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Cytogenetics and occupational exposures in acute nonlymphocytic leukemia and myelodysplastic syndrome

by Stefania **Rodella,** MD,[1] Giovanni Ciccone, MD,[2,3] Giovanna Rege-Cambrin, MD,[2] **Paolo** Vineis, MD,[2] Working **Group** on the Epidemiology of Hematolymphopoietic Malignancies in Italy[4]

RODELLA S, CICCONE G, REGE-CAMBRIN G, VINEIS P, WORKING GROUP ON THE EPIDEMIOLOGY OF HEMATOLYMPHOPOIETIC MALIGNANCIES IN ITALY. Cytogenetics and occupational exposures in acute nonlymphocytic leukemia and myelodysplastic syndrome. ***Scand J Work Environ Health*** 1993;19:369—74. Studies on the association between cytogenetic aberrations and environmental or occupational exposures **of** patients with acute nonlymphocytic leukemia and myelodysplastic syndrome were selected from the literature and reviewed. Chromosome abnormalities **as** a whole and specific aberrations involving chromosomes ***5***, 7, ***8***, and 21 were considered. **Oc**cupational exposures were also considered as a whole or, whenever possible, as specific substances. An association between all occupations and any chromosome aberration has been observed in earlier studies but was not confirmed in later studies. Similar results have been observed when specific aberrations, or specific substances(ie, solvents) have been considered. Methodological issues and the comparability of the reviewed studies are discussed, and suggestions are made for refining epidemiologic investigations.

Key *terms*: chromosome aberrations, epidemiologic perspective, hematolymphopoietic malignancies, occupation, review.

Results from several studies suggest that some leukemias, particularly acute nonlymphocytic leukemia, may be caused by environmental or occupational exposures. Except for benzene, radiation, and alkylating agents, however, conclusive studies have not been performed (1).

Leukemias as a whole represent a heterogeneous group of diseases with different prognoses and responses to therapy, as well as different immunologic characteristics (1). Recent improvements in laboratory techniques for cytogenetic analysis have revealed nonrandom chromosome changes in the majority of patients with acute nonlymphocytic leukemia. Moreover, cytogenetic changes that are secondary to cytotoxic therapy for prior medical conditions have been described in almost all cases of this disease (2). These observations have suggested that environmental factors might be related to cytogenetic aberrations in human leukemias.

In myelodysplastic syndrome, representing clonal abnormalities of hematopoietic stem cells that may undergo leukemic proliferation (3). the proportion of patients with an abnormal karyotype can also be high, approaching 60% **(4). As** in acute nonlymphocytic leukemia. therapy-induced myelodysplastic syndromes have characteristic cytogenetic features; a possible association with exposure to environmental cytotoxic agents has been suggested for this category of disorders as well (3).

From an epidemiologic point of view, classifying patients with leukemia or other hematolymphopoietic malignancies by the presence of specific chromosome abnormalities may strengthen the possibility of identifying risk factors in etiologic research.

Recent studies have investigated the association between some occupational exposures and cytogenetic aberrations in patients with acute leukemia, particularly acute nonlymphocytic leukemia, and other malignancies of the hematolymphopoietic system, with different outcomes.

The purpose of this paper is to review such studies and discuss their results, especially focusing on methodological aspects and comparability issues and suggesting some priorities for future research.

Methods

All ***of*** the studies on the association between cytogenetic aberrations and environmental or occupational exposures among patients with acute leukemias or other hematolymphopoietic neoplasms were selected from the published literature. The literature search

[1] Institute ***of*** Pathology, Verona University, Italy.
[2] Department **of** Biomedical Sciences and Human Oncology, Turin University. Italy.
[3] Hospital Management Unit, Molinette Hospital. Local Health Unit No 8, Turin, Italy.
[4] Paolo Crosignani, Vittorio Demicheli, Arabella Fontana, Giovanna Masala, Lucia Miligi, Paola Pisani, Valerio Ramazzotti, Miranda Ricci. Stefania Rodella. Adele Seniori Costantini. Emanuele Stagnaro. Piero Tosi. Rosario Tumino. Clotilde Vigano`, Paolo Vineis.

