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Research Article

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Serial Studies of Immunocompetence of Patients Undergoing Chemotherapy for Acute Leukemia

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ABSTRACT Immunocompetence was followed serially for 1 yr from the onset of treatment in 55 adult patients with acute leukemia. The tests used were delayed hypersensitivity responses to a battery of five recall antigens (dermatophytin, dermatophytin 0, candida, streptokinase-streptodornase, and mumps) and in vitro lymphocyte blastogenic responses to phytohemagglutinin and streptolysin 0. There was a strong correlation between immunocompetence at the start of treatment and a good prognosis; 32/39 patients who subsequently entered remission were initially immunocompetent compared to 4/15 who failed to enter remission. In the complete remission group there was a decline in competence starting from 2 to 5 mo after the onset of treatment. In those who remained in remission for 1 yr, competence recovered at 6 mo and remained vigorous thereafter. In those who relapsed before 1 yr, the decline in competence occurred 1 mo before relapse and competence continued to decline progressively during the 1 yr follow-up period. These studies suggest that therapeutic approaches which restore immunocompetence or prevent its decline will improve both the remission rate and the remission duration of patients with acute leukemia.

INTRODUCTION

Immunological surveillance has been established as an important mechanism in the etiology and pathogenesis of experimental cancer and is probably also implicated in the natural defense against cancer in man (1). During the last several years, a number of investigators have established that the immunocompetence of the cancer patient is directly related to a better prognosis. This has been demonstrated in Hodgkin's disease (2), carcinoma of the lung (3), squamous cell carcinoma (4), and malignant melanoma and other solid tumors (5), to name a few.

We have previously demonstrated this phenomenon in patients with solid tumors using both in vivo delayed hypersensitivity responses to recall antigens, and in vitro lymphocyte blastogenic responses to mitogens and antigens (6). In a study in 25 patients with acute leukemia (7), we demonstrated that vigorous reactivity to recall antigens, the development of vigorous reactivity to a primary antigen, and in vitro lymphocyte blastogenic responses to mitogens and antigens, could be used to identify at the outset of treatment, those patients who subsequently had a good prognosis as a result of chemotherapy.

In the current study we have extended these observations to a group of 55 patients with acute leukemia. Patients were studied initially and then followed serially for approximately 1 yr. In addition to confirming the previously demonstrated correlation between vigorous immunocompetence and good prognosis, we have demonstrated that a decline in immunocompetence precedes frank relapse of this disease. The data generated in this study provide a rational basis for nonspecific immunotherapy of acute leukemia. It suggests that the addition of immunotherapy early in the chemical treatment of patients with acute leukemia could be highly effective in improving the response rate. Its continuation during remission could prolong remission duration.

METHODS

The skin test antigens used included dermatophytin (1:20, Hollister-Stier Labs., Spokane, Wash.), dermatophytin O (1:20, Hollister-Stier Labs.), candida (1:20, Hollister-Stier Labs.), streptokinase-streptodornase (1:40, Lederle Laboratories, Pearl River, N. Y.), and mumps (1:20, Eli Lilly and Company, Indianapolis, Ind.). All antigens were applied by intradermal inoculation in a volume of 0.1 ml through a 27-gauge needle. The skin test sites were evalu-

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TABLE I

Delayed Hypersensitivity Responses to a Battery of Five Recall Antigens in Acute Leukemia. Analysis of Initial Test Results

Parameter	Complete remission	Partial remission	Failure
Number	33	6	15
Median, *mm**	8‡	4.5§	0
Range	0–13	0–12	0–12
Zero no., %	7, 21	2, 33	11, 73
Mean	6.2	5.0	3.3
SE	0.8	1.9	1.7

* The median refers to the median of the median skin test reaction (to the five test antigens) for each patient. Thus, it is the median of 33 medians.

‡ Complete remission and failure significantly different by chi-square test, $P < 0.005$.

§ Partial remission not significantly different than complete remission or failure, $P > 0.10$.

ated for induration at 24 and 48 h, and the value recorded was the average of the induration measured at two right angles, recorded in millimeters. No lower limit was applied to defining a skin test reaction as positive. If there was measurable induration as small as 2 mm, this was called a positive test. Smaller reaction sites could not be measured accurately and were interpreted as negative.

Patients were defined as being immunocompetent if two or more skin tests were positive and were defined as immunoincompetent if zero or one of the battery of five skin tests was positive.

