Long-Term Survivors in Acute Leukemia[1]

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SUMMARY

By means of a questionnaire survey data from 71 patients with acute leukemia who have survived 5–12 years since the diagnosis of the disease have been collected. Thirty-six out of 53 children and 6 out of 18 adults are living and well with no evidence of leukemia more than 5 years after the diagnosis. Theoretical reasons have been considered for differences in response between these long-term survivors and the usual cases of acute leukemia.

A registry of these cases will be available at the Acute Leukemia Task Force, National Cancer Institute, Bethesda, Maryland.

Long-term remissions and rare, so-called "cures" in acute leukemia had been reported occasionally even prior to the development of specific forms of therapy for this disease. Forkner (14), however, in reviewing those published prior to 1937, considered that in the majority the diagnosis of acute leukemia was not adequately substantiated. Tivey (40), reviewing 218 untreated cases of acute leukemia in children, found a median survival of 3.9 months from the first symptom of the disease to death and a 10% survival of approximately 10 months. Southam *et al.* (37), reporting the experience at Memorial Hospital from 1926 through 1947, a period when none of the drugs now recognized to be active therapeutic agents were available, found that only 3 of the 150 patients in his series of both adults and children survived more than a year, and all were dead by 14 months.

With the advent of specific chemotherapy, aminopterin and amethopterin in 1948 (11), adrenocorticotropin and cortisone in 1949 (12, 30), 6-mercaptopurine in 1953 (3), cyclophosphamide in 1960 (13, 39), and vincristine in 1962 (10, 21, 22, 32, 38) and the increased interest in the treatment and survival times in acute leukemia shown by various investigators, including those in the cooperative groups under the aegis of the Cancer Chemotherapy National Service Center, it became apparent that not only were the median and the 10% survival times increasing significantly, but also there were occasional long-term survivors (4, 7, 18, 19, 43).

Our own experience (27) with these long-term survivors and that of investigators such as Zuelzer (42), Dameshek and Mitus (6), Brubaker *et al.* (1), and others (M. S. Sacks, personal communication) suggested that these patients or their disease must be different from the majority of cases of acute leukemia which, even in spite of excellent drug-induced temporary remissions, do not survive more than 2 years from the onset of the disease. It appeared that, if a significant number of patients surviving with no evidence of acute leukemia 5 years or more from the diagnosis of the disease could be found, studies of the original marrow, the type of and response to treatment, and the present status of the patient from the virologic and immunologic point of view might be helpful in explaining these differences.

In order to ascertain the number and location of such cases, a simple preliminary questionnaire was prepared under the aegis of the Acute Leukemia Task Force of the National Cancer Institute and the Chemotherapy Panel of the Union Internationale Contre le Cancer, requesting the names, ages, date of diagnosis, treatment, and present status or date of death of all cases of acute leukemia surviving 5 years or more from the time of diagnosis. These questionnaires were sent to all members of the American Society of Hematology from the membership list kindly supplied by the secretary, Dr. Wayne Rundles. They were also incorporated in the regular newsletters sent to members of the International Society of Hematology by Drs. Georges Mathé and James Tullis. The response has been gratifying. The purpose of this paper is to indicate that, although such long-term survivals are extremely rare, enough cases are available for carefully planned immunologic, virologic, and biochemical studies.

A total of 71 such cases have so far been reported (Table 1). We have been advised of several more such cases, but complete data from the questionnaires are not available as yet. Of these, 53 are children, of whom 36 are living with no evidence of disease at the present time (Chart 1). The other 17 either have evidence of leukemia at present or have died. Of the 18 adults, 6 have no evidence of disease at the present time, and 12 others either have manifestations of leukemia or have died. It is of interest that, of the 17 children who have died of leukemia or have evidence of the disease at present, none has lived beyond 8 years, whereas of those with no evi-

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TABLE 1

INVESTIGATORS REPORTING LONG-TERM SURVIVORS IN ACUTE LEUKEMIA

Investigator	No. of cases
Blom	1
Bowman	1
Brubaker	8
Burchenal	2
Chew	1
Cooper	2
Dameshek	1
Darte	2
Davis	1
DeMarsh	1
Doan	1
Feldman	1
Gaffney	4
Hall	1
Hill	3
Holland	1
Josephson	1
Kraus	1
Lee	1
Malinvaud	1
McElfresh	1
McIlvanie	2
Meyers	2
Muller	1
Osgood	1
Pavlovsky	2
Pearson	1
Pierce	1
Propp	1
Read	1
Sacks	1
Sakol	1
Schwartz	1
Spurling	1
Stuckey	2
Sullivan	1
Tishkoff	1
Watson	1
Wilkinson	1
Wilson	2
Wintrobe	1
Zinkham	2
Zuelzer	8
Total	71

