Extracorporeal Irradiation of Blood (ECIB) in Man
II. Treatment of Acute Myelocytic Leukemia

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All present forms of therapy for acute myelocytic leukemia (AML) injure or destroy normal as well as leukemic cells. The action of anti-metabolic chemotherapeutic drugs is largely directed at disrupting nucleic acid synthesis and, thus, replication of cells. The alkylating agents and whole body radiation are effective in reducing cell production by slowing the generative cycle and directly killing both replicating and interphase cells. We hoped to achieve effective treatment of AML and, at the same time, avoid injury to normal cells by irradiating circulating leukemic cells in an extracorporeal circuit that diverted blood, alone, through a radiation field.

At least two theoretical consequences can be considered as a result of killing leukemic cells in this manner. First, if circulating cells are functioning or potential leukemic stem cells, and especially if they are exchanging with tissue counterparts, one may be able to deplete the body of a large reservoir of leukemic stem cells. Lajtha and co-workers1 and Oliver and Shepstone2 have discussed this possibility. If the reservoir of leukemic stem cells is then significantly reduced by ECIB, one may have a greater probability of obtaining a chemotherapeutic remission.3 If there is a self-regulating peripheral blood compartment of cells as has been postulated in chronic myelocytic leukemia,4 ECIB might well prove to be effective treatment. Second, killing leukemic cells in the peripheral blood may influence leukemic cell growth by altering feedback mechanisms which theoretically may have some role in determining population size.

The established chemotherapy of AML has proven to be rather disappoint-
ing, with median survival times only slightly better than a decade ago\(^8\); therefore it was considered justifiable to attempt this method of therapy in untreated as well as unsuccessfully treated patients. To our knowledge, this is the first series of patients thus reported, although one patient with myelomonoblastic leukemia received two short treatments (5 and 8 hours) with a blood irradiator in 1962.\(^1\) The number of patients we have treated to date is relatively small, but our experience may provide some useful information for other investigators who are using, or may be contemplating using, ECIB. In the period between November, 1964, and October, 1966, we used ECIB to treat 14 adult patients with AML.

**METHODS**

Daily Hgb, Hct, RBC, WBC with differential, platelet counts and reticulocyte counts were performed on hospitalized patients. Hemoglobin determinations were performed by the cyanmethemoglobin method, hematocrits by the microhematocrit method, RBC and WBC counts by electronic methods (Coulter), platelet counts by phase contrast,\(^9\) and reticulocyte counts by the new methylene blue staining method with the Miller eyepiece.\(^10\) All WBC differentials were performed by one hematology technician. Blood for these procedures was drawn, wherever possible, in the morning to obviate diurnal variations. Serum chemistries were performed by standard methods with the exception of urinary uric acid.\(^*\)

Patients were hospitalized and, after variable periods of observation, semipermanent arteriovenous (A-V) shunts were implanted under local anesthesia. These Teflon\(\textregistered\)-silicone rubber shunts\(\uparrow\) were placed in the radial artery and a forearm vein as described by Scribner et al.\(^11\) Patients were maintained in reverse isolation until there was no evidence of continued bleeding. At the time of treatment, patients were placed in a bed adjacent to the irradiator, and venous and arterial sides of the shunt were sterilely connected to the two ends of the silicone rubber irradiation coil (6–25 ft.).\(^12\) Most of our patients were thrombocytopenic, and regional heparinization during the ECIB procedure, although used in the first two patients, was found to be unnecessary.

Patients were initially treated for four hours every day. After a variable time period, usually of several weeks duration, the number of treatments were reduced to one to three every week. If pre-ECIB leukocyte counts were very high at the onset of therapy, the first few sessions were limited to two hours to avoid excessive uric acid production following the breakdown of cells. Allopurinal administration abrogated the necessity of short treatment times in the last patient (DON II) in this series.

