lymphocytic leukemia, complete remission rates of 85 to 100% have been achieved with this combination. The combination of prednisone and 6-mercaptopurine has also given complete remission rates greater than 85% because 6-mercaptopurine is only mildly myelosuppressive and is highly active in inducing remissions. Finally, with multiple drug combinations, such as vincristine, prednisone and 6-mercaptopurine, remission rates of over 90% can be observed.

2. Management of Complications

During remission induction therapy, in the time needed for recovery of the normal hematopoietic elements after chemotherapy, the patient must be protected from three major complications: hemorrhage, infection and renal failure secondary to uric acid nephropathy.

a. The Management of Hemorrhage

The major cause of hemorrhage is thrombocytopenia, the best quantitative measurement of which is the platelet concentration in the circulating blood. Freshly collected human platelets, obtained by plasmapheresis or as a by-product from whole blood, when transfused into the thrombocytopenic recipient, are consistently effective in elevating the concentration of circulating platelets. The platelet count will increase by 12 to 15,000/mm³ for every unit of platelets (the

Canad. Med. Ass. J.
June 24, 1967, vol. 96

FREIREICH: LEUKEMIA 1607

platelets derived from 500 c.c. of whole blood—approximately 10^{11} platelets) per M^2 of body surface area of the recipient.[4, 5] The platelet half-life is approximately 24 to 48 hours in the thrombocytopenic recipient. As a result, a transfusion of a sufficient dose of platelets that will elevate the count 30 to 50,000/mm³ if repeated two or three times a week will maintain the platelet levels in excess of 20,000/mm³. With such a program, the frequency of hemorrhagic complications, particularly fatal complications, can be significantly decreased.

b. The Control of Infection

The major factors in the control of infection are prompt recognition, and prompt and appropriate antibiotic or chemotherapeutic therapy with specific agents. Since the discovery of penicillinase-resistant penicillins, Staphylococcus aureus has been virtually eliminated as a major cause of fatal infection and septicemia. In patients who develop fever or other physical signs of infection, antibiotics should be started as soon as appropriate cultures are obtained. If necessary, the chemotherapy can be altered to more appropriate agents when the organisms have been identified and in vitro sensitivities established. However, prompt antibiotic therapy is important because the time from the appearance of physical signs of infection, such as fever, to a fatal outcome may be as short as 24 to 48 hours.

Infection is still the major cause of fatal complications in acute leukemia. Most of these infections are due to organisms that normally are saprophytic but which become pathogenic in the leukemic person receiving chemotherapy that is both immunosuppressive and myelosuppressive. The most important causative organisms are the gram-negative "rods" including Pseudomonas, Klebsiella and Proteus. For these organisms, antibiotics are available which are effective in persons with normal leukocytes (i.e. normal as to numbers and quality), but are comparatively ineffective in patients with leukemia. This is because of the leukopenia; and because these antibiotics have limitations in terms of the duration of administration (i.e. total dose) with the result that control of infection is very often temporary, since recurrent infection with the same organism is the rule rather than the exception in leukemia patients. Finally, certain viral infections, particularly cytomegalovirus, are becoming more important as a complication of leukemia. It has been demonstrated that replacement of leukocytes, particularly granulocytes, by transfusion is feasible, but it is not yet possible to collect adequate numbers of granulocytes for transfusion. The lack of effective techniques for the separation and collection of leukocytes, and their very short life-span—under 12 hours—makes necessary further research into leukocyte replacement transfusion. The feasibility of temporary bone marrow homografts has been demonstrated in severely pancytopenic patients with acute leukemia who are also receiving immunosuppressive therapy. Because such homografts can maintain platelets and granulocytes at normal levels, this is an effective form of supportive therapy. Unfortunately, because of our limited understanding of donor-recipient histocompatibility this is available only on an experimental basis.

c. Uric Acid Nephropathy

In the patient with active acute leukemia, particularly the patient who has a large volume of tumour, the concentration of uric acid in the serum and in the urine can become markedly elevated. This concentration is raised still further when antileukemic chemotherapy is started and the uric acid load on the kidney may be greatly increased. When the urine concentration of uric acid becomes high, uric acid is precipitated in the tubules and produces a tubular obstructive uropathy. This complication can be avoided by maintaining a high urine volume through water diuresis and by keeping the pH of the urine at neutral or alkaline by the administration of sodium bicarbonate. In addition, allopurinol, a xanthine oxidase inhibitor, prevents the conversion of hypoxanthine to uric acid and thus reduces greatly the renal uric acid load. By these measures uric acid nephropathy can be prevented.