Reprint requests to: Dr S Rodella. Istituto Anatomia Patologica, Policlinico Universitario Borgo Roma, 1-37134 Verona, Italy.

was based on data banks (Medline) and personal files. The chromosome aberrations were indicated with AA (clonal abnormalities in all analyzed cells) and AN (clonal abnormalities in a portion of the metaphases). Among the specific cytogenetic aberrations, we singled out those analyzed in all (or most) studies, namely, complete or partial loss of chromosome 5 (-5/5q-), monosomy 7 or deletion of its long arm (-7/7q-), trisomy 8 and 21, and translocation t(8;21). This choice was made to compare the frequency of specific abnormalities in different studies and their association with exposure. As the loss of sequences belonging to chromosomes 5 and 7 is the hallmark of treatment-induced hematological malignancies (5), these chromosome abnormalities were analyzed separately to disclose a possible preferential involvement of these rearrangements also in environmental-induced acute leukemias.

Eight studies were selected, published between 1978 and 1990. Seven of them (6—11) included cases of acute nonlymphocytic leukemia, and only one concerned cases of non-Hodgkin's lymphoma (12). A paper published in 1979 (13) was not completely comparable with the other studies because it also included patients with nonclonal chromosome aberrations. Therefore, this study was not reviewed. In one of the seven studies regarding cases of acute nonlyniphocytic leukemia, cases of myelodysplastic syndrome were also considered (11). In another study myelodysplastic syndrome, chronic myeloid leukemia, chronic lymphatic leukemia. and acute lymphocytic leukemia were considered in addition to acute nonlyniphocytic leukemia (14).

This review mainly refers to acute nonlymphocytic leukemia and myelodysplastic syndrome. The only study regarding non-Hodgkin's lymphoma has been considered separately in the text.

All of the studies included patients with a diagnosis of acute nonlymphocytic leukemia or myelodysplastic syndrome and an available cytogenetic analysis. Cases with a previous diagnosis of myeloproliferative disorder. cases receiving cytotoxic therapy before cytogenetic analysis. and cases of secondary leukemia were always excluded or analyzed separately. Therefore, it is reasonable to assume that all of the cases considered in these studies were incident (ie. newly diagnosed) cases, even though this definition was clearly used in only four papers.

The recruitment of cases was prospective in three studies (9. 10. 14). In four a large proportion of the cases was identified retrospectively (6—8. 11). All of the reviewed studies can be considered analyses of case series, but in one the term "case-control study" was used (11), because the comparison group (acute nonlyniphocytic leukemia patients without chromosome aberrations) was selected to resemble the case group as nearly as possible.

In each study sonic cases were excluded because of insufficient information on occupation. The exclusion was based on poor quality of clinical records in three studies (6—8) and on refusal or other impediments to interview in two studies (11, 14). The proportion of cases excluded was rather important in some of the studies (6, 8, 9). In one study (7) 22% of the patients were excluded because the chromosome examination had failed or there was insufficient information about occupation, but the number of patients in each category was not specified in the paper. Finally, the proportion of patients excluded because of a missing cytogenetic test (44 of 367, 12%) was reported in only one study (10).

The type of information collected was rather poorly defined in four studies (6—9) ("previous or present occupation"). In two studies (11, 14) the patients were interviewed about their lifelong occupational history. Finally, in one study (10). the occupational history of the patients was classified according to three categories (usual, current, exposure to specific agents).

Allegedly, in all of the studies data on occupation and exposure were collected and categorized by one or more experts who had no knowledge of the cytogenetic status of the subjects.

The number of exposed and unexposed patients with presence or absence, respectively, of abnormal karyotype was reported or computed from the original data, whenever possible.