Four hour ECIB treatments, in most patients, allowed for the passage of blood equivalent to four or five blood volumes past the irradiation source, ensuring a high percentage of irradiated leukocytes. The minimum and maximum numbers of irradiated leukocytes can be calculated from the following information: (1) flow rate of blood in the shunt of 100 ml/min, (2) 10,000 leukemic leukocytes/mm\(^3\) of blood, (3) blood volume of 5,000 ml, and (4) four hour ECIB session. The number of irradiated cells would be minimal if no circulating leukemic cells were replaced during the period of irradiation, i.e., \(5 \times 10^{10}\) cells. The number of irradiated cells would be maximal if all irradiated cells were immediately removed from the circulation and replaced by previously non-circulating cells, i.e., \(2.5 \times 10^{11}\) cells. The actual figure would lie between these limits.

The extracorporeal irradiators\(\uparrow\) used in this study were described in detail in a previous publication.\(^12\) Briefly, they consisted of 4,000 Ci \(^{137}\)Cs gamma-ray-emitting sources around which was bent one, and in a later modification, two, stainless steel tubes. The silicone

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\*Procedure devised by Dr. Lawrence Hankes, Medical Research Center, Brookhaven National Laboratory.

\(\uparrow\)Purchased from Quinton Instruments Co., Seattle, Washington, and Extracorporeal and Medical Specialties Co., Inc., Mt. Laurel, New Jersey.
rubber irradiation coil was threaded through this tubing just before beginning ECIB. The maximum total body radiation exposure was less than two mr/hr to the exposed patient; probably nearer to 0.5 mr/hr. Nurses and other personnel received no significant exposure as measured by film badges.

**Patient Material**

The 14 patients we studied ranged in age from 21 to 78, with an average age of 48.4 years and a median age of 47.0 years. The average age of seven men was 56.4 years and of seven women 40.3 years. There were 13 Caucasians and one Negro in the group. One individual had a known radiation exposure 18 years prior to diagnosis (CIE), but there was no known potential etiologic exposure for the remaining patients. The average time from onset of symptoms to diagnosis was 2.9 months and from diagnosis to admission to Brookhaven National Laboratory, Medical Research Center (BNL, MRC), 4.0 months. Patients were thus receiving therapy for their leukemia for an average of 4.0 months before being admitted. Three patients (SEI, TER, SKO) were untreated on admission, two had had prednisone (DOH, DON) only, and the rest had received two or more cytotoxic drugs.

Sixteen courses of ECIB were administered to the 14 patients. One male (SKO) and one female (DON) received two courses of ECIB. Hereafter the 16 patient-courses will be referred to as 16 individual treatments, except where survival statistics are concerned.

One of the 14 patients (TER—Fifth Case Summary), in retrospect, appears to have a more benign "myelocytic" (rather than "myeloblastic") form of leukemia. In view of the uncertainty surrounding his actual diagnosis, the survival data will be limited to the 13 other patients.

The patients presenting symptoms were typical of those found in others with AML, anemia, infection and hemorrhage predominating.\textsuperscript{13,14} Forty-four per cent had received antibiotics within a four-month period, and each had received an average of seven units of blood prior to admission. Their initial WBC's ranged from 3.000/mm\textsuperscript{3} to 242,000/mm\textsuperscript{3} with a median of 30,000/mm\textsuperscript{3}. The recognizably leukemic cells in the peripheral blood were all "blasts" in 56 per cent of the patients and either combined blasts and atypical immature cells\$ or all atypical immature cells in the others. In some patients with atypical cells, morphology was observed to alternate rapidly between atypical immature cells and blasts, often in the space of a few days. Auer rods were found in peripheral blood cells of 75 per cent, mitotic figures in 41 per cent and pseudo-pelger cells in 75 per cent of our patients.

Whenever possible, we performed bone marrow aspirations to confirm the referring diagnosis. When aspiration could not be done or was unsuccessful, Vim-Silverman needle biopsies were taken or predmission bone marrows reviewed.