The study group consisted of 55 adult patients with acute leukemia admitted to the acute leukemia service of the Department of Developmental Therapeutics of The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute from 26 May 1971 until 21 February 1972. They were followed for 1 yr, unless they expired before that time.

There were 34 patients with acute myelogenous leukemia (AML),[1] 16 with acute lymphocytic leukemia (ALL), and 1 with acute undifferentiated leukemia (AUL). There were 30 patients who had not received extensive prior chemotherapy, and there were 25 patients who had received extensive prior chemotherapy. Chemotherapy during this study consisted of a variety of regimens, but most patients received either a four drug combination of cyclophosphamide, vincristine, cytosine arabinoside, and prednisone or a three drug combination of vincristine, cytosine arabinoside, and prednisone. These were given in 5-day courses repeated every 2–3 wk.

Initial skin tests were applied 48 h before the second course of chemotherapy in all patients. The second set was applied 48 h before the third course and subsequent tests were applied at approximately monthly or bimonthly intervals thereafter, but always approximately 48 h before the next course. Thus, an attempt was made to apply the skin tests at a time as long as possible from the preceding course.

[1] *Abbreviations used in this paper:* ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia; AUL, acute undifferentiated leukemia; PHA, phytohemagglutinin-M; SI, stimulation index; SLO, streptolysin O.

The response to therapy was determined as complete remission, partial remission, or treatment failure according to standard criteria (8). An attempt was made to correlate the immunocompetence of the patients with the course of their disease and with their prognosis in terms of their response to the regimen of therapy initiated at the start of the study.

Lymphocyte cultures were set up as previously described (7) simultaneously with skin testing. Peripheral venous blood was drawn and defibrinated by swirling with glass beads. The erythrocytes were sedimented with dextran. Lymphocyte cultures consisted of 1 ml of autologous serum, 2 ml of minimal essential medium, and 10^6 peripheral blood lymphocytes. Cultures were either unstimulated or stimulated with 0.05 ml phytohemagglutinin-M (PHA) and streptolysin O (SLO). Cultures were harvested after 5 days. 3 h before harvesting 2 μCi of [^{3}H]thymidine (sp act 1.9 Ci/mM) was added and the blastogenic response of the stimulated and unstimulated lymphocytes was measured by [^{3}H]thymidine incorporation. Results were reported as either net counts per minute (cpm) or the stimulation index (SI). The net cpm was the cpm in the stimulated culture minus the cpm in the control, and the SI was the cpm in the stimulated culture divided by the cpm in the control.

Data were analyzed mainly by the chi-square test using the 2×2 contingency table. The calculation was done using a program written for the Wang series 600 computer (Wang Laboratories, Tewksbury, Mass.), which yielded approximate P values as follows: P: $0.05 = 0.05 > < 0.025$, P: $0.025 = 0.025 > < 0.01$, P: $0.01 = 0.01 > < 0.005$, P: $0.005 = 0.005 > < 0.001$. Selected data were also analyzed by the Wilcoxon-signed rank test. Median values are used frequently in the tabulation of the data. Unless otherwise indicated these are medians of the median value of the five skin tests for each patient. Thus, for example, the value for the 33 complete remission patients reported in Table I is a median of 33 medians of five skin tests. Similarly, means for each group were the means of the mean of the five values.

RESULTS

The results of the first battery of delayed hypersensitivity skin tests with recall antigens, done between the first and second courses of chemotherapy for remission induction, are shown in Table I. Patients who subsequently entered complete remission showed vigorous delayed hypersensitivity and only 21% had a median skin test diameter (of the five skin tests) of zero. In contrast, patients who subsequently failed to enter remission had very poor reactivity and 73% had a median skin test diameter of zero. This difference was highly significant. Because of the small number of patients in the partial remission group, they did not differ significantly from the other two groups. Of interest, of the 7 patients in the complete remission group who had a median skin test diameter of zero, only 1 remained in remission at 1 yr; whereas of the 26 who had a median diameter greater than zero, 11 remained in remission at 1 yr. The median and mean values did not differ significantly.

