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# Association of Specific Chromosome Abnormalities with Type of Acute Leukemia and with Patient Age[1]

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## ABSTRACT

Complete data regarding age, sex, karyotype, and French-American-British Cooperative Group classification were available for 239 unselected patients with acute nonlymphocytic leukemia. Of these, 128 were classified as having acute myeloblastic leukemia (M1 or M2); within the acute myeloblastic leukemia group, 83 (65%) of the patients were chromosomally abnormal. Except for 16 patients with a t(8;21), the percentage of patients with an abnormal karyotype increased with age, particularly above the age of 50 years. Besides the patients with t(8;21), there were 29 patients with loss of part or all of chromosomes 5 and/or 7, 11 patients with +8, and 27 patients with other abnormalities. Of 70 patients with acute myelomonocytic leukemia (M4), on the other hand, 28 (40%) were chromosomally abnormal, only three had loss of chromosomes 5 or 7, one was −7,+8, and four were +8, whereas 20 had other abnormalities. This difference may reflect different etiological factors in these two types of leukemia.

## INTRODUCTION

A major unresolved issue in human cancer is whether the nonrandom chromosome patterns that are observed are in any way related to the carcinogenic agent that may have "caused" the cancer. Whereas there is evidence supporting such an association in experimental animals (10), no direct data are available for humans. There are some indirect, very preliminary data, however, that may help to answer this question.

Evidence from my laboratory and that from others has shown that a very high percentage of patients with ANLL[3] who have received cytotoxic therapy previously for some other malignant or nonmalignant disorder have an aneuploid clone in their leukemic cells (4, 13, 15, 16, 18). In my laboratory, an aneuploid clone was present in 31 of 33 patients with secondary leukemia (Refs. 15 and 16; Footnote 4). Moreover, the types of chromosome changes were distinctly nonrandom; 29 of the 31 patients with aneuploidy had a loss of part or all of chromosome 5 and/or chromosome 7. Another significant observation was that the great majority of our patients with ANLL had either AML [M1 and M2 in the FAB classification (1)] or EL (M6).

The question can therefore be raised whether there is any evidence that patients with AML or EL, who have abnormalities of chromosomes 5 and/or 7, have leukemia because of exposure to mutagens. The data of Mitelman *et al.* (11, 12) suggest that they do; thus, abnormalities of chromosomes 5 and 7 were much more common in individuals who had worked in chemical industries and with pesticides than in those who had not been so exposed.

Epidemiological data may also be relevant to an approach to this question. Changes in the incidence of leukemia have been described recently in several European countries as well as in the United States. Since the investigators used different parameters to measure the changes, direct comparison of the studies is difficult. The results, however, are consistent in showing that there has been a significant increase in the incidence of leukemia in recent years. Geary *et al.* (7) reported that the incidence of myeloid leukemia (acute and chronic) in Lancashire, England, in 1971 to 1976 was twice that in 1965 to 1970. Linos *et al.* (9) reviewed the data for Olmstead County, Minn. (the area served by the Mayo Clinic), from 1940 to 1970. The incidence of ANLL remained relatively stable from 1935 to 1964. In the 10-year period from 1965 to 1974, however, the incidence in males doubled, whereas it was constant in females. When the change was plotted according to age, it was found to be due to a substantial increase in the frequency of ANLL in males who were 50 years old and older. Thus, the mean annual incidence for males 50 years old or older increased from 5 of 100,000 in 1940 to about 10 of 100,000 in 1960 to 20 of 100,000 in 1970. An almost identical change in the incidence of acute leukemia of all types was reported by Brandt *et al.* (3) in Sweden. The incidence of leukemia in males aged 20 to 40 years remained 2 to 3 of 100,000 from 1964 to 1973; during the same period, the incidence in males aged 50 to 64 years increased from about 3 of 100,000 to 6 of 100,000, and for males aged 65 to 79 years, the incidence rose from 10 to about 18 of 100,000 population.

