Formal Discussion: Long-Term Survivors[1]

WOLF W. ZUELZER

The Child Research Center of Michigan, Detroit, Michigan

My remarks are based on three kinds of interrelated experience, clinical, cytologic, and cytogenetic, all restricted to human and specifically to childhood leukemia. To begin with some definitions, Dr. Burchenal's assumption that there must be something unique about "long-term survivors" or their disease rests on what one chooses to call "long-term" in acute leukemia. His discussion implies a minimum of 5 years. Only a short time ago 2 years would have seemed very impressive for a disease with a natural median survival time of less than 4 months. A reasonable definition ought to be related to some standard of experience such as the median of a series of adequate size, even though it might prove to vary from time to time and from institution to institution.

Let me illustrate the point with our own data. If we were to choose twice the median value as the arbitrary limit beyond which patients become long-term survivors, on the basis of a completely unselected series of 285 cases of all types of childhood leukemia including the immediate deaths, we would arrive at a figure of 20 months, and 70 patients, or approximately 25%, would qualify. Obviously this would not be a useful standard. Let us try 3 times the median, surely a stringent definition. Our group then would consist of 36 patients, or about 12.5%. If this is still not satisfactory, we shall take 4 times the median or 40 months, which gives us 20 long-term survivors or 7.0%.

This is not playing with figures, nor do I seriously wish to propose any of these standards. I merely wish to call attention to the fact that the relationship between these figures, 25, 12.5, and 7, is almost exactly geometric and reflects a rather regular progressive decrease in the number of survivors. In other words, under the conditions existing in our series Dr. Burchenal's inference that the survival curve in acute leukemia becomes discontinuous at some point to the extent that there is no transition between "short-term" and "long-term" survivors was not borne out, and with this premise the myth of the uniqueness of the long-term survivors evaporates.

This is not to say that the study of truly exceptional survivals is not worthwhile, but only if it is done in the proper perspective. We must examine every survival with respect to a number of parameters and consider carefully the characteristics of each group; otherwise we shall deprive ourselves of important clues. Let us examine without insistence on too strict a definition some of the factors which seem to make for prolonged survival.

One such factor, long recognized but not generally accepted, is the cytologic type of leukemia. While there is a margin of error which, incidentally, is common to all morphologic classifications of cancer, the correlations one obtains with careful cytologic diagnosis made at the outset in each case are surprisingly good, at least in childhood leukemia. In our series the cases initially designated as stem-cell or lymphoblastic leukemia showed 2–3 times the remission rate and 3 times the mean and median survival of each of the other types encountered (Table 1). From a merely practical point of view these distinctions must be recognized, just as the pathologist recognizes differences between, say, adenocarcinoma and squamous-cell carcinoma and, for the same reason, their prognostic implications.

But the importance of proper cytologic classification goes well beyond its practical usefulness. The different response to therapy furnishes a hint to the nature of the effective mechanism. In our cases the common denominator was the systematic use of steroids early in the course. The vastly superior response of the stem-cell leukemias as compared to all other types, but especially the acute granulocytic variant, suggests that the effect of steroids is partly due to their specific action on a particular cell type, presumably lymphoid, an expression of the general susceptibility of lymphoid derivatives to these hormones, in contrast to myeloid cells. This effect appears to be different from, and independent of, the presumably non-specific metabolic injury caused by anti-metabolites. Our data indicate that the 2 kinds of agents potentiate each other in stem-cell leukemia.

This leads me to a consideration of therapy. Dr. Burchenal has already touched on the fact that the long-term survivors which his survey brought to light usually had some form of combination therapy involving steroids. I am delighted with this observation, since our approach has been based on the rationale that combination therapy might eradicate malignant cells more rapidly and completely than the use of single agents, and our experience over a period of 9 years seems to have borne this out by producing what appears to be an exceptionally large number of prolonged survivals (4, 5). Our total number of 5-year survivors during this period now stands at 8, to which another patient must be added who, embarrassingly but interestingly enough, like the famous case of Dr. Sacks, has received no therapy after the 1st year and is now living and well 12 years after diagnosis. Table 2 shows the % survival of 175 patients with stem-cell leukemia, exclusive of those dying in less than 30 days, who were treated with the particular form of combination therapy developed in our laboratory in 1955. The high degree of continuity of the survival times may again be noted. Apart from its simultaneous use of steroids and an antimetabolite, this combination therapy has a second feature (Chart 1) which we consider of possible signifi-

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TABLE 1

INCIDENCE OF REMISSIONS AND MEAN SURVIVAL IN ALL EXPIRED PATIENTS (ALL TYPES), 1955–63

TYPE	NO.	REMISSIONS (%)	SURVIVAL AFTER DIAGNOSIS (mo.)		
			Mean	Median	Range
Stem Cell	153[a]	92.8	15.8	14.2	1–101
Acute granulocytic	33	42.4	5.0	4.0	0–13
Monomyelogenous	10	50.0	5.2	3.7	1–11
Monocytic	19	31.6	4.6	2.9	0–21
"Atypical"	4	25.0	8.5	5.0	1–24

[a] Includes 10 immediate deaths and 10 patients receiving treatment other than composite cyclic therapy.