The results of each study were expressed using the odds ratio as a measure of the association between chromosome abnormalities and occupational exposures considered as a whole and, whenever possible, as specific substances. The odds ratio was reported in the original paper in a few studies; when not available it was computed by us from the published raw data. Confidence intervals for the odds ratios were also computed by us, according to Miettinen (15), when not present in the original paper.

Results

The most relevant aspects of each study were synthesized, and the results are given in two tables, to make possible a comparative interpretation of study designs (table 1) and the results (table 2). The following comments are presented according to the layout of tables 1 and 2.

Each study had eligible cases that were not included in the subsequent analyses either because a cytogenetic test was not available (see footnotes to table 1) or insufficient data on occupational history were collected. The hypothesis of an association between a missing cytogenetic test and probability of exposure, although rather unlikely, cannot be definitely excluded. This might be a potential source of bias.

The exclusion of all of the prevalent cases and of previously treated patients is very important when one focuses on environmental exposures. in order to exclude all secondary chromosome rearrangements

Table 1. Desig nonlymphocyti

Authors	Path-ology	
Mitelman et al, 1978 (6)	ANLL	
Mitelman et al, 1981 (7)	ANLL	I
Golomb et al, 1982 (8)	ANLL	I
Mitelman et al, 1984 (9)	ANLL	I
Crane et al 1989 (10)	ANLL	I
Narod & Dube 1989 (11)	ANLL MDS	C
Vineis et al 1990 (14)	ANLL MDS	Ir

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d Four hundred ant and one because and 9 nonrespon
e Out of 270 respo Out of 97 nonres
f Fifteen cases an
g Cases with chron with MDS were

Table 1. Design of studies on cytogenetics and occupational exposures in hematolymphopoietic malignancies.[a] (ANLL = acute nonlymphocytic leukemia, MDS = myelodysplastic syndrome, CT = chemotherapy, RT = radiotherapy)

Authors	Pathology	Selection criteria	Recruitment	Eligible subjects (N)	Analyzed subjects (N)	Excluded subjects N(%)	Sources of information	Type of information	Occupational exposures	Non-occupational exposures	Exposure attribution
Mitelman et al, 1975(6)	ANLL	Incident cases?, no previous myelopro-liferative disorders, no previous treatment, age > 15 years	Retrospective 1 July 1972—31 Oct 1977	93	56	Insufficient data on occupation 37 (39%)	Clinical records	Previous or present occupation	Solvents, insecticides. petroleum products	Not investigated	Blindly (1 person)
Mitelman et al, 1981(7)	ANLL	Incident cases?, no previous myelopro-liferative disorders, no previous treatmenl, age > 15 years	Retrospective? 1972—1980 1974—1980	208?[b]	162	Insufficient data on occupation ??	Clinical records (+ interview of cases and relatives)	Previous or present occupation	Solvents, insecticides, petroleum products	Not investigated	Blindly (1 person)
Golomb et al, 1982 (8)	ANLL	Incident cases?, no previous myelopro-liferalive disorders, no previous treatment, age > 17 years	Retrospective Feb 1970—April 1981	128	74	Insufficient dala on occupation 54 (42.2%)	Clinical records (+ interview of relatives)	Previous or presenl occupation	Insecticides, solvents + chemicals + metals, petroleum products	Hobbies (in not exposed)	Blindly (3 persons)
Mitelman et al, 1984 (9)	ANLL	Incident cases?, age > 16 years	Prospective 1 Jan 1980—31 March 1982	595[c]	361	Insufficient data on occupation 234 (39.3%)	Personal interview (standardized questionnaire)	Previous or present occupation	Insecticides, chemicals, radiation. petroleum products, metals/ minerals, biological agents, undefined exposure	Not investigated	Blindly (? number of persons)
Crane et al 1989 (10)	ANLL	Incident cases, age > 18 years. resident in Texas	Prospective 1 Jan 1976—30 June 1983	323[d]	235[e] (270 respondents)	Refusals or not located: 88 (27%) (97 nonrespondents)[f]	Personal interview (N = 89), telephone interview (N = 57), postal questionnaire (N = 124) (standardized questionnaire)	Usual occupation. current occupation. specific exposure	Asbestos, benzene, pesticides, dyes, glues, varnishes, metals, paints, radialion	CT or RT, smoking, alcohol, hobbies	A priori malrix
Narod & Dubé, 1989 (11)	ANLL MDS	Cases: no previous CT or RT chromo. some aberration 5 or 7; controls: no chromo. some aberration 5 or 7	Case-referent, retrospective	44 cases, 38 referents	44 cases, 38 referents	Insufficient data on occupation ??	Telephone interview of subjects and their relatives	Occupalional history	Metals, pesticides. radiation. chemicals, petroleum products	Not investigated	Blindly (3 specialists in occupational medicine)
Vineis et al, 1990(14)	ANLL MDS	Incident cases, age > 15 years	Prospective Oct 1988—June 1989	22 6[n]	22 6	—	Personal interview (standardized questionnaire)	Occupational history	Organic solvents	Smoking	Blindly (1 person). 3 exposure categories