The epidemiological data, combined with the evidence of consistent chromosome changes in patients with secondary leukemia, suggested that an analysis, based on the FAB classification (1), of the karyotype of leukemia cells of patients with ANLL *de novo* classified according to age, sex, and the type of leukemia could provide evidence related to the following question. Do patients with ANLL *de novo* show a karyotypic pattern in their leukemia cells that allows one to distinguish patients who probably have been exposed to some leukemogenic agent from those who have not?

There are, unfortunately, insufficient data for an answer to this question at present. Many laboratories have reported on chromosome changes in ANLL, but the patients usually are selected so that only those with abnormal karyotypes are included, and sometimes information on age, sex, or FAB classification is omitted.

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[3] The abbreviations used are: ANLL, acute nonlymphocytic leukemia; AML, acute myeloblastic leukemia; FAB, French-American-British Cooperative Group; EL, erythroleukemia; AMMol, acute myelomonocytic leukemia; APL, acute promyelocytic leukemia; AMOL, acute monocytic leukemia.

[4] J. D. Rowley, H. M. Golomb, and J. W. Vardiman, unpublished observations.

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Data from all series of patients on whom complete information is available have been used to provide some preliminary evidence on this question.

## MATERIALS AND METHODS

All reported series of unselected patients with ANLL *de novo* were reviewed for the completeness of information provided, specifically age, sex, FAB classification, and karyotype. Patients with secondary leukemia, *i.e.*, those who had cytotoxic therapy for some other disease, were excluded. In addition to 109 patients studied at the University of Chicago (8, 17),[5] there are 56 cases from Sweden (11), 42 from Australia (6), and 32 from Russia (14) for whom all of the data are given. Within each FAB group, the data have been arranged by age according to the intervals used by Brandt *et al.* (3).

## RESULTS

A total of 239 cases is available for analysis (Table 1). The percentages of the various FAB subtypes are similar to those for cases in the First International Workshop on Chromosomes in Leukemia (5). Within each FAB group, the percentage of patients with a normal karyotype for the 239 patients analyzed in this report is similar to that for the patients studied in Helsinki, although only about 30% of the patients are identical in the 2 studies.

**Patients with AML (M1 and M2).** The FAB subgroup containing the largest number of patients is AML (M1 and M2). Except for the data from Chicago, M1 and M2 have been combined by the investigators and are considered together in this analysis. Of the 128 patients in the AML group, 72 are female, and 56 are male. This is the reverse of the expected ratio, since acute leukemia is more common in males. The excess of females is largely a result of the ratio of 32 females to 16 males from Chicago. At present, information on the occupations of these patients is not available. Most of the patients in the low age group (0 to 19 years) were from Russia (11 of 16). With these exceptions, the distribution of patients appears to be comparable in the 4 series.

Patients with clonal abnormalities are grouped in Table 2 as follows: patients who had a missing chromosome 5 (−5) or a deletion of the long arm of 5 (5q−), similar abnormalities for chromosome 7 (−7 or 7q−), or an extra chromosome 8 (+8); patients who had a t(8;21); and patients with all other abnormalities. Within the first of these groups, 9 and 8 patients had a −5 or 5q−, respectively, 13 and 14 had a −7 or 7q−, and 11 were +8. A −7 and either a −5 or 5q− were seen together in 4 patients, and a 7q− and −5 were present in one. There were therefore 29 patients (73%) who had some abnormality of chromosomes 5 and/or 7, compared with only 11 who were +8. The median age for patients with abnormalities other than t(8;21) was 49 to 50 years; for t(8;21) patients, it was 26 years; and for patients with a normal karyotype, it was 43 years. Since the t(8;21) patients were younger and may constitute a special category, data on these patients have been considered separately from those on other aneuploid patients. Thus, although the relative number of patients with abnormalities tends to increase with age, no patient with t(8;21) in this series was older than 50 years. As can be seen from Table 2, excluding t(8;21), 40 patients had abnormalities of chromosomes 5, 7, or 8, and 27 had other changes; within each group, about two-thirds of the patients were 50 years old and older. For each age group, the percentage of patients with normal karyotypes was about the same, although it decreased from about 40% in ages 0 to 49 to 32% in ages 50 and above. Chart 1 shows clearly that one-half of the patients ages 0 to 34 years with an abnormal karyotype had a t(8;21), whereas none of the patients above 50 years old had a t(8;21). The entire increase in aneuploidy in older (more than 49 years) compared with younger patients therefore is due to an increase in other abnormalities, among which changes in 3 chromosomes (5, 7, and 8) account for 60%. The great majority of these abnormalities affected chromosomes 5 and 7.