At the start of ECIB, 81 per cent of our patients were thrombocytopenic (below 150,000/mm\textsuperscript{3}) and 50 per cent reticulocytopenic (below 25,000/mm\textsuperscript{3}). The median platelet count was 20,000/mm\textsuperscript{3}. Fifty-six per cent had abnormal liver function tests (mostly 3+ to 4+ cephalin flocculation) before ECIB, but none was icteric. Average total serum proteins and albumin were within normal limits, but the globulin fraction was slightly elevated. The increase in globulin was noted in $\beta$ and $\gamma$ fractions. Uric acid determinations were elevated in those patients with marked leukocytosis. Serum vitamin B\textsubscript{12} determinations were elevated, with a mean of 2747 pg/ml and a range of 213 to 12,535 pg/ml. Folic acid determinations were generally high normal with a mean of 13.7 ng/ml. Mean serum iron determination was 127 $\mu$g\% (although 5 patients were in the iron deficient range) and the mean total iron binding capacity was 262 $\mu$g\%. Serum haptoglobin levels were normal with the exception of one individual (KIN) who also had a positive indirect Coombs test. One other patient (ROB) had a positive indirect Coombs test, and the individual later had a hapto-
Fig. 1.—Comparison of survival data in adult acute myelocytic leukemia. Data was abstracted from references 5, 6, 7, and 23.

...globin determination in the low normal range. Mean serum fibrinogen, BUN, and serum Na and K were normal.

In summary, our group of patients did not appear to differ from other patients with AML. All were advised of the nature of their illness and were fully appraised of the experimental nature of the program and informed consent was obtained in every instance.

RESULTS

Survival

Survival from diagnosis to death is utilized to determine efficacy of treatment and to compare the results of one series to another. Survival calculations based upon onset of symptoms is unreliable and is not reported. All 13 patients have died. Their average survival time was 9.9 months with a median survival of 8.0 months (Fig. 1). The median survival from admission to death was 4.0 months.

Clinical Course

We did not obtain any complete remissions, except in patient DON I who received 6-MP subsequent to ECIB, nor did we obtain any partial remissions as strictly defined by the acute Leukemia Group B. All examinations of peripheral blood smears and bone marrow specimens, during and subsequent to ECIB treatment, revealed leukemic cells, except for patient DON I when she was in remission.
Immature leukocytes decreased in 12 of 16 patient-courses of ECIB, rose during one, and remained stable in three. "Normal" granulocytes decreased in 9 and did not change in seven patient-courses of treatment. In seven of the 16 patient-courses of treatment, there was a marked fall in immature cells followed by a low, stable period and a subsequent rise in the number of immature cells while ECIB continued. There was an increase in uric acid excretion in eight of 15 patient-courses (DON II received allopurinol) of ECIB. The maximum uric acid excretion in a 24-hour period was slightly over 6 grams.

Four patients (who had received only ECIB at this point) had a rise in total reticulocyte count, six had a fall, and six had no change. Of the four patients whose reticulocyte counts increased, three subsequently had a decline.

At the start of treatment, all but three patients were thrombocytopenic. Subsequent to treatment the platelet counts of one of those three fell, and the other two remained normal. Two thrombocytopenic patients had a slight rise, and one a marked rise, in the number of platelets.

In general, after a variable period of well-being, these patients all manifested clinical and laboratory evidence of exacerbation of disease. Fifty-six per cent had hepatomegaly and 69 per cent splenomegaly. Nine patients became icteric, of whom three were believed to have serum hepatitis. Two patients developed subcutaneous tumors, and three had leukemic skin infiltrations. One patient had a splenic infarct, and four had clinically diagnosed pulmonary embolic episodes. There was no significant change in serum protein or globulin concentration. Wherever possible, ECIB was used alone, but nine patients subsequently received chemotherapy. Four received 6-MP, 2 vinblastine, and 3 received 2 or more cytotoxic drugs. With the exception of DON I, none of these regimens produced a remission.

Bone marrow scans with 99mTc-S-colloid were performed during 12 of the 16 patient-courses. Good visualization (normal uptake) was found in 67 per cent and poor visualization (decreased uptake) in 33 per cent. In five patients (42 per cent) there appeared to be increased activity and/or extension of the reticuloendothelial bone marrow compartment in the knees, ribs, shoulders and/or humeri.