This difference was also clearly demonstrable when the number of positive skin tests per patient was examined (Table II). 28 out of 33 patients who subsequently

TABLE II

Number of Patients with Indicated Number of Positive Hypersensitivity Reactions

Remission status	Number of positive skin tests					
	0	1	2	3	4	5
Complete	4	1	2	9	4	13
Partial	1	1	0	0	4	0
Failure	8	3	0	0	3	1

Complete remission and failure were significantly different by the chi-square test $P < 0.005$.

TABLE III

Competence of Delayed Hypersensitivity with Time on Serial Study

Test period*	Hematological remission status		
	Complete	Partial	Failure
First	28/5‡	4/2	4/11§
Second	30/3	6/0	4/11
Third	18/15	2/4	1/5‖

* Test periods. First: between chemotherapy course 1 and 2; second: within 1 mo of first; third: last test done; this was at 12 mo in the complete remission and partial remission patients and at a median of 4 mo (range 3–6 mo) in the failure patients. In all instances the skin tests were done 48 hr before the next course of therapy and 2–4 wk after the preceding course of therapy.

‡ Competent/Incompetent; competence defined as two or more positive skin tests.

§ Significance data: first period: complete remission more competent than failure $P = 0.005$; second period: complete and partial remission more competent than failure: $P < 0.005$ and 0.025, respectively; third: no significant differences. Chi-square tests.

‖ Other nine in failure group did not receive third test.

entered complete remission had two or more positive skin tests out of the battery of five, whereas only 4 of the 15 failure patients had two or more positive skin tests. This difference was highly significant.

The most important feature of this study was the immunological follow-up of the patients. An overview of this follow-up is given in Table III. Immunocompetence was measured during three arbitrarily selected skin test periods. The initial period has already been discussed and was between the first and second courses of chemotherapy. The second skin test period was during the 1st mo after the start of therapy between the second and third course, and the third skin test period was taken as the last set of tests done in each patient. Immunocompetence was defined as two or more positive skin tests. As already noted, the majority of complete remission patients were competent whereas the majority of failure patients were incompetent. From the opposite point of view only 7 of 18 incompetent patients entered remission but only 4 of 36 competent patients failed to enter remission.

In the complete and partial remission groups immunocompetence improved slightly during the second skin test period. In the failure group it remained poor. In contrast, during the third skin test period, immunocompetence declined dramatically and significantly in the complete and partial remission groups.

This decline in immunocompetence in the complete remission patients is analyzed in detail in Table IV. By 2–3 mo after the start of chemotherapy, there was a dramatic increase in the percent of subjects whose median skin test diameter was zero. This increase in immunoincompetence from 21 to 64% was highly significant.

The same phenomena were observed in the partial remission group. There was an initial improvement in skin test reactivity during the first mo of the study (from 33% with a median skin test diameter of zero to none) and subsequently there was a steady increase in the percent of subjects who were immunoincompetent (86% with a median skin test diameter of zero at 1 yr). By 6–7 mo after the start of chemotherapy, one-half of the patients had a median skin test diameter of zero. In the patients who failed to enter remission, there was also an initial improvement in skin test reactivity. During the 1st month, immunoincompetence (median skin test diameter of zero) declined from 73 to 39%. However, at 2–3 mo and subsequently more than one-half of the failure patients had negative skin test.

This improvement in skin test reactivity deserves further comment. Improvement was recorded when the median skin test diameter converted from negative to positive or increased more than 100%. Between the first and second skin test periods, 15 patients (in all three groups) showed improvement although only 6 showed

TABLE IV

Delayed Hypersensitivity Responses to a Battery of Five Recall Antigens in Acute Leukemia. Serial Studies during Therapy in Patients in Complete Remission

Parameter	Months of study						
	0	1	2–3	4–5	6–7	8–9	10–12
Number studied	33	32	30	33	20	26	45
Median, *mm*	8*	7	0	0	0	0	0
Zero, %	21	25	53	64	55	65	64

* Significance data: month 0 significantly greater than all time periods except month 1; month 1 significantly greater than 2–3, 4–5, 8–9, and 10–12. No other significant differences by chi-square test.

TABLE V

Relationship between Immunocompetence as Measured by Median Delayed Hypersensitivity Responses to a Battery of Five Antigens and Duration of Complete Remission in Acute Leukemia

Duration of remission in months	No. of cases	Parameter	Time of skin test evaluation*				
			Initial test	1st mo of therapy	Month before relapse	Month of relapse	Last test
> 12 (Group 1)	12	Median, *mm*	8.0‡	7.5	—	—	9.0
		% Zero	8.3	25			25
< 12 (Group 2)	21	Median, *mm*	8.0	6.5	0	0	0
		% Zero	28.5	25	66.6	52.3	80.9

* Initial test done between courses 1 and 2 of chemotherapy; last test done at 1 yr after start of therapy.