Data from both Brandt *et al.* (3) and Linos *et al.* (9) suggested that the increased incidence of leukemia was particularly evident in individuals more than 50 years old; of the 112 patients [omitting the t(8;21)] analyzed here, 23 of 47, or 49%, of those less than 50 years old and 44 of 65, or 68%, of those more than 49 years old had an abnormal karyotype. Although the difference in percentage of chromosomally abnormal patients at older compared with younger ages is fairly large, it is not statistically significant at the 5% level because of the small number of patients studied.

**Patients with AMMol (M4).** Seventy patients were classified as having AMMol (M4); more than one-half (43) of these were from the Chicago series (Table 1). There was a slight excess of males (39:31). Sixty % of the patients with M4 had a normal karyotype; these include more females (71%) than males (51%) (Table 3). The median age for chromosomally normal patients was 54 years, and that for abnormal patients was 49 to 50 years. Slightly less than 30% of all abnormalities involved chromosomes 5, 7, and 8, whereas in AML, 60% involved these chromosomes. Of AMMol patients with abnormalities of chromosomes 5, 7, and 8, one each was −5, −7, and 7q−; one was −7 and +8; and 4 were +8. Four of the patients listed as abnormal were males whose cells were lacking a Y chromosome; they tended to be younger than −Y individuals identified in the general population, with ages of 21, 29, 58, and 60 years. Only one −Y patient (age, 63 years) was noted in the AML group. About one-half (54%) of the abnormalities occurred in older patients, compared with AML in which 68% of the abnormalities occurred in older patients.

**Patients with Other Leukemias.** Patients with other types of leukemia were relatively less common; 12, 17, and 11 patients had APL (M3), AMOL (M5), and EL (M6), respectively (Table

Table 1

*Two hundred thirty-nine unselected patients classified according to investigator and FAB type*

| | FAB classification | | | | | | |
|---|---|---|---|---|---|---|---|
| | AML | | | | | | |
| Laboratory | M1 | M2 | APL M3 | AMMol M4 | AMOL M5 | EL M6 | Total |
| Prigogina (14) | 21 | | 0 | 6 | 7 | 0 | 32[a] |
| Garson (6) | 24 | | 3 | 7 | 5 | 3 | 42 |
| Mitelman (11) | 34 | | 2 | 14 | 4 | 2 | 56 |
| Rowley (8, 17) | 25 | 24 | 7 | 43 | 4 | 36 | 109 |
| Total | 128 [54][b] | | 12 [5] | 70 [29] | 18 [8] | 11 [4] | 239 |
| First workshop[c] | 57 | | 7 | 25 | 2 | 3 | |

[a] Three patients with secondary leukemia have been omitted.
[b] Numbers in brackets, percentage of subgroup among total 239 patients.
[c] Percentage of subgroup among 241 patients included in the First International Workshop on Chromosomes in Leukemia; 5% of the 241 were unclassified (5).

[5] J. D. Rowley, unpublished observations.