Multiple spleen scans with 99mTc-S-colloid were also performed in 12 patients. Spleen size was measured by planimetry of the photoscan. The spleen was noted to increase in seven, and decrease in size in three patients during treatment. In two of the latter cases, there was an initial increase followed by reduction to less than the original size.

**Arteriovenous Shunts**

In order to attain maximum flow rates and thus diminish clotting difficulties, the largest possible Teflon cannulae were placed in the artery and vein. Wounds were allowed to heal, whenever possible, for several days before starting ECIB, the average time being 5.2 days with a range of 0 to 29 days. Shunt complications were not uncommon. Infections at the shunt site occurred in five cases and in all but one (BUR) were controlled with antibiotics. Five
Table 1.—Average Transit Dose and Total Hours of ECIB

<table>
<thead>
<tr>
<th>Patient</th>
<th>Total Hours of ECIB</th>
<th>Average ECIB Transit Dose (Rads)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUR</td>
<td>57</td>
<td>277</td>
</tr>
<tr>
<td>DOH</td>
<td>72</td>
<td>279</td>
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<tr>
<td>KIN</td>
<td>72</td>
<td>434</td>
</tr>
<tr>
<td>DON II</td>
<td>80</td>
<td>535</td>
</tr>
<tr>
<td>WIL</td>
<td>176</td>
<td>256</td>
</tr>
<tr>
<td>SKO I</td>
<td>196</td>
<td>285</td>
</tr>
<tr>
<td>MAD</td>
<td>196</td>
<td>236</td>
</tr>
<tr>
<td>HIN</td>
<td>232</td>
<td>389</td>
</tr>
<tr>
<td>SKO II</td>
<td>260</td>
<td>292</td>
</tr>
<tr>
<td>DAN</td>
<td>336</td>
<td>490</td>
</tr>
<tr>
<td>DON I</td>
<td>360</td>
<td>377</td>
</tr>
<tr>
<td>ROM</td>
<td>392</td>
<td>317</td>
</tr>
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<td>SEI</td>
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</tr>
<tr>
<td>CIE</td>
<td>443</td>
<td>442</td>
</tr>
<tr>
<td>TER</td>
<td>760</td>
<td>342</td>
</tr>
<tr>
<td>ROB</td>
<td>880</td>
<td>352</td>
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</table>

individuals required fresh whole blood transfusions to control postoperative bleeding. In no instance was bleeding severe enough to warrant removal of the shunt. One patient developed a mild thrombophlebitis which was successfully treated with local heat and rest. One complete revision and two venous revisions of the A-V shunts were necessary in this group of patients.

Our reasons for stopping ECIB were multiple. A deteriorating clinical condition was the major factor in four patients whose shunts were still patent. Five patients died while still on treatment. Six shunts clotted, and it was decided, for clinical reasons, not to renew ECIB. One patient had persistent bleeding and severe local infection, and another (BUR) had severe cellulitis. The arterial cannula of one patient's shunt spontaneously came out, fortunately while the patient was hospitalized, and bleeding was easily controlled. Two patients developed subcutaneous tumors at the operative sites in addition to other regions of the body. The average life of the A-V shunt was four months, including those in which treatment was halted by death. A complete review of the technical aspects of A-V shunts in patients with leukemia will be published.17

ECIB

The total hours of ECIB varied directly with survival from diagnosis to death after the start of ECIB. The transit dose is defined as the amount of radiation received by a segment of blood flowing through the irradiation coil, and in these irradiators, it is inversely related to the flow rate of blood through the shunt. The average transit dose varied from 236 rads to 535 rads (Table 1).