[a] Unexposed categories of the studies: reference 6: housewives, students and white-collar workers; reference 7: housewives. students, white-collar workers and others; reference 8: housewives. students. white-collar workers and others; reference 9: housewives, students, white collar workers and others; reference 10: managers, [illegible] workers and others; reference 11: those exposed < 1 year in 30 last years or disagreement among experts; reference 14: —.

[b] The 162 patients analyzed represent 78% of the total number of patients identified by the authors; 22% was excluded because of failure of the cytogenetic examination or insufficient data on occupation (the number in each category of clinical exposure not reported).

[c] Six hundred and sixty patients were initially identified. but 65 of them were excluded because of their age (< 16 years).

[d] Four hundred and sixty patients were initially identified. but 70 were excluded because they were foreign, two because of their age (< 18 years) and 65 because of a previous diagnosis. Moreover. we have not included in the number of eligible cases (N = 367) the 44 patients (35 respondents and 9 nonrespondents) with a cytogenetic test insufficient or not performed.

[e] Out of 270 respondents 31 had an insufficient test. In four did not have a test performed.

[f] Out of 97 nonrespondents seven had an insufficient test and two did not have a test performed.

[g] Fifteen cases and one reference with secondary leukemia are not considered.

[h] Cases with chronic myeloid leukemia, chronic lymphatic leukemia. and acute lymphatic leukemia are not considered in the review. 11 patients with MDS were initially identified. but five of them did not have a test performed.

Table 2. Results of studies on cytogenetics and occupational exposures in hematolymphopoietic malignancies (OR = odd ratio, 95% CI = 95% confidence interval, AA = clonal abnormalities in all analyzed cells, AN = clonal abnormalities in a portic of the metaphases)