Table 2

*One hundred twenty-eight patients with AML (M1 and M2), grouped according to age and sex*

| | 0–19 yr | | 20–34 yr | | 35–49 yr | | 50–64 yr | | 65–83 yr | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Karyotype | F | M | F | M | F | M | F | M | F | M | Total | |
| −5,5q− | 0 | 1 | 1 | 1 | 1 | 2 | 4 | 2 | 2 | 0 | 14[a] | 8 F<br>6 M |
| −7,7q− | | 2 | | 1[b] | 1[b] | 2[b] | 3 | 1 | 2[b] | 3[b] | 15 | 6 F<br>9 M |
| +8 | 0 | 1 | 1 | 1 | 0 | 0 | 3 | 1 | 2 | 2 | 11 | 6 F<br>5 M |
| t(8;21) | 2 | 3 | 4 | 3 | 3 | 1 | 0 | 0 | 0 | 0 | 16 | 9 F<br>7 M |
| Other | 0 | 1 | 2 | 1 | 4 | 0 | 7 | 4 | 4 | 4 | 27 | 17 F<br>10 M |
| Normal | 2 | 4 | 7 | 3 | 6 | 2 | 6 | 6 | 5 | 4 | 45 | 26 F<br>19 M |
| Total | 4 | 12 | 15 | 10 | 15 | 7 | 23 | 14 | 15 | 13 | 128 | 72 F<br>56 M |

[a] Five other patients also had −5 or 5q−.
[b] One also had −5 or 5q−.

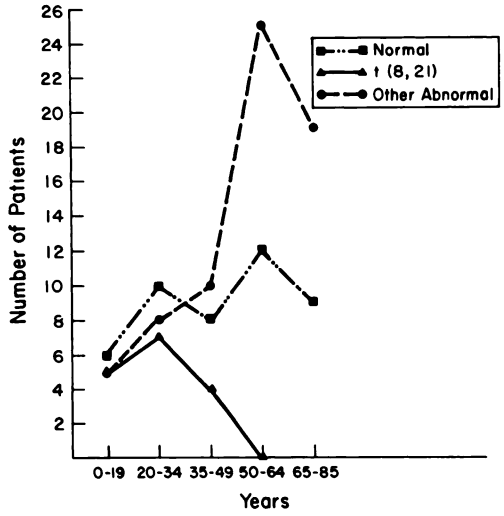


Chart 1. The relationship of karyotype pattern in leukemia cells to age of patients with AML (M1 and M2). Note the absence of patients with the t(8;21) above the age of 50 years and the sharp increase in the number of patients who have other chromosome abnormalities.

4). The percentages of patients with aneuploidy were 66, 42, and 64%, respectively. The majority of aneuploid APL patients had a t(15;17); except for one patient, they were young, all being in the 20- to 34-year age group, with a median age of 26 years. All patients with the t(15;17) were in the Chicago group.

Among the 7 patients with AMOL and chromosome abnormalities, 3 were +8, and one each was +1q, 5q−, or 7q−. None had abnormalities of 11q which have recently been reported in patients with the blastic variant of AMOL (2). Seven patients with EL were abnormal; 2 were +8, and 2 were 5q−. Within this small series, 7 of the 11 EL patients were abnormal; none of the patients was less than 30 years old.

## DISCUSSION

Nonrandom chromosome changes occur in human acute leukemia. In 2 subgroups of ANLL, specific chromosome translocations are observed, namely, a t(8;21) in AML (M2) and a t(15;17) in APL (M3) (15). The median age is substantially lower in patients with a specific translocation than in those with the same FAB type who had other abnormalities or who were chromosomally normal.

Three chromosomes are involved in a large number of abnormal karyotypes: −5; 5q−; −7; 7q−; and +8. This is the case especially in AML (M1 and M2), in which 60% of all cases of aneuploidy are the result of abnormalities of these chromosomes. The largest number of patients was in the AML (M1 and M2) category, which comprised more than one-half of the patients; this group has a high percentage of aneuploidy (65%), with a distinct difference in the incidence of abnormalities in younger (less than 50 years) (49%) compared with older (68%) patients. This may be related to reports by a number of investigators that there is a significant increase in the incidence of acute leukemia in individuals above the age of 50 years, particularly in males (3, 7).