Pathological Findings

An autopsy was not performed on the one patient who died outside the hospital, and one autopsy permission was denied. Organ infiltration in the
Fig. 2.—Illustrative case summary 1, Patient DON.
remaining 11 was found to be consistent with previously reported findings in adult AML, and will not be documented further. One patient (SEI), aside from AML, also had a neurolemmoma of the adrenal gland, follicular carcinoma of the thyroid gland, and an adenocarcinoma of the kidney. Splenic infarcts were found in two patients and a pulmonary infarct in one. Two patients had pseudomembranous colitis, and one had a mycotic abscess. The causes of death of the 13 ECIB-treated patients were determined on combined clinical and pathological bases, and multiple causes account for the total number greater than 13. Cerebral hemorrhage caused the death of 3 patients; gastrointestinal bleeding—1; disseminated infection and septicemia—6; bronchopneumonia—6; pseudomembranous colitis with bleeding—2; and massive sarcomatous invasion of soft tissues—2.

Illustrative Case Summaries

1. Patient DON (Figure 2). This 21 year old Caucasian female was found to have AML when 4 months pregnant. For a short time she received small doses of prednisone but declined cytotoxic drugs because of fear of fetal injury. Treatment with ECIB had been employed for 25 days when she delivered a
premature but otherwise normal, viable infant, ECIB was continued to the 97th day, but because of deteriorating clinical condition she was, additionally, started on 6-MP. A complete clinical and hematologic remission was achieved for a period of 4 months. Combined treatment with 4 drugs and ECIB was started on the 404th day after the beginning of the initial course of ECIB and continued until death on the 459th day. Survival from diagnosis was 16.5 months. She received a total dose of 440 hours of ECIB with an average transit dose of 377 rads for the first course and 535 rads for the second course of ECIB.

Remarks. It was possible to carry this patient through part of her pregnancy without the use of cytotoxic drugs. Subsequently 6-MP induced a remission of four months duration. We now consider pregnancy to be one indication for the use of ECIB alone, if the patient is aware of the consequences of withholding a possible remission-causing drug.

2. Patient CIE (Figure 3). This 42 year old Caucasian male was diagnosed as having AML nine months before admission. Eighteen years previously he had been exposed to radiation in a criticality accident. A review of the exposure, and his early clinical and laboratory status was presented by Hempleman et al.19 as Case No. 8, and a complete summary of the leukemia was recently published by Greenberg et al.20 During the 9 months preceding admission to BNL, he was treated with 6-MP, methotrexate, vincristine and prednisone. He exhibited toxicity and was resistant to all drugs when admitted. His WBC had risen exponentially from 40,000/mm³ to 235,000/mm³ in six days. Treatment with ECIB resulted in a marked decrease of the leukocyte count and a rise in platelets and total reticulocytes. Initial treatment with ECIB did not affect a meningeal infiltration, signs of which developed just prior to starting ECIB and which was treated with intrathecal methotrexate and intravenous citrovorum factor 10 days later.

After two-and-one-half months, his clinical condition deteriorated again, and he was experimentally treated with large doses of tritiated thymidine.20 After a brief response, including a decrease in subcutaneous tumor masses, he expired three and a half months after admission. Survival was 12.0 months after diagnosis. He received 443 hours of ECIB with an average transit dose of 442 rads.

Remarks. This patient exhibited toxicity or resistance to standard chemotherapeutic measures. We feel that these are indications for the use of ECIB in AML. In addition, the marked drop in peripheral leukocytes probably indicated a successful attempt to avoid leukostasis in small blood vessels.

3. Patient ROB. This 55 year old Caucasian male was diagnosed as having AML about one month prior to admission. He was treated with prednisone, five days of 6-MP and two injections of methotrexate. ECIB was started eight days after the last doses of 6-MP and methotrexate and within four days he commenced a period of profound pancytopenia. After recovery from the latter, daily and then intermittent ECIB was continued for 500 days. His course was complicated by serum hepatitis and hemosiderosis, and he expired 570 days after the start of ECIB. Survival from diagnosis was 18.0 months. He re-
ceived 880 hours of ECIB with an average transit dose of 352 rads.

Remarks. It is unclear whether the small amount of chemotherapy, alone or in combination with ECIB, produced the pancytopenia. His long survival in the absence of hematologic remission suggests benefit from treatment with ECIB.

