

## What Are Normal Blood Values for Leukemia in Remission?

By CAROL B. HYMAN, EDUARDO BORDA C. AND GOPALASWAMI DIGUMARTHI

**E**XPERIENCES with the "Criteria for the Evaluation of Response to Therapy in Acute Leukemia"<sup>1</sup> have led us to question whether the criteria for complete blood remission should be based upon established normals or should make allowances for the pharmacologic effects of the particular chemotherapeutic agent being employed. In an attempt to answer this, data have been accumulated on values for hemoglobin, total white blood cells, granulocytes, lymphocytes and monocytes in a group of children with acute lymphatic leukemia in remission.

### CLINICAL MATERIAL AND METHOD OF PROCEDURE

Values for hemoglobin concentration and white blood cells, taken at approximately the midpoint of complete bone marrow remissions [ $A_1$  of the Criteria],<sup>o</sup> were extracted from the records of children with acute lymphatic leukemia under continuous therapy. The drugs employed were 6-M.P. (6-mercaptopurine) alone or in combination with azaserine (O-diazoacetyl-L-serine) or DON (6-Diazo-5-oxo-L-norleucine), amethopterin and prednisone.

The onset of a complete bone marrow remission was considered to be midtime between the observation showing complete remission and the preceding observation showing partial or complete relapse. The termination of complete remission was considered to be midtime between the last observation showing complete remission and the first bone marrow examination showing partial or complete relapse. If the interval from onset to termination of complete remission was less than 30 days, the 15-day midpoint was considered too short to permit stabilization of blood values. Remissions of this type were excluded from the study. If there was no blood count done at the midpoint, the two nearest determinations, one preceding and one subsequent to the midpoint, were averaged.

All patients in this study were treated with 6-mercaptopurine, alone or in combination, as the initial chemotherapeutic agent; amethopterin and prednisone were not used initially in any of the patients.

There were 78 complete bone marrow remissions lasting 30 days or longer. Table 1 lists the number of patients, their ages and duration of the remissions which occurred with each of the drugs employed. For comparison with the values observed in the 78 re-

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From the Hematology Research Laboratories, Los Angeles Childrens Hospital, and the Department of Pediatrics, University of Southern California School of Medicine, Los Angeles, Calif.

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<sup>o</sup>*Criteria for the Evaluation of Response to Therapy of Acute Leukemia.* A. Marrow (per 200 cells counted): (1) Absence of cells that can be individually identified as leukemic, and reduction in the number of blasts to less than 5 per cent of total nucleated cells for adults and 10 per cent for children, with lymphocytes to less than 10 per cent for adults and 20 per cent for children. There should be essentially normal-appearing granulopoiesis, erythropoiesis and thrombopoiesis both qualitatively and quantitatively, except for morphologic changes definitely attributed to the medication employed.

TABLE 1.—Blood Values for Leukemia in Remission under Continuous Therapy  
Clinical Material

	Normal	6-M.P.*	6-M.P. plus Azaserine†	6-M.P. plus DON‡	Ametho- pterin	Pred- nisone
No. Patients	56	27	20	6	16	9
Age, Range (yrs.)	2.3-14	3-12	1.4-10	3-11	2-7	1.6-10
Age, Mean (yrs.)	6.5	4.4	3.7	6	4.2	4.7
Duration of Remission, Range (days)	—	30-479	34-573	83-271	67-214	42-199
Duration of Remission, Mean (days)	—	120	177	190	113	103

\*6-Mercaptopurine.

†0-diazoacetyl-L-serine.

‡6-diazo-5-oxo-L-norleucine.

missions, the admission blood counts were extracted from the records of 56 well children hospitalized for elective eye surgery or hernia repair. The range and mean ages of these children are also included in the table.