TABLE 2

SURVIVAL OF A SERIES OF 175 STEM-CELL LEUKEMIA PATIENTS TREATED WITH COMPOSITE CYCLIC THERAPY[a]

PERIOD OF OBSERVATION	POSSIBLE MINIMUM SURVIVAL (yr)	NO. OF CASES	SURVIVING AT END OF PERIOD	
			No.	%
1955–62	1	155	109	70.3
1955–61	2	142	44	31.0
1955–60	3	119	21	17.6
1955–59	4	91	12	13.2
1955–58	5	73	5	6.8

[a] Not included are 16 cases (1963 cohort) still living, 2 cases lost to follow-up, and 2 early intracurrent deaths.

cance, namely the cyclic use at 3-month intervals of 2 antimetabolites, 6-mercaptopurine and methotrexate, in an attempt to prevent or delay "resistance," or "adaptation." The mean survival for this group was just under 18 months with a median of 14.5 months. Of interest was the fact that most of the time allotted to patients with prolonged survival was accounted for by the first uninterrupted remission (Table 3). To sum up this aspect of the problem, it appears that combination therapy, of all the regimens now available, offers the greatest chance for prolonged survival, a fact which has considerable theoretical implications.

The results just referred to appear substantially better than those obtained with combinations consisting only of anti-metabolites such as reported by Frei and his colleagues in 1961 (1). The difference between the two kinds of regimens is significant. In our program steroids were given at the beginning. The many long remissions subsequently observed make one wonder if the initial therapeutic measures might not be the decisive ones, deter-