4. Patient SKO. This 57 year old Caucasian male with untreated AML was started on ECIB about 20 days after diagnosis. The first course of treatment resulted in a three month period of well-being, but not a hematologic remission. ECIB was resumed 150 days later because of clinical deterioration and a rising leukocyte count. There was a marked fall of immature leukocytes in the peripheral blood, followed by a moderate rise and subsequent steady state. A short course of vinblastine, administered when the patient was in a preterminal state, was unsuccessful. Survival from diagnosis was 11 months. He received a total of 456 hours of ECIB. The average transit dose was 285 rads for the first and 292 rads for the second course of treatments.

Remarks. This patient had only ECIB treatment until he was preterminal. The subsequent slow rise in peripheral leukemic cells in the months following the first treatment may indicate a leuko-suppressive action induced by the first course of ECIB. In addition, the response to the second course of treatment is against the development of radioresistance in the leukemic myeloid cells as a result of previous ECIB.

5. Patient TER. This 69 year old Caucasian male was admitted shortly after a diagnosis of AML was made. There is an uncertainty regarding his diagnosis, as mentioned previously and he is not included in the survival statistics. After initial daily treatment with ECIB, he was treated twice weekly for one year. At that time, his A-V shunt clotted and all treatment was discontinued. He is alive at the time of writing 24 months post diagnosis, and six months post treatment. It is of interest that his leukocytes rose from about 10,000/mm³, when ECIB stopped, to 25,000–50,000/mm³ after 2.5 months. He received a total of 760 hours of ECIB with an average transit dose of 342 rads.

Remarks. This patient had a remarkably stable course for 15 months while on treatment with ECIB. After cessation of treatment, his peripheral leukocytes rose by a factor of five. This probably indicates a suppressive action by ECIB upon the peripheral blood count. In view of the theoretical value of ECIB in diseases involving the immune mechanisms, it is of interest to note that this patient’s rheumatoid arthritis did not change during the intensive treatment with ECIB.

Discussion

The median survival time of 8.0 months in the absence of any strictly defined remission, besides suggesting benefits of ECIB, may be the result of at least two other factors: selection of patients and good supportive therapy.

Although we accepted for admission all adult patients referred to us with acute leukemia, five were not used in the ECIB study. Among these five was one individual who died the day of admission and several who died within two
weeks of admission. If one included these cases, our average survival time would decrease from 9.9 to 8.9 months, and the median survival time would decrease from 8.0 to 7.5 months. The latter is as good as, if not better than, other published survival data (Fig. 1). The fact that our patients were treated elsewhere for an average of four months before admission is also a selection factor, inasmuch as these patients lived to survive the immediate post-diagnosis period. It does, however, make this series more comparable with several recent ones in which patients were included only if they survived the initial course of treatment, had hematologic improvement, or lived at least two months post-diagnosis7,22-24 (Fig. 4). Since no patient had a hematologic remission (except DON I), it is pertinent to note that our survivals are comparable to those in which hematologic remissions were observed.

The small number of patients reported here should not be treated with more statistical sophistication, and it would be misleading to attempt to do so. In addition, it should be noted that only one patient (TER) out of the 14 received no other treatment besides ECIB. He is the patient still alive at the time of writing and morphologically seems to have a disease which is "myelocytic" rather than "myeloblastic." All other patients received chemotherapy before, after, or in conjunction with ECIB. Thus, no "pure" series can be assumed when comparing our results with others, nor can we use our own previous patients for comparison purposes. Seven patients with adult AML
were treated at BNL, MRC, from 1949 to 1964. Their average survival time from diagnosis to death was 2.9 months with a median of 1.5 months. These patients, however, did not receive as extensive chemotherapy as is now generally given.

By “good supportive therapy,” we mean immediate blood replacement and antibiotics when needed. Patients were isolated as required to minimize introduction of pathogens. No sterile environments were utilized, however, but the staff masked, gowned, and donned shoe covers.