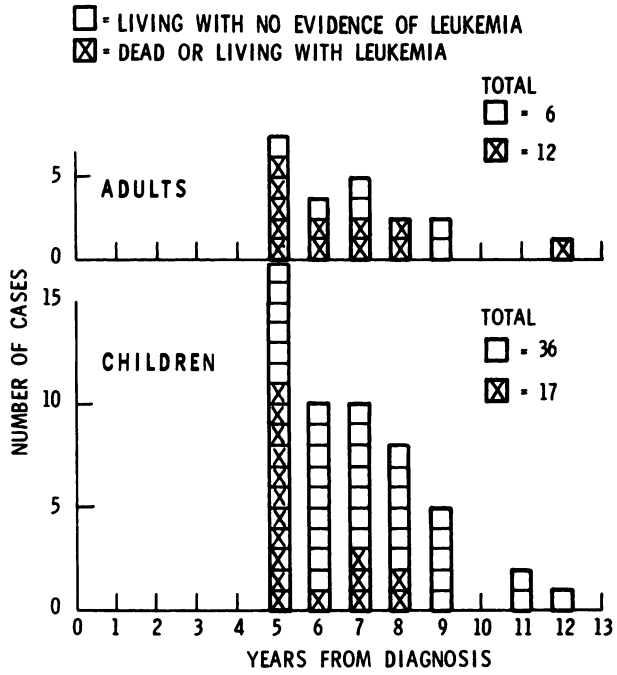

CHART 1.—Survival of 71 patients with acute leukemia living 5 years or more from diagnosis.

TABLE 2

TYPE OF TREATMENT USED IN 42 LEUKEMIC PATIENTS WHO NOW HAVE NO EVIDENCE OF DISEASE MORE THAN 5 YEARS AFTER DIAGNOSIS

Treatment	No. of cases
Steroids only	3
6-Mercaptopurine only	4
Methotrexate only	3
Steroids + 6-mercaptopurine	10
Steroids + methotrexate	2
6-Mercaptopurine + methotrexate	4
Steroids, 6-mercaptopurine, methotrexate	8
Cyclic, with 6-mercaptopurine + methotrexate or steroids, 6-mercaptopurine, methotrexate	8
Total	42

dence of disease 7 are living at 8 years, 6 at 9 years, 2 at 11, and 1 at 12 years. It is well recognized that there is a continuous fall-off in the survivors of acute leukemia, certainly up to 5 years, and, from the children of this series, up to 8 years. It is possible that the lack of deaths after 8 years may represent a discontinuous phase of the curve. Obviously the series is too small at present to more than suggest such a possibility. No data on incidence can be given for these long-term remissions, however, since there is no indication from how large a population of acute leukemias these 71 cases came.

A 2nd letter has been sent out to all those reporting 5-year survivors, requesting the original marrow slides for study. At the time of writing this paper, only 24 marrows have been submitted. From our preliminary examination 18 of these, 9 out of 12 in the cases which at the present time have no evidence of leukemia, and 9 out of 12 in those cases which have present evidence of leukemia or have resulted in death from the disease, appear to be unequivocally acute leukemia. The other marrows submitted either are inadequate for us to confirm the diagnosis or are subsequent marrows showing the effect of treatment. At the time of writing, sufficient slides have not been examined to allow any definite statement regarding the morphology except that acute lymphoblastic and stem-cell leukemias seem to predominate, but that acute granulocytic and acute monoblastic leukemias are also represented.

When slides have been received on the majority of the patients, they will be submitted for morphologic classifi-

cation to various groups of hematologists selected by the Acute Leukemia Task Force. Drs. Doan, Wintrobe, Dameshek, Zuelzer, and Brecher have consented to review these slides.

Rough qualitative data on the treatment regimens were given for 42 patients now living with no evidence of disease and are broken down in Table 2. It is notable that all received either steroids, 6-mercaptopurine (6-MP), or methotrexate, or various combinations thereof, and that none needed cyclophosphamide or vincristine. Three remissions occurred on steroids alone, 4 on 6-MP only, and 3 on methotrexate only. In those who survived more than 5 years, but who either have evidence of leukemia at present or have died of the disease, there was a tendency to use cyclophosphamide, other alkylating agents, vincristine, as well as various experimental agents when steroids, 6-MP, and methotrexate failed.

It is interesting to speculate why these cases should behave so differently from the usual cases of acute leukemia. These differences may reside in the leukemic cell or in the host response to the disease.