Authors	Patients with chromosome aberrations/ eligible patients	Exposed patients/ analyzed patients	Type of exposure	Type of chromosome aberration	Exposed, chromosome aberration		Unexposed, chromosome aberration		OR	95% CI
					Yes	No	Yes	No		
Mitelman et ai, 1978 (6)	27/56 (48.2 %[a])	23156 (41.1 %)	All	AN + AA	19	4	**8**	**25**	14.80	4.29—51.34
				−5/5q-, −7/7q-	9	4	1	25	56.25	9.15—345.6
				+8, +21, t(8;21)	10	4	1	**25**	***62.50***	10.35—377.3,
			Solvents	AN + AA	13	—	**8**	**25**	**[81.25][b]**	[1.62—568.0
			Insecticides	AN + AA	3	—	**8**	**25**	[18.75][b]	1.63—216.1'
			Petroleum products	AN + AA	3	4	**8**	**25**	2.34	0.43—12.67
Miteiman et al, 1981 (7)	741162 (45.7 %[a])	521162 (32.1 %)	All	AN + AA	39	13	35	75	6.43	3.16—13.08
				−5/5q-, −7/7q-	17	13	13	75	7.54	3.15—18.08
				+8, +21, t(8;21)	19	13	**8**	75	13.70	5.49—34.17
			Solvents	AN + AA	24	3	35	75	17.14	6.04—48.59
			Insecticides	AN + AA	**11**	—	35	**75**	[47.14][b]	7.90—281.2~
			Petroleum products	AN + AA	4	10	35	75	**0.86**	0.25—2.94
Golomb et al, 1982 (8)	37174 (**50.6%[a]**)	16/74 (21.6 %)	All	AN + AA	12	**4**	***25***	33	3.96	1.19—13.18
				−5/5q-, −7/7q-	**8**	4	7	33	**9.43**	2.45—36.26
				+8, +21, t(8;21)	1	4	7	33	1.18	0.11—12.52
			Solvents + chemicals + metals	AN + AA	5	2	**25**	33	3.30	0.63—17.37
			Insecticides	AN + AA	1	—	**25**	33	**[2.64][b]**	0.09—74.59
			Petroleum products	AN + AA	6	**2**	**25**	33	**3.96**	0.80—1970
Mitelman et al, 1984 (9)	165/299 (**55.2 %[c]**)	103/299 (34.0 %)	All	AN + AA	69	34	96	100	2.11	1.30—3.46
				−5/5q-, 7/7q-	14	24	**22**	100	1.87	0.87—4.04
				+8, +21, t(8;21)	15	**34**	20	100	2.21	**1.02—4.75**
			Chemicals	AN + AA	24	15	96	100	1.67	0.83—3.36
			Insecticides	AN + AA	20	11	96	100	1.89	0.87—4.13
			Petroleum products	AN + AA	17	7	**96**	100	2.53	1.03—6.23
			Minerals	AN + AA	**8**	1	**96**	100	8.33	1.41—49.38
Crane et al 1989 (10)	178/323 (55.1 %)	621235 (26.4 %)	All (usual)	AN + AA	38	24	**88**	**84**	1.50[d]	0.84—2.73[d]
		461235 (19.6 %)	All (current)	AN + AA	29	17	97	91	1.70[d]	0.82—3.106
				−5/5q- 7/7q-	—	**23(?)**	97	**91**		
				+8, +21 t(8;21)	6(?)	**36(?)**	97	91	**0.16[d]**	
			Benzene	AN + AA	6	5	?	?	**1.10[d]**	0.30—3.W
			Pesticides	AN + AA	10	15	?	?	**0.60[d]**	0.30—1.40[e]
			Metals	AN + AA	18	12	?	?	1.504	0.70—3.m
			Asbestos	AN + AA	17	7	?	?	**2.60[d]**	1.00—6.W
			Dyes. glues	AN + AA	16	17	?	?	**0.80[d]**	**0.40—1.80[e]**
			Paints	AN + AA	16	6	?	?	**2.60[d]**	**0.90—6.80[e]**
			Radiation	AN + AA	6	5	?	?	1.10[d]	
Narod & Dubé, 1989 (11)	44182 (53.6 %)	17 cases144 (38.6 %) 14 referents/38 (**36.8 %**)	All	Abnormality 5 or 7	17	14	**27**	**24**	1.18'	0.40—3.31[e]
			Chemicals	Abnormality 5 or 7	11	10	27	**24**	0.91'	0.29—2.84[e]
			Pesticides	Abnormalily 5 or 7	**2**	1	27	24	1.78'	0.15—21.10[e]
			Petroleum products	Abnormaiity 5 or 7	**4**	5	**27**	24	0.79'	0.17—3.59[e]
			Metals	Abnormality 5 or 7	6	3	27	24	2.12'	0.42—10.60[e]
			Radiation	Abnormality 5 or 7	0	**2**	27	**24**	—[f]	—[e]
Vineis et al, 1990 (14)	10128 (35.7 %)	9/28 (32.1 %)	Solvents	AN + AA	*3*	6	7	12	1.00'	0.20—4.70[e]

[a] This percentage was computed only for analyzed cases because the number of chromosome abnormalities in patients excluded from the analysi: was not mentioned by the authors (See the text)
[b] Since the value in one of the cells is 0, the OR is equal to inlinity. The value between brackets has been computed using correction to 0 5 Only palients 30 years and older are considered (separately analyzed in the original article).
[d] OR reported in the original article.
[e] 95% CI reported in Ihe original article.
[f] Age-adjusted OR reported in the Original article

or abnormalities induced by antineoplastic therapies. This criterion of selection was correctly adopted by all of the authors.