‡ Significance data: last test group 1 greater than group 2, $P < 0.01$; group 2: initial and 1st mo greater than month before and month of relapse, $P < 0.05$; group 2: initial and 1st mo greater than last, $P < 0.005$; no other significant differences by chi-square test.

a decline. This suggests that a reduction in the tumor burden, commonly greatest between the first and second courses of therapy, was associated with improved reactivity and that the tumor load may produce immunosuppressive factors.

The nature of the decline in immunological reactivity in the complete remission group is defined in Table V. There were 12 patients in the complete remission group who remained in remission for 1 yr or longer. There were 21 who relapsed before the end of 1 yr. These groups showed no difference in immunological reactivity in the 1st mo after the start of treatment. However, on the last test, those still in remission showed a median skin test diameter of 9 mm and only 25% had a median skin test diameter of zero. In contrast, on the last test, the median skin test diameter in those who lost their remission was zero, and 80.9% of the patients fell into this category. The overlap between the groups is worthy of note however in that 25% or more of the patients with prolonged remission did indeed show, immunological deficiency.

Of greatest interest was the observation that 1 mo before relapse this group had a median skin test diameter of zero and this comprised 66.6% of the patients. Thus, it appears that the decline in immunological reactivity in the complete remission group is due entirely to those patients who lose their complete remission and the decline in immunological reactivity occurs before the relapse can be detected by the usual clinical methods. However, even in the complete remission group who stayed in remission more than a year, some diminution in immunological reactivity was observed (Table VI). During the 2nd through the 5th mo of the study, the percent of subjects in this group with a median negative skin test rose from 8.3 to 58%, and this was a significant change. Subsequent to the 5th mo, there was an improvement in reactivity so that the median skin test diameter again became and remained positive. This transient decline

TABLE VI

Delayed Hypersensitivity Responses to a Battery of Five Recall Antigens in Acute Leukemia. Serial Study in Patients Remaining in Complete Remission for 1 Year or Longer

Parameter	Month of study						
	0	1	2–3	4–5	6–7	8–9	10–12
Number studied	12	12	11	12	9	11	17
Median, *mm*	8.	7.5	0	0	7	8	7
% Zero	8.3	25	55	58	44	36	47
*P** compared to 0	—	> 0.10	0.05	0.05	> 0.10	> 0.10	> 0.10

*Significance determined by chi-square test.

TABLE VII

In Vitro Lymphocyte Responses to PHA and SLO in Patients with Acute Leukemia, First Study

Parameter	Complete remission	Partial remission	Failure
PHA			
Median cpm*	49	75	53
Mean cpm	57	63	61
SE	6.8	19.8	10.1
PHA			
Median SI‡	79	88	53§
Mean SI	138	119	126.1
SE	30.2	49.4	49.1
SLO			
Median cpm	12	3	2
Mean cpm	17	16	12
SE	3.7	11.7	4.7
SLO			
Median SI	8	6	2§
Mean SI	63	44	17
SE	25.2	37.3	10.3

* CPM = counts per minute per 10^6 lymphocytes $\times 10^{-3}$.
‡ SI = stimulation index, cpm stimulated culture/cpm unstimulated culture.
§ Significantly lower than complete remission $P = 0.05$.

might be attributed to the very intensive chemotherapy these patients received during the remission induction and consolidation phases of treatment, which last for approximately 4–5 mo.

The initial lymphocyte culture results are shown in Table VII. The responses of the failure group to both PHA and SLO were significantly suppressed in terms of the SI. Table VIII shows the serial studies of the PHA response. There was no major decline in reactivity with time except in the failure group. Table VIII also shows the serial study of the response to SLO. In the complete remission group there was an initial decline in the response on the second test with subsequent recovery. There was no terminal decline as seen with the skin tests except in the failure group.

The two subgroups within the complete remission group were also compared. Significant findings were made only during the last evaluation period. In those patients whose remission lasted less than 12 mo, both the PHA and SLO responses were lower than those whose remission lasted greater than 12 mo. The SLO responses in these two groups were significantly different (30,500 vs. 9,800 cpm and 49.5 vs. 15 SI).