Patients received blood (whole, fresh, or packed RBC) as needed. They received a total of 606 units of blood or an average of 7.5 units per month. Part of this transfusion requirement was iatrogenic in origin, since ECIB, in the amounts given, has been shown to shorten the red cell life span and cause anemia. The exact blood transfusion requirements directly attributable to ECIB, however, are impossible to measure in patients that have reduced blood production or hemolysis from other causes.

Their antibiotic requirements were considerable; the 14 patients received 90 courses of antibiotic and antifungal agents for an average of 5.6 courses per patient. Twenty-two different antibiotics were utilized depending upon clinical judgment and sensitivity data.

An attempt has been made to correlate various clinical and laboratory findings with survival. No correlation has been found between survival time and the following features: (1) type and amount of chemotherapy before ECIB, (2) cells with or without Auer rods, (3) mitotic figures in peripheral blood, (4) cells with or without the pseudo-pelger anomaly, (5) type and amount of adjuvant or subsequent chemotherapy after ECIB, (6) peripheral extension of bone marrow on scanning, (7) WBC, platelet or reticulocyte counts before ECIB.

Two features, however, have positive correlations with survival time. Four patients with poor bone marrow uptake of $^{99m}$Tc-S-colloid and poor marrow scans survived 7.3 months, whereas eight patients with good visualization and presumably good bone marrow reticuloendothelial function, survived 11.6 months. The $P$ value for this difference lies between 0.05 and 0.10. Because of the limited number of cases, only further studies can reveal if scanning has any prognostic value or if good reticuloendothelial function is a positive factor in survival.

It was of great interest to us to find that there is some connection between survival time and transit dose of ECIB (Fig. 5). No individual receiving a transit dose of less than 320 rads survived more than 11.6 months after diagnosis. Four of the seven patients receiving a transit dose more than 340 rads survived more than 16.0 months, and five survived longer than any patient receiving a dose less than 320 rads. The difference between these two groups ($0.0025 < P > 0.005$) is highly significant. A presumptive reason for this difference in survival probably relates to the radiation sensitivity of AML cells and their residence time in the blood. Since little is known about either, only supposition is possible. It may be that substances released from ECIB-killed cells (as opposed to ECIB-damaged cells) inhibit leukemic cell growth. Thus, a
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Fig. 5.—Survival time of our patients with acute myelocytic leukemia in relation to their transit dose of ECIB. The dashed line represents the arbitrary figure of 340 rads.

high transit dose of ECIB might act to induce a feedback control upon leukemic cell proliferation. Alternatively, some patients may have cells which are only injured by less than 340 rads. Longer patient survival and increased radiosensitivity of cells may also exist coincidentally in the same patient for some other reason. Regardless of the underlying reason it would seem desirable to treat future AML patients with high transit doses (over 350 rads). For that reason, in treatment of AML, high intensity gamma ray irradiators seem preferable to presently available β particle irradiators.25-28

Complications arising from the mechanical process of placing A-V shunts in patients should be considered in this analysis. Hemorrhage has not been an insurmountable problem, nor local infection. We do not feel that systemic infection has been fostered by A-V shunts; pre- and postmortem cultures of the shunts have been consistently negative. The shunt is an easily accessible mode of entry for bacteria, and meticulous care, therefore, is a necessity which does not need emphasis.

The majority of patients occasionally develop fibrin strands or even frank clots within the visible portion of the shunt. It is usually easy to remove the clots, but when declotting the venous side, one must be aware of the possibility of dislodging a portion or the whole clot directly into the circulation. The four individuals with clinically diagnosed pulmonary emboli did not have more frequent clotting in shunts than the others, nor was there any direct relationship with a declotting procedure. This potential complication remains, although only one was confirmed at autopsy. The incidence of pulmonary infarction in AML is not well-documented. Green and Nichols29 reported on this complication in two out of 34 patients with AML, and Nathan and Sanders30 in none out of 59 cases of acute leukemia. It should also be noted, however, that it is rare to read of pulmonary infarction complicating renal
hemodialysis and, in fact, was not even mentioned in a recent review of dialysis hazards.\textsuperscript{31}

The extent of organ infiltration and causes of death in this series did not differ significantly from those found in other reports. In two patients with definite subcutaneous tissue masses, similar tumors could also be found at the site of the A-V shunts. This may merely represent metastatic growth of cells in an area where culture conditions are ideal, i.e., serum and blood exudation after surgery.