In the earlier studies with a retrospective recruitment of patients (6—8) most of the inforniation about occupational exposures was drawn from clinical records with occasional integration from other sources of data (ie, telephone interview of patients or their next-of-kin). Moreover the type of information collected on occupation was not clearly described. and the expression "previous or present occupation" was used. On the contrary, a better quality of information would be expected from prospective studies (9, 10, 14) in which standardized questionnaires were used for personal interviews and a lifelong occupation history was collected.

The percentage of patients showing chromosome abnormalities over the total of eligible patients was similar among the studies (table 2) and ranged. in most of them. between 45.7 and 55.2%. In the study of Vineis et al (14) a proportion of 35.7% was observed, hut the small number of cases might explain

ic malignancies. (OR = odds
ıal abnormalities in a portion

OR	95% CI
14.80	4.29—51.34
56.25	9.15—345.61
62.50	10.35—377.39
(81.25)[b]	11.62—568.04
(18.75)[b]	1.63—216.19
2.34	0.43—12.67
6.43	3.16—13.08
7.54	3.15—18.08
13.70	5.49—34.17
17.14	6.04—48.59
(47.14)[b]	7.90—281.28
0.86	0.25—2.94
3.96	1.19—13.18
9.48	2.45—36.26
1.18	0.11—12.52
3.30	0.63—17.37
(2.64)[b]	0.09—74.59
3.96	0.80—19.70
2.11	1.30—3.46
1.87	0.87—4.04
2.21	1.02—4.75
1.67	0.83—3.36
1.89	0.87—4.13
2.53	1.03—6.23
8.33	1.41—49.38
1.50[d]	0.84—2.73[d]
1.70[d]	0.82—3.10[d]
0.16[d]	
1.10[d]	0.30—3.80[e]
0.606	0.30—1.40[e]
1.506	0.70—3.20.
2.606	1.00—6.50[e]
0.80[d]	0.40—1.80[e]
2.60[d]	0.90—6.70[e]
1.10[d]	0.30—3.60.
1.18[f]	0.40—3.31[f]
0.91[f]	0.29—2.84[e]
1.78[f]	0.15—21.10[e]
0.79[f]	0.17—3.59[e]
2.12[f]	0.42—10.60[e]
—[f]	—[e]
1.00[f]	0.20—4.70[e]

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of cases might explain

this difference. In three studies (6—8) the results of the cytogenetic test were not reported for patients excluded from the analyses because of poor information on occupation. The blind procedure for exposure assessment should have avoided a selection bias with regard to the chromosome findings. The reported prevalences of aberrations closely approached data reported by other authors. In fact, in the earlier literature, approximately half of the patients with acute nonlymphocytic leukemia were found by different authors to have clonal aberrations and, more recently, at least two-thirds of these patients have been estimated to be affected by recognizable clonal chromosome abnormalities at diagnosis (16).

The proportion of exposed patients showed some variations among the studies, ranging between 4 1.1% (6) and 19.6% (10) for all exposures as a whole. These discrepancies could reflect either a different prevalence of exposure among the populations under study or the application of different criteria in the exposure assessment. A decreasing prevalence of exposure among patients with chromosome aberrations and, conversely, an increasing prevalence among patients without chromosome aberrations were observed when earlier (ie, 6, 7, 9) and later (ie, 11, 14) studies were compared. Selection bias in the earlier studies cannot be ruled out.