3. Prognostic Factors

The three factors of established importance in prognosis are the morphological diagnosis, the age of the patient, and the extent of disease.

a. Morphological Diagnosis

Patients with acute lymphoblastic leukemia are much more responsive to chemotherapy than patients with acute granulocytic leukemia. The latter group includes those with monocytic or myelomonocytic leukemia.

b. Age

The effect of age has been very clearly demonstrated, particularly in acute lymphoblastic leukemia where the response rate is very high: more than 90% of patients between the ages of

2 and 10 will achieve at least one complete hematological remission. The older the patient, the poorer the prognosis. In patients with myeloblastic leukemia, where the response rate is low, the effect of age has not been clearly demonstrated, although some evidence indicates that patients over the age of 30 have a much poorer prognosis than those under that age.

c. Extent of Disease

An important parameter in prognosis is the extent of leukemic disease as reflected by the height of the circulating leukocyte count: the higher the number of circulating blast cells, the poorer the prognosis. In patients whose blast concentration exceeds 300,000/mm^3, there is more than a 75% probability that a fatal intracranial hemorrhage will occur within the following week. Other factors such as the degree of organ enlargement (particularly liver, spleen and lymph nodes), evidence of infiltration of the kidney or central nervous system, severe thrombocytopenia, granulocytopenia and anemia are also associated with poor prognosis. Finally, in acute granulocytic leukemia, evidence of leukemic cell maturity reflected by the presence of Auer rods and/or significant specific neutrophilic granulation is important in prognosis: the greater the maturation, the better the prognosis.

The more favourable prognostic features— such as the specific diagnosis of acute lymphocytic leukemia, a young patient, less extensive disease—are associated with more frequent hematological remissions and longer remissions for those who achieve them. The more favourable prognostic features indicate better overall survival, which is due to a longer period in remission, rather than a longer period of resistance to the active disease.

THERAPY DURING HEMATOLOGICAL REMISSION

The present evidence indicates that the patients who achieve a complete hematological remission still harbour persistent leukemic cells. If chemotherapy is discontinued in the patient during a complete hematological remission, the disease will recur rapidly. The median duration of "unmaintained" remissions, i.e. those in which specific maintenance therapy was not given, will be approximately eight weeks and more than 95% of patients will have a recurrence before 20 weeks. In contrast, if chemotherapy is continued in the patient during a hematological remission, the remission can be substantially prolonged—in the "median patient" to almost a year. Moreover, extensive histopathologic study of patients in hematological remission[6, 7] has re-

vealed that, in many, leukemic cell infiltration persists in areas other than the bone marrow. For these reasons therapy is definitely indicated for the patient in complete hematological remission. However, the principles governing therapy during remission are quite different from those for the induction of a remission. The agents most useful for remission induction, vincristine and prednisone, are of little value in maintaining a remission.

The reason for this seems to be that while these drugs have little or no toxicity during short-term administration, both have serious side effects when given over a prolonged period such as six to eight months; these limit the time during which such therapy can be given. These two agents should not be used as the only therapy for remission maintenance. In contrast, the antimetabolites such as 6-mercaptopurine and methotrexate, which are of limited value for remission induction, are extremely useful for remission maintenance because they can be given over long periods without much cumulative toxicity. Also, in contrast to experience in remission induction therapy, combinations of agents have not proved to be more effective than a single agent in remission maintenance. However, if methotrexate is used to maintain remissions, the dosage schedule is extremely important.[8] Methotrexate by an intermittent, twice-weekly schedule gives a median duration of remission in childhood acute lymphocytic leukemia of nearly a year. Daily 6-mercaptopurine therapy gives six- to seven-month remissions. Other approaches to remission maintenance include the alternation of chemotherapeutic agents while the patients are in remission, or treatment with vincristine and prednisone in addition to other maintenance therapy; however, none of the techniques have proved superior to a single agent given by its optimal schedule and route.

Since available data indicate that the patient in remission has persistent disease, it would seem reasonable to give intensive chemotherapy early in the course of remission in an effort to eradicate persistent leukemic cells. In experimental animals it is possible by measuring the animal's life span following a given treatment or cell inoculation to accurately estimate the number of persistent leukemic cells in the animal after the treatment or cell injection. In man, the duration of unmaintained hematological remissions can be used to estimate the quantity of disease persisting when therapy was discontinued.[9] We have estimated that the child with acute lymphocytic leukemia has 10^{12} or approximately 1 kg. of leukemic cells at the earliest time the diag-