Another problem which faces the physician treating patients with leukemia is how to keep them most comfortable. Although our patients did undergo minor surgery, the inconvenience of prolonged hospitalization, and the initial problem of learning to care for the shunt, most of them felt that the discomfort and inconvenience involved were minor. The majority of patients spent weekends or longer times at home. Several attempted to return to work, although they had only limited success. It is our opinion that the “quality” of their remaining life was not altered to any significant degree.

Finally, it is worth reemphasizing that, although we have been unable to demonstrate any remissions (except DON I), our survival rate was as good as has been obtained in patients treated with intensive chemotherapy. At this time we feel that ECIB is useful for two classes of patients: (1) patients in whom chemotherapy may be contraindicated, e.g., pregnant patients or those with toxicity from and/or resistance to previous chemotherapy and (2) patients in danger of leukostasis in whom a rapid decrease in the WBC is desirable.

**Summary**

Fourteen adults with acute myelocytic leukemia (AML) received 16 courses of extracorporeal irradiation of the blood (ECIB). The median survival time of 8.0 months, taking into consideration many of the variable factors, was as good as, if not better than, studies previously reported despite the absence of hematologic remissions. This group of patients is small, however, and no definitive evaluation of ECIB treatment for AML can be made. Although no significant bone marrow changes were noted, there was a marked decrease in the peripheral leukemic cells of 75 per cent of the patients. There appears to be a correlation of increased survival time with a transit dose of ECIB over 340 rads. At the present time, the usefulness of this mode of treatment in the overall management of AML is uncertain, although it might be considered as an alternative form of therapy for patients in whom chemotherapy is contra-indicated and to prevent leukostasis. When used, the possibility of complications related to the shunt should always be borne in mind.

**SUMMARIO IN INTERLINGUA**

Dece-quatro adultos con acute leucemia myelocytic (ALM) recipeva 16 cursos de extracoporee irradiation del sanguine (ECIS). Le superviventia median de 8,0 menses—considerante numerose factores variabile—eseva equal o superior a illos de previemente re-portate studios, sed remission hematologic non occurreva in ulle del casos. Tamen, le gruppo del patientes eseva micre, e le resultatos non permitte un evalutation definitive de ECIS in le tractamento de ALM. Ben que nulle significative alterationes del medulla ossee eseva
EXTRACORPOREAL IRRADIATION OF BLOOD IN MAN

notate, 75 pro cento del patientes manifestava un marcate declino in le numeration peripheric de cellulas leucemic. Il pare existier un correlation inter le augmento del tempore de supervivientia e le dosage de transito de ECIS in supra del nivello de 340 rad. A iste tempore le utilitate del forma de tractamento in question in le therapeutica general de ALM es incerte, sed illo pote esser reguardate como un alternativa in le caso de patientes in qui modalitates chimotherapeutic es contra-indicate o in qui le objectivo es le prevention de leucostasis. Quando le methodo es usate, le possibilitate de complicationes relationate al shuntage debe esser rememorate.

ACKNOWLEDGMENTS

We are indebted to Miss Margaret Bell and the large group of nurses without whom this study would have been impossible. We also wish to thank Mr. Gerd Borner who performed all the leucocyte differential counts, and Dr. Victor Herbert, Mt. Sinai Hospital, New York, for performing vitamin B12 and folic acid determinations.

ADDENDUM

Patient TER (case summary No. 5) expired 27 months after diagnosis. Death was attributed to Staphylococcal septicemia following superinfection of large, confluent Herpetic Zoster lesions.

REFERENCES

15. Acute Leukemia B Group Protocol No.


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