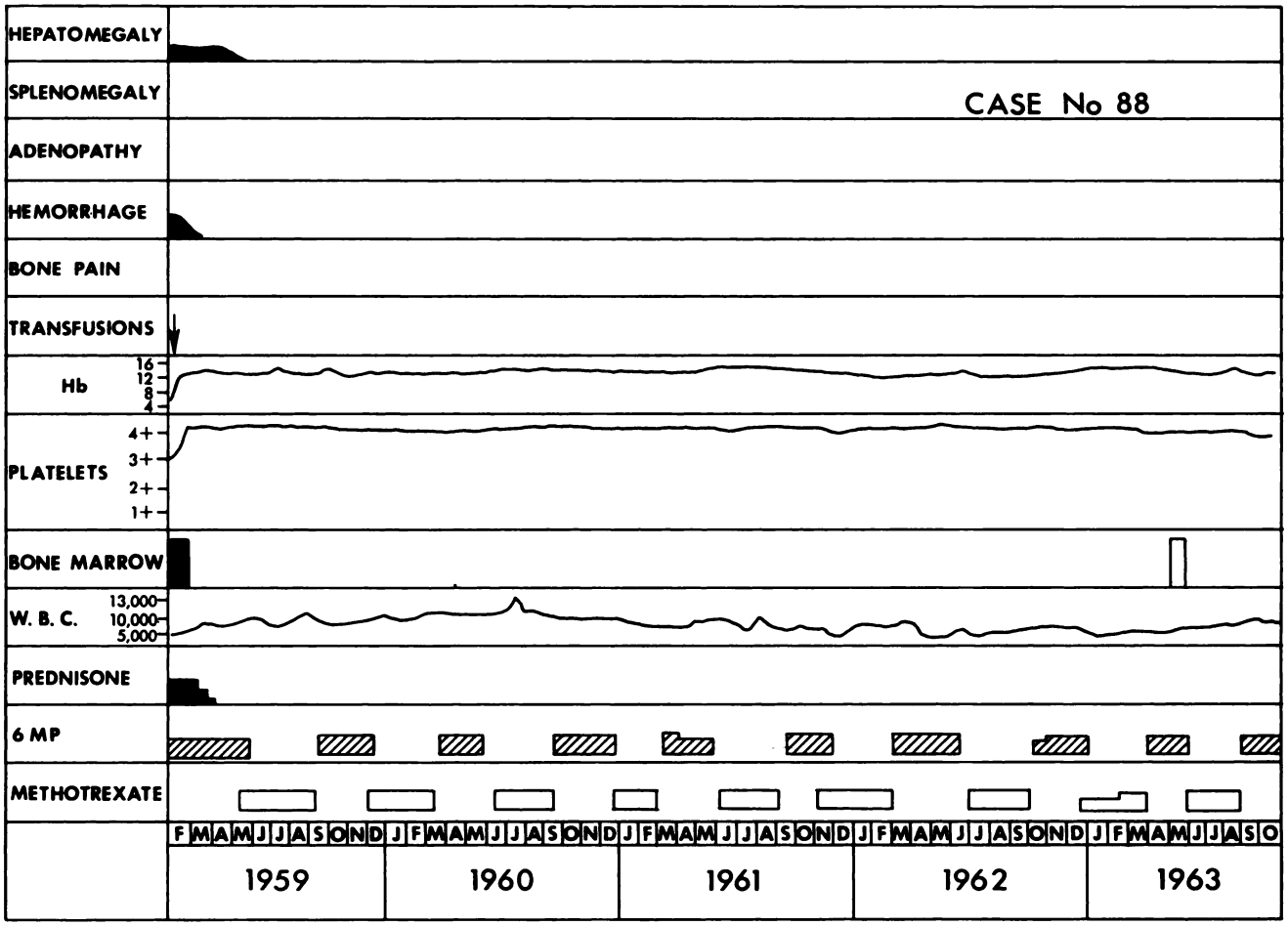

CHART 1.—Representative example of composite cyclic therapy.

TABLE 3

DURATION IN COMPLETED MONTHS OF 1ST REMISSION IN 44 PATIENTS SURVIVING 2 YEARS OR MORE

Total survival	Length of 1st remission	Total survival	Length of 1st remission
106	106[a]	35	32
101	78	35	18
74	74[a]	34	28
65	33	32	30
63	63[a]	32	24
59	59[a]	32	19
56	51[b]	32	18
56	46	32	8
53	53[a]	31	29
51	51[a]	30	22
50	50[a]	29	29[c]
48	19	29	29[a]
47	34	29	20
45	41	28	28[a]
45	33	27	25
44	36	27	23
42	6	25	23
40	32	25	20
38	13	25	16
36	36[a]	24	24[a]
36	24	24	19
36	13	24	13

All remissions: mean, 32.9; median, 29.7.
[a] Still continuing.
[b] Intercurrent death.
[c] Lost to follow-up.

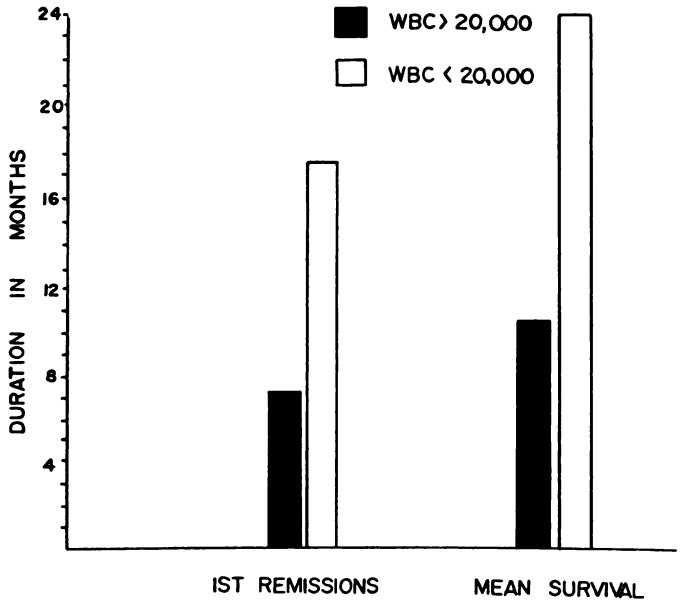

CHART 2.—Relation of initial white blood count to course, based on 175 cases of stem cell leukemia.

mining as if in a single "push" the total course. I would like to return to this question later.

That the conditions existing at the start of the disease or, I should say, at the time of diagnosis, are of critical importance is indicated by our observations regarding the initial white blood count, which others have confirmed. Taking a count of 20,000 as the dividing line, we found almost exactly twice the mean survival and nearly twice the median in cases with initially "low" as with initially "high" white counts (Chart 2). The influence of the factors governing the height of the white count has been apparent in the untreated disease and with various forms of therapy. Under the regimen described earlier, because of the many long survivals, these differences came even more sharply into focus than before, as illustrated by the fact that of 44 patients in our series of 175 stem-cell leukemias who survived for 2 years or more, 43 had initially shown white counts of less than 20,000 and usually less than 10,000.