The blood counts were first related to the duration of the remissions in which they occurred. The counts were then grouped according to the therapeutic agent employed, and for each treatment group the range and mean values for the hemoglobin concentration, total white blood cell count, granulocytes, lymphocytes and monocytes were obtained. These values were then compared to those of the normal controls and the differences analyzed statistically.<sup>2</sup>

## RESULTS

No correlation was found between the blood counts and length of the remissions in which they occurred. This observation eliminates the possibility that differences in blood values within a particular group are related to the duration of therapy rather than the agent itself. It also eliminates the possibility that differences between groups occur because some agents induce longer remissions than others.

Table 2 contains the range of values, the mean, standard deviation and median for the concentration of hemoglobin, white blood cells, granulocytes, lymphocytes and monocytes for the normal and treated groups.

The mean *hemoglobin concentration* was approximately one gram lower than normal in the 6-M.P. remissions, whether the drug was given alone or in combination with azaserine or DON. Statistical analysis shows this depression to be significant in the remissions with 6-M.P. alone or with azaserine, but not with DON. In this last group the number of observations was smaller and the mean hemoglobin concentration was slightly higher than in the other two. The mean hemoglobin concentration in the amethopterin remissions was approximately the same as the control; with prednisone the mean was about 0.5 gram per 100 cc. higher. This difference is not significant.

Mean values for the *total white blood cells* per cu.mm. of blood were significantly lower than normal at the midpoint of the remissions with 6-M.P., alone or in combination, and also with amethopterin, but not with prednisone. In the three 6-M.P. groups the means were similar, approximately 50 per cent

TABLE 2.—Influence of Continuous Chemotherapy on Blood Values during Complete Bone Marrow Remission

		Hemoglobin Gm./100 cc.	W.B.C. 10 <sup>3</sup> /mm. <sup>3</sup>	Granulocytes 10 <sup>3</sup> /mm. <sup>3</sup>	Lymphocytes 10 <sup>3</sup> /mm. <sup>3</sup>	Monocytes 10 <sup>3</sup> /mm. <sup>3</sup>
Normal	Range	9.1-15.6	5.6-15.3	1.6-10.7	1.3-9.6	0.05-0.88
	Mean	13.2 ± 1.24*	9.2 ± 2.32	5.1 ± 1.72	3.5 ± 1.67	0.40 ± 0.22
	Median	13.4	8.7	5.1	3.1	0.88
6-M.P.	Range	8.0-14.1	1.6-8.9	0.46-0.9	1.0-2.9	0.00-0.33
	Mean	12.0 ± 1.45	4.5 ± 3.36	2.3 ± 1.52	1.9 ± 0.57	0.20 ± 0.12
	Median	12.1	4.4	1.9	2.1	0.18
6-M.P. + Azaserine	Range	8.0-14.9	2.3-7.1	0.21-4.8	0.87-3.9	0.06-1.1
	Mean	11.7 ± 1.91	4.7 ± 1.58	2.4 ± 1.23	2.0 ± 0.91	0.28 ± 0.23
	Median	11.8	4.5	2.3	1.9	0.26
6-M.P. + DON	Range	8.1-14.1	2.9-7.1	1.9-4.2	0.72-2.7	0.10-0.8
	Mean	12.4 ± 2.2	4.7 ± 1.58	2.5 ± 0.81	1.9 ± 0.75	0.30 ± 0.24
	Median	13.2	4.5	2.2	1.4	0.20
Amethopterin	Range	9.6-15.4	2.3-9.3	1.0-5.3	0.76-3.9	0.00-0.81
	Mean	13.5 ± 1.91	5.6 ± 1.93	3.4 ± 1.33	1.8 ± 0.79	0.21 ± 0.2
	Median	12.4	5.9	3.5	1.9	0.15
Prednisone	Range	11.6-15.6	4.8-10.8	2.4-6.8	1.2-5.7	0.09-0.75
	Mean	13.7 ± 1.96	8.2 ± 2.08	4.2 ± 1.38	3.6 ± 1.44	0.41 ± 0.21
	Median	13.9	8.5	4.7	4.3	0.43

\*Standard deviation.

below normal. With amethopterin and prednisone the means were about 40 per cent and 10 per cent below the normal, respectively.