First, let us consider the leukemic cell. Are the cells in these particular cases so sensitive to therapy that every leukemic cell is destroyed, so that none remains to develop resistance and produce a relapse? This does occur, for instance, in strains of transplanted mouse leukemia in which a high percentage of mice can be cured by certain of the phthalanilide and phthalamidine derivatives (2).

It is possible in some cases that with combination therapy the number of leukemic cells has been so lowered by 1 drug that cures can be accomplished by a 2nd. Skipper *et al.* (35, 36) and Goldin *et al.* (15) have shown in transplanted leukemia L1210 that curability depends directly on the number of cells inoculated. The fact that there appears to be a proportionately higher number of 5-year survivors in the 2 groups of cases treated with cyclic therapy by Zuelzer (42) and by Brubaker (1) supports this theory.

In some of the patients the development of resistance to 6-MP or 6-MP and azaserine may have caused an increased collateral sensitivity to methotrexate, so that the subsequent treatment with the latter drug was able to destroy all these resistant cells. The development of such increased collateral sensitivity to methotrexate in strains of L1210 leukemia made resistant to 6-MP has been demonstrated by Law *et al.* (25), and suggestive data for such increased sensitivity have been reported in patients by Ellison and Burchenal (9). The fact that in several children in this series, in whom remissions of over 4 years were produced by methotrexate, there had been a previous response followed by the development of resistance to 6-MP supports this possibility.

In some patients it is possible that an altered host metabolism or excretion of the therapeutic agent might produce higher or more effective blood levels of the drug and so destroy cells which might not be killed by the blood levels obtained by similar dosage schedules in the usual patient.

Now let us consider the possibilities that differences in host reactions have contributed to these long-term survivals. There is a possibility, although not a necessity, that mutant leukemic cells contain a new and foreign antigen. It is also well known that there are innate differences in the ability of hosts to produce antibodies against foreign antigens. This theory might be subject to confirmation, if the sera of a few of these apparently healthy patients were tested against a broad spectrum of acute leukemic cells from many different patients.

It is possible that in some of the long-term survivors the disease may have been virus-induced and that in this manner a new antigen has been produced, as in the Rous sarcoma (41), polyoma (16, 33, 34), the SV 40 virus-induced tumors (8, 17, 24, 26), or the Gross virus-induced lymphoma (23). This possibility would be suggested by the appearance of one 5-year survivor among the 8 "Niles cluster" cases (20, 31) and by Pavlovsky's case (personal communication), in which a sibling also developed acute leukemia shortly after the patient and died of the disease.

It is also theoretically possible that hypertrophy of the reticuloendothelial system by preexisting infections may influence the course of the disease. Such a situation due to hyperinfection with malaria or other parasites has been put forward by Edington (personal communication) to explain why the lymphosarcoma of the jaw (Burkitt's tumor) in African children grows only in localized tumors rather than progressing to a diffuse acute leukemia as so often occurs in generalized lymphosarcoma in Europe and America. Burkitt has also suggested (personal communication) that the percentage of patients with this African disease who have survived long periods without recurrence of the disease despite discontinuation of chemotherapy is considerably greater than in the acute leukemias (28). Perhaps in an occasional acute leukemia a moderately hyperplastic reticuloendothelial system might act to hold in check a disease already suppressed markedly by chemotherapy. Old *et al.* (29) have shown that nonspecific stimulation of immunologic activity by BCG infection inhibits the growth of certain transplanted tumors in mice.

Burkitt has reported (personal communication) that in none of his cases with complete regression has he ever seen recurrence at the site of the original lesion. This fact suggests that the recurrence may be due to the reinduction of a new tumor by a virus, and, since certain other studies (5) suggest that Burkitt's tumor is indeed associated with a virus, the long-term remissions occasionally seen in this tumor might also support the possibility of a virus-induced antigenic difference as mentioned in the preceding paragraph.

Since during the initial stages of their disease most of the patients were on steroids or anti-metabolites, both of which are known to suppress the immune response, the difference in the host capacity to produce antibodies in the presence of such suppressors may be important. Since, however, this would be suppression of preexisting antibody rather than of the induction of an immune response, the effect of drugs may not be important.

A registry of these and all subsequently reported cases of acute leukemia will be set up by the Acute Leukemia Task Force of the National Cancer Institute, Bethesda, Maryland, so that the names of the patients and the names and addresses of the doctors reporting them will be avail-

able to those investigators who wish to study their immunologic status in regard to acute leukemia or to viruses. It is hoped that through such carefully planned studies something may be learned regarding the differences between the great majority of patients with acute leukemia who respond only temporarily to chemotherapy and these few whose remissions have lasted so long.

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