I have observed that patients with leukemia secondary to treatment of some other disease, particularly malignant lymphoma, have a high frequency of AML, that they almost invariably are chromosomally abnormal, and that the abnormalities consistently involve chromosomes 5 and 7 (15, 16). It is, thus, tempting to speculate that those patients with AML (M1 and M2) *de novo* who have abnormalities involving chromosomes 5 and 7 may have developed leukemia as a result of exposure to mutagenic agents. On the other hand, an extra chromosome 8, which is the most frequent change in all of the myeloproliferative disorders, may provide a general proliferative advantage to myeloid cells and may be less directly related to exposure to mutagens. This possibility, as well as the relationship of specific chromosome changes to mutagenic agents in experimental animals, is discussed in more detail in Ref. 15. Only chromosome analysis of a larger number of patients, with availability of complete data on possible exposure to mutagens as a result of occupation, medical treatment, or hobbies, will answer this question.

It is important to recognize that, when our present techniques are used, many patients are found to have leukemia cells that

Table 3

*Seventy patients with AMMol (M4), grouped according to age and sex*

| | 0–19 yr | | 20–34 yr | | 35–49 yr | | 50–64 yr | | 65–85 yr | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Karyotype | F | M | F | M | F | M | F | M | F | M | | Total |
| −5,−7,7q− | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 2[a] | 3 | 0 F<br>3 M |
| +8 | 0 | 0 | 1 | 0 | 0 | 1[b] | 0 | 1 | 1 | 1 | 5 | 2 F<br>3 M |
| Other | 1 | 1 | 1 | 4 | 2 | 1 | 2 | 6 | 1 | 1 | 20 | 7 F<br>13 M |
| Normal | 1 | 2 | 5 | 3 | 3 | 4 | 6 | 5 | 7 | 6 | 42 | 22 F<br>20 M |
| Total | 2 | 3 | 7 | 7 | 5 | 7 | 8 | 12 | 9 | 10 | 70 | 31 F<br>39 M |

[a] One was −5.
[b] One also was −7.

Table 4

*Patients with other leukemias, grouped according to age and sex*

| | 0–19 yr | | 20–34 yr | | 35–49 yr | | 50–64 yr | | 65–85 yr | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Karyotype | F | M | F | M | F | M | F | M | F | M | Total |
| APL M3 | | | | | | | | | | | |
| t(15;17) | | | 3 | 2 | 0 | 1 | | | | | 6 |
| Other abnormal | | | | | | | | 1 | | 1 | 2 |
| Normal | | | 1 | 1 | | 1 | 1 | | | | 4 |
| AMOL M5 | | | | | | | | | | | |
| Abnormal | 1 | 1 | 2 | 0 | 1 | 1 | | | | 1 | 7 |
| Normal | 1 | 0 | 1 | 1 | 3 | 1 | 1 | 2 | | | 10 |
| EL M6 | | | | | | | | | | | |
| Abnormal | | | | | 1 | 2 | | 2 | 1 | 1 | 7 |
| Normal | | | | | 2 | | | 1 | | 1 | 4 |

appear to have a normal karyotype. These patients tend to have a better response to treatment and a longer survival than do patients with an abnormal karyotype (8), suggesting that these leukemia cells are biologically different from the abnormal ones in some as yet undetermined manner. Many patients also have abnormalities other than consistent translocations or those affecting chromosomes 5, 7, and 8. In AML, the incidence of these other abnormalities also increases with age; again, the question of whether these reflect chance phenomena or are secondary to mutagenic damage cannot be determined. The potential contribution of genetic susceptibility to this complex situation is still unresolved.

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