The mean values for *granulocytes* per cu.mm. of blood were significantly lower than normal in all treated groups, irrespective of the drug employed. The values in the 6-M.P. remissions were all approximately the same, about 50 per cent below normal. With amethopterin, the mean was 30 per cent and with prednisone 18 per cent less than normal. In the prednisone group the depression of the total white cell count was accounted for entirely by the reduction in granulocytes.

The mean values for *lymphocytes* per cu.mm. of blood were significantly lower than normal in the remissions produced by 6-M.P., alone or in combination, and by amethopterin. Numerically, the mean values for the lymphocytes in these remissions were approximately the same, about 40 per cent below normal. The values in the prednisone remissions were the same as those for the normal group.

The mean values for *monocytes* per cu.mm. of blood were significantly reduced in the 6-M.P. remissions, alone or with azaserine, and also in the amethopterin remissions. In the remissions with 6-M.P. plus DON and with prednisone the reductions did not attain statistical significance.

#### DISCUSSION

Statistical analysis of the data accumulated in this study confirms our impression that blood values for leukemia in remission under continuous therapy vary significantly from values observed in normal children. The differences are more marked in the white cells than in the hemoglobin.

In general, the blood values in remissions controlled by 6-M.P. given alone

or in combination with azaserine or DON were reduced approximately to the same degree. The reductions were more marked than those in the amethopterin or prednisone remissions; the latter drug had the least effect.

Unfortunately, data are not available on blood values at the midpoint of spontaneous or transfusion-induced remissions. If this information were available, it could be considered the "normal" for leukemia in remission. Since we do not have this information one cannot say that changes in the blood noted in drug-induced remissions are entirely due to the medication employed. They may, at least in part, be a manifestation of the natural course of the disease. On the other hand, when the findings vary according to the chemotherapeutic agent controlling the remission, the differences logically can be attributed to the drug and not the natural course of the disease.

From the clinical standpoint, the objective in treating leukemia is to return the patient to as nearly a normal state as possible. In this regard, comparison of blood values in remission to values occurring in the normal individual is correct. However, to understand the meaning of this comparison, knowledge on the influence of the drug employed is essential.

#### SUMMARY AND CONCLUSIONS

1. The values for hemoglobin concentration, total white blood cells, granulocytes, lymphocytes and monocytes at the midpoint of 78 drug-induced remissions in a group of children with acute leukemia have been presented. These values have been compared with those from a group of normal children, and the differences analyzed statistically.

2. Statistical analysis shows that, in general, blood values in remission are reduced by the particular agent employed. White blood cells are more markedly affected than hemoglobin.

3. The effects are essentially the same with 6-M.P. given alone or in combination with azaserine or DON.

4. The reduction in values is greatest with 6-M.P., alone or in combination, less with amethopterin and least with prednisone.

5. The data presented indicate that criteria for complete blood remission should make allowances for the influence of the drug employed.

#### SUMMARIO IN INTERLINGUA

1. Le valores pro concentration de hemoglobina, pro leucocytos total, pro granulocytos, pro lymphocytos, e pro monocytos al medie termino de 78 remissiones pharmacotherapeutic in un gruppo de patientes pediatric con leukemia acute es presentate e comparate con le valores correspondentemente in un gruppo de juveniles normal. Le differentias es analysate statisticamente.

2. Le analyse statistic monstra que, a generalmente parlar, le valores hematologic durante le remission es reducite per le agente particular usate. Leucocytos es afficite plus marcatemente que hemoglobina.

3. Le effectos es essentialmente le mesme pro 6-mercaptipurina sol e pro 6-mercaptipurina in combination con azaserina o 6-diazo-5-oxo-L-norleucina.

4. Le reduction del valores es le plus grande con 6-mercaptopurina, sol o in combination. Illo es minus grande con amethopterin. Illo es le plus basse con prednisona.

5. Le datos presentate indica que le criterios pro complete remission hematologic deberea prender in consideration le influentia del droga usate.

## REFERENCES

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