These data were also analyzed for the possible effects of factors known to influence the prognosis of patients with acute leukemia. These include the age of the patients, the type of leukemia, and the history of prior therapy. The findings in this study could not be explained on the basis of any of these factors (Tables IX and X).

TABLE VIII

Median In Vitro Lymphocyte Responses to PHA and SLO in Patients with Acute Leukemia, Serial Studies

Parameter	Remission status	Study periods: First	Second within 30 Days	Last regardless of timing	Last at 12 mo
PHA cpm ($\times 10^{-3}$)	Complete	49	67	65	68
	Partial	75	101	49	95
	Failure	53	56	29*	—
PHA SI	Complete	79	196‡	112‡	118
	Partial	88	221	143	135
	Failure	53*	192	31*	—
SLO cpm ($\times 10^{-3}$)	Complete	12	2.9	19§	23
	Partial	3	23	3.5	—
	Failure	2	4	0*	—
SLO SI	Complete	8	3.5	21‡	31‡
	Partial	6	10	7	—
	Failure	2	4	2*	—

All tests by chi-square and Wilcoxon-signed rank test.
* Failure significantly lower than complete remission at same study period.
‡ Indicated value significantly higher than value at first study period in complete remission group.
§ Indicated value greater than second test value.

For example, although the majority of the failure group were AML patients, the correlation between immunocompetence and prognosis was seen in both AML and ALL. Thus (Table X), among the AML patients

TABLE IX

Clinical and Therapeutic Data on Study Subjects

Parameter	Remission status: Complete	Partial	Failure
Age, *yr*			
Median	28*	31	38
Range	14–79	15–60	17–80
Type of leukemia, *no. of patients*			
AML	21*	3	13
ALL	11	3	2
AUL	1	0	0
Prior treatment, *no. of patients*			
> 5 courses	12*	2	10
2–5 courses	3	0	0
< 2 courses	18	4	5

* None of the groups differed significantly from each other.

TABLE X

Response (Median) to First Skin Test in Patients with Various Clinical and Therapeutic Situations

Parameter	Complete remission				Failure		
	n	Median	Zero	< 5 mm	*n*	Median	Zero
		mm	*n* (%)	*n* (%)			*n* (%)
Age							
14–30 yr	18	8	5 (27)	7 (39)	6	0	6 (100)
31–50 yr	9	10	1 (11)	1 (11)	4	5	2 (50)
51–80 yr	6	2	1 (17)	4 (67)	5	0	3 (60)
Type of leukemia							
AML	21	8	4 (19)	8 (38)	13	0	9 (69)
ALL	11	8	3 (27)	4 (36)	2	0	2 (100)
AUL	1	13	0 (0)	0 (0)	0	—	—
Prior treatment							
> 5 courses	12	7	3 (25)	5 (42)	10	0	7 (70)
2–5 courses	3	8	1 (33)	1 (33)	0	—	—
< 2 courses	18	8	3 (17)	6 (33)	5	0	4 (80)

who entered complete remission the median skin test diameter was 8 mm compared to 0 mm in the AML failures. Only 19% of the AML complete remission patients had a median skin test of zero compared to 69% of the AML failure patients. The same differences were seen in ALL.

DISCUSSION

The findings in this study confirm and extend our previous observations (7). Thus, in patients with acute leukemia, immunocompetence relates to a good prognosis while immunoincompetence relates to a poor prognosis. The data in this study are particularly striking with regard to delayed hypersensitivity responses to recall antigens and are less striking but show this same trend in regard to in vitro lymphocyte blastogenic responses. This is the first study in which we are aware that serial studies of immunocompetence have been carried from the onset and during the course of intensive intermittent chemotherapy in patients with acute leukemia.