Canad. Med. Ass. J.
June 24, 1967, vol. 96

FREIREICH: LEUKEMIA 1609

nosis can be made. If complete remission is induced with vincristine or prednisone, the median duration will be 40 to 60 days if no further chemotherapy is given. From the doubling rate of leukemic cells, it is possible to estimate the extent to which leukemic cells have been reduced with such therapy: somewhere between 10^8 and 10^9 cells, approximately 1 g. of leukemic cells. On the other hand, after intensive therapy with a four-drug combination (vincristine, prednisone, methotrexate and 6-mercaptopurine) in four to six courses early in remission, the median duration of unmaintained complete remission is approximately 130 days, and between 10 and 100 leukemic cells will persist after therapy is discontinued. In addition, the rate of recurrence of leukemia in patients on four-drug therapy was somewhat lower than in those with vincristine-prednisone remissions. From this one would predict that some patients may have reached the point where there were no persistent leukemic cells and the cellular phase of their disease may have been eradicated. Of 23 patients who received five to six courses of intensive therapy early in remission, we have observed three who had remissions longer than two years, without any maintenance chemotherapy. These patients are currently being followed up.[10] There is a striking similarity between the pattern of recurrence following intensive chemotherapy given early in remission and the pattern following remissions induced with prednisone and maintained with 6-mercaptopurine. This suggests that maintenance chemotherapy may consist chiefly of sequential therapy given early in the remission. Thus, both the pattern or the rate of recurrence following the induction of a remission, and the duration of the remission, are useful in evaluating the effectiveness of therapy in acute leukemia.

As remission maintenance chemotherapy becomes more effective and the durations of remissions are prolonged, other complications are being observed with increasing frequency. For example, meningeal leukemia occurs in most of those who have complete remissions of longer than six months. This complication, fortunately, can be effectively managed with intrathecal methotrexate in almost every instance. However, the meninges may well harbour leukemic cells and frustrate all efforts to eliminate residual leukemic cells during remission. In addition, chronic maintenance chemotherapy often reveals new toxicities that are not observed during shorter courses, e.g. chronic suppression of the immunity mechanisms with subsequent infections and liver disease as a complication of prolonged antimetabolite chemotherapy.

TREATMENT FOR RECURRENT DISEASE

While available chemotherapy is highly specific and results in a return of the patient to normal, the period of hematological remission eventually passes and the disease inevitably recurs. The treatment of the recurrent disease follows the same principles which have been described for the treatment of the original disease in the patient. That is, remission induction chemotherapy must again be used. In general, therapy which was administered when the patient's disease recurred will not be effective for reinducing remission. For example, if 6-mercaptopurine is used for both remission induction and for maintenance of the remission, and if the disease recurred while 6-mercaptopurine maintenance therapy was being given, then 6-mercaptopurine will not be effective for reinducing remission. However, if combination therapy employing vincristine and prednisone is used for remission induction and not used again during the maintenance phase of the program, the use of vincristine and prednisone for reinduction of remission is effective in a very high proportion of patients (more than 75%). Remission induction therapy with vincristine and prednisone may be effective for a third treatment course in most patients. As a result, it is possible to recommend vincristine and prednisone for remission induction, followed by intermittent methotrexate for remission maintenance. When the disease recurs while the patient is receiving methotrexate maintenance chemotherapy, vincristine and prednisone can be used again for remission induction. If remission is achieved, then daily oral 6-mercaptopurine can be used as maintenance therapy. If the patient has recurrence on daily 6-mercaptopurine, then vincristine and prednisone can be used for a third remission induction with good probability of success. Unfortunately, the patient's disease eventually becomes resistant to all the available agents and treatment is no longer effective. For this reason it is clear that palliative treatment designed to repeatedly induce hematological remission will always provide only palliation. Clearly, what is needed is the development of therapeutic agents and techniques which will eradicate the disease in any patient.

SUMMARY

The therapy of acute leukemia has improved rapidly in the last two decades. Using available therapeutic agents, complete clinical and hematological remission can be achieved regularly in children with acute lymphocytic leukemia. The choice of chemotherapeutic agent, management of complications of hemorrhage and infection, and recogni-

1610 HASSELBACK AND OTHERS: LEUKEMIA

Canad. Med. Ass. J.
June 24, 1967, vol. 96

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.

REFERENCES

1. FARBER, S. et al.: New Eng. J. Med., 238: 787, 1948.
2. FREIREICH, E. J. AND FREI, E., III: Progr. Hemat., 4: 187, 1964.
3. BOGGS, D. R., WINTROBE, M. M. AND CARTWRIGHT, G. E.: Medicine (Balt.), 41: 163, 1962.
4. FREIREICH, E. J.: Transfusion, 6: 50, 1966.
5. DJERASSI. I., FARBER, S. AND EVANS, A. E.: New Eng. J. Med., 268: 221, 1963.
6. NIES, B. A. et al.: Blood, 26: 133, 1965.
7. MATHE, G. et al.: Brit. Med. J., 1: 640, 1966.
8. Acute leukemia group B: J. A. M. A., 194: 75, 1965.
9. FREI, E., III, AND FREIREICH, E. J.: Advances Chemother., 2: 269, 1965.
10. JOHNSON, R. E., ZELEN, M. AND FREIREICH, E. J.: Cancer, 19: 481, 1966.

The Influence of Morphology on Prognosis in Acute Leukemia

R. HASSELBACK, M.D., F.R.C.P.[C], JOHN CURTIS, M.D.,
MARJA SOOTS, M.D., G. L. ROBERTSON, M.D.,
D. H. COWAN, M.D., F.R.C.P.[C] and
G. D. HART, M.D., F.R.C.P.[C], Toronto

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