The odds ratios observed in the earlier studies indicated an association, even though of different strength, between all of the occupations considered and any chromosome aberration, but these observations were not confirmed in the later studies (table 2). A similar difference between earlier and later studies was observed when specific aberrations involving chromosomes 5 and 7 or trisomy 8 and 21 were analyzed (table 2). The differences observed among the studies were even more impressive since some of them were conducted with very similar methods. However, the very large confidence intervals in the earlier studies motivate special caution when conclusions are drawn from these results. Similar caution must be applied when the association between solvent exposure and any chromosome abnormality is considered.

Insecticides or pesticides were considered in six studies (6—11). The odds ratios were not significant (9—11), or the numbers observed were too small (6—8). Exposure to petroleum products was analyzed in five studies (6—9, 11). and the odds ratios ranged between 0.79 and 3.96. Other exposures (metals, minerals, dyes. paints, radiation) or some specific chromosome aberrations were analyzed only in a few studies, and it was not possible to compare the results.

Compared with the several studies on acute leukemias, only one study, to our knowledge. has been performed on non-Hodgkin's lymphoma (12). The paper discusses the relation between chromosome aberrations in 54 incident cases of non-Hodgkin's lymphoma and occupational exposure to organic solvents, assigning patients to three categories according to the number of cytogenetic events producing clonal aberrations. (This number was used as an indicator of karyotypic complexity.) The results suggest that chromosome aberrations, particularly a 14q+ abnormality, are more frequent in patients with occupational exposure to organic solvents. This finding seems to be similar to findings concerning acute nonlymphocytic leukemia. The number of patients in this study was very small, and more formal investigations are needed to confirm these results.

Discussion

The majority of the studies published so far, to our knowledge, concerning the association between chromosome aberrations and occupational exposures in hematolymphopoietic malignancies are limited to acute nonlymphocytic leukemia. There are probably different reasons for this choice. Its incidence has been increasing over time in the United States in the last few decades (1), especially among men. Gender and age-related differences in temporal trends suggest that some of the increased incidence may be real and possibly attributed to occupational or environmental exposures (1). Many epidemiologic studies have suggested the role of environmental factors like benzene or radiation in the etiology of acute nonlymphocytic leukemia. Chromosome rearrangements are recognizable at diagnosis in at least two-thirds of the patients with acute nonlymphocytic leukemia (16).

The results of our review deserve some important comments. Refinements in cytogenetic techniques over time are not sufficient to explain the discrepancies observed among the studies. First, the overall prevalence of chromosome abnormalities in acute nonlymphocytic leukemia is similar in all of the reports, and these data make the results largely comparable. Second, the specific abnormalities which have been analyzed, namely, -5/5q- -7/7q-, trisomy 8 and 21, and t(8;21) are rather gross rearrangements which can be detected also in poorly banded chromosome preparations.

Conversely, methodological issues in study design, especially concerning the retrospective recruitment of patients, poor definitions of occupational exposures. the exclusion of large proportions of eligible patients, and a lack of analysis of confounding factors. like age, gender and other exposures. are likely to influence strongly the results of the earlier studies. In addition, a chance effect cannot be excluded completely.

Finally, a clear causative role in leukemogenesis has not been established for broadly defined exposures like "solvents" or "petroleum products." The association between chromosome aberrations and chemical exposures should follow a clear demonstra-

tion of a causative role of such exposures in the etiology of acute nonlymphocytic leukemia.

In conclusion, further epidemiologic investigations are needed, that fulfill standard epidemiologic requirements of analytical studies such as the prospective enrollment of patients, control of selection and information biases, collection of accurate information on both exposures and confounders, and adequate statistical analysis. In addition, quality control of cytogenetic tests should be performed, and the source of interobserver variability should be studied. Internal comparison of case series for cytogenetic damage should be focused on known risk factors for leukemias.

In addition, little is known about the etiology of myelodysplastic syndrome, and an investigation on exposure to environmental cytotoxic agents was recommended in a recent report of a cooperative study group (3). Including this group of diseases in future research on the relationship between cytogenetics and chemical exposures in hematolymphopoietic malignancies would be of great interest.

Acknowledgments

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