Although patients who initially had positive delayed hypersensitivity skin test reactivity entered complete or partial remission, both the complete and partial remission groups had a gradual but highly significant decline in this immunological reactivity in subsequent months. On more detailed analysis of the data, this decline in reactivity was shown to be much more pronounced among those patients who had entered remission but relapsed subsequently. The decline occurred or was detectable during the month before relapse. Thus, an immunocompetent patient with acute leukemia in complete remission, who loses his immunocompetence, is in danger of relapse. In contrast, the patients who entered remission and stayed in remission 1 yr or longer maintained their immunocompetence although it went through a transient decline. This decline occurred during the 2nd through the 5th mo of treatment, and was followed by partial recovery. This was the period when remission induction and consolidation therapy was most intensive and presumably the immunodepression was the result of chemotherapy. It can be assumed that the immune system in this group is vigorous enough to recover from the suppressive effects of chemotherapy whereas in the group which eventually relapses it is not. The fact that the latter group were immunocompetent initially when they had a tumor burden, but became incompetent before relapse, also suggests that their decline in immunocompetence is the result of chemotherapy acting on a susceptible immune system and not an immunosuppressive effect of the tumor burden.

Another interesting feature of these studies was the improvement in skin test reactivity between the first and second studies done during the 1st mo of treatment. Improvement in skin test reactivity was seen in each response category. This was not significant but the trend was clear. This suggested that reduction in the tumor burden, as a result of the chemotherapy, permitted the skin test reactivity to improve. A return of immunocompetence, associate with a reduction in tumor burden, has been described in other malignancies (9).

These same trends were evident among the in vitro lymphocyte responses to SLO and PHA, but in general they were less striking. This might be related to the fact that a standard number of lymphocytes were used per culture. Any deficiency detected therefore represents intrinsic lymphocyte damage. Recently a whole blood

method for lymphocyte cultures was described which the authors felt more accurately reflects the lymphoid organ and its overall response to mitogens (10). On the other hand, the majority of studies using methods similar to ours in cancer patients have yielded useful data and similar clinical correlations (11, 12).

Several important conclusions can be drawn from these observations. They can be put into a general scheme concerning the relationship between the immunocompetence and the prognosis of the cancer patient. First, it appeared that individuals vary in their level of immunocompetence. Those who are more immunocompetent in spite of their immunosuppressive tumor burden (and any residual effects of prior therapy) have a greater probability of entering remission than those who are less immunocompetent. Furthermore, the chemotherapy that the patients receive is immunosuppressive. However, the ability to recover from this immunosuppression is associated with prolonged remission, whereas the failure to develop or to recover is competence after this suppression is associated with a short remission. Thus the complex relationship of immunocompetence to prognosis in leukemia can be explained. The leukemia (tumor-burden) innate (presumably genetic and age-related) defects in immune status, and immunosuppressive therapy each play a role. We feel that no single factor can adequately explain the immunological-clinical correlations described in this paper.

These observations form a rational basis for the development of nonspecific active immunotherapy for leukemia. This should be applied early during remission induction to improve the immunocompetence of those incompetent patients who would not normally enter remission. The hope would be that they would become competent and would enter remission. Nonspecific active immunotherapy should also be given during remission maintenance to delay or prevent the decline in immunocompetence which is associated with the relapse in these patients. Indeed, nonspecific active immunotherapy (combined with active specific immunotherapy) has been shown to prolong complete remission in acute leukemia (13, 14).

One might also consider which component of the immune system is predominantly involved in the immunological deficiency observed in these patients. Defects in delayed hypersensitivity represent either a macrophage (15) or a T-lymphocyte (16) defect. Both are suppressed by chemotherapy (17) and malignancy (18). Humoral immunity is important in host defense against leukemia (19) and our observation that SLO responses in these patients were more suppressed than PHA responses suggests that a B-lymphocyte defect was also present.

Many studies of various types of cancer patients confirm and are extended by the observations in this paper. A relationship between a good prognosis and a high level of immunocompetence has been observed in Hodgkin's disease (2), malignant melanoma and other solid tumors (5), head and neck cancer (4), lung cancer (3), and in acute leukemia (7). Prolonged chemotherapy in acute leukemia of childhood is associated with severe immunological incompetence which gradually recovers after the chemotherapy is stopped (20). The findings in these studies suggest that the time has now arrived when immunocompetence evaluation should become a regular part of the evaluation of the cancer patient. Studies must be done in which relatively simple and reproducible tests are applied on a broad scale to determine their usefulness in a general cancer therapy clinical setting. Such studies should be done serially, not only in patients receiving chemotherapy but also in patients receiving surgery, radiotherapy, and immunotherapy. An attempt should be made in a broad framework to see if these tests can be used to guide therapy, to develop new, less immunosuppressive therapies, and to indicate when therapy needs to be changed or reapplied in a patient in imminent danger of relapse.

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