If I may be permitted to speculate on the nature of these factors which are so clearly determinants in the disease, I suggest that they may indeed reflect an immunologic parameter. The hypothesis that the leukemic cells represent antigenically distinct "non-self" elements is vastly strengthened by the demonstration of chromosomal abnormalities in leukemia. In collaboration with Dr. Leonard Reisman, Dr. Muneo Mitani, and Mrs. R. I. Thompson (2, 3), I was able to show in 75 patients with acute leukemia a consistent correlation between the cytologic state of the bone marrow and chromosomal constitution (Table 4). During initial as well as subsequent relapse, aneuploidy with chromosomal modes ranging from 47 to 65 was consistently found, whereas during remission the diploid number of 46 was invariably restored, regardless of the time elapsed or the manner of treatment. Moreover, in 8 cases thus far available for serial studies, the number of chromosomes found in a given patient during a later relapse was identical with the number found initially or during an earlier relapse. This would seem to be conclusive evidence for the existence of a true leukemic stem line and to indicate that acute leukemia involves a cellular mutation.

Assuming that the mutant is antigenically distinct, a question which, as Dr. Burchenal has suggested, is susceptible to analysis by immunologic methods, one can visualize the following situation: Cellular mutations ought to be fairly common occurrences but are probably suppressed, either through immunologic mechanisms or because of metabolic or other competitive handicaps. Viewed in this perspective, leukemia might be exceptional

TABLE 4

SUMMARY OF BONE MARROW CHROMOSOME STUDIES IN 75 CASES OF ACUTE LEUKEMIA

	Chromosome constitution	No. of cases
Relapse	Aneuploid	41
	Diploid	1
	Total	42
Remission	Aneuploid	0
	Diploid	33
	Total	33
Total No. of cases		75

not because of the occurrence of mutants but because of failure by the organism to control or altogether eliminate them. To some extent the control mechanism may be preserved in patients with leukopenia, as opposed to hyperleukocytosis, in which the ability to contain the mutant has been completely lost. If this were true, the comparatively more effective restoration under therapy in the leukopenic cases might also be responsible for the long-lasting remissions. This interpretation is compatible with, and supplements or implements the reasoning based on, kinetics of cell proliferation.

A corollary of the observations concerning chromosomes in leukemia to which I have referred is that, with the demonstration of a characteristic stem line in the individual patient, the disease becomes, as it were, a "private" disorder, and if the different modal numbers were found to correspond to different antigenic structures, immune therapy of leukemia may indeed require a high degree of individualization. As for relationships between number or kind of chromosomes in the aneuploid stem lines and response or duration, we have as yet no data to suggest correlations.

The cytogenetic data permit a more specific definition of a "cure" and also a clearer visualization of its possibility than before. If, regardless of its ultimate etiology, a mutation is involved, it becomes possible to conceive of its loss or elimination from the body, accidental or otherwise, as opposed to its mere suppression. The former then should happen occasionally, and such cases would require no further therapy. This was the case in our 12-year survivor and in the case from Baltimore. Interestingly, many of our other "long-term survivors" have become lax in maintaining the therapeutic regimen; at least 2 have not taken medication regularly in several years but are still in complete "remission."

Testing this hypothesis in 1 child who initially received very intensive therapy, including massive weekly doses of both methotrexate and cyclophosphamide, we deliberately thereafter have withheld all treatment, thus far without any evidence of relapse. This is 1 case and a short period of observation, but it is of interest in view of the general assumption that therapy must be continuous to maintain remission. How well founded this assumption is, remains to be seen. It is only fair to add that we observed 1 patient who remained in continuous remission for 6 years under therapy and then relapsed and has since died. This obviously was a true "remission" in which the mutant must have remained in a dormant state and in numbers too small to be detected. To state the hypothesis in another way, conditions were such that control could be maintained over the alien cells in a very effective way and for a long period of time. It was this kind of observation that led us to consider the possibility that the initial therapeutic "push" might be the decisive factor in the treatment of acute leukemia.

To sum up our impressions, some of the factors that make for prolonged remissions and survivals can now be identified. They are, however, not unique to the "long-term survivors" in Dr. Burchenal's sense. Two of these are indeed inherent in the patient or in the disease, namely the cytologic character of the leukemia and the hypothetical mechanisms governing the height of the initial white blood count. There may be others that we cannot identify as yet. Immunologic studies and further refinements of chromosome analysis might prove helpful in this respect. Another factor is extrinsic and seems to apply chiefly to lymphoblastic leukemia, namely the therapeutic regimen. At the present time we may say that of all patients with acute leukemia, the best chances for long-term survival and possibly even a cure are those of a child with stem-cell leukemia, a low initial white blood count, and preferably, but not necessarily, in good clinical condition who receives combined therapy such as the regimen we have designated as composite cyclic therapy. This summary, then, must make us rather pessimistic about the achievements of anti-metabolites and about all forms of therapy thus far available for the other forms of leukemia. Nevertheless, we now have a more concrete framework on which to establish the concept of a cure.

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