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CYTOGENETIC AND ENVIRONMENTAL FACTORS IN THE ETIOLOGY OF THE ACUTE LEUKEMIAS IN ADULTS

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Much has been written about the leukemias in adults. Despite the extensive literature devoted to the subject, little has been learned about risk factors for the disease (1–3). Studies have shown that persons with high-dose radiation exposure (4), occupational exposure to benzene (2, 5), and prior treatment with chemotherapeutic agents (6, 7) are at increased risk of leukemia, yet these exposures are relatively rare and not likely to account for many of the cases seen today. Results from a variety of studies suggest that a proportion of the leukemias, particularly acute nonlymphocytic leukemia, might be due to environmental or occupational exposures, but definitive studies have not been done. Continuing increases in the incidence of acute leukemias through the late 1970s, especially for acute nonlymphocytic leukemias among males, are also consistent with an environmental etiology.

The apparent lack of success in identifying important environmental risk factors for leukemia has led to the widely held belief that application of epidemiologic methods to the study of the leukemias in adults is not likely to yield further insights. However, closer inspection of the literature indicates that few well-controlled epidemiologic studies have actually been conducted. Studies have generally included too few leukemia cases for evaluation of risk factors or combinations of risk factors, have included inappropriate or no comparison groups, have lacked rigor in defining and/or classifying leukemia patients, and have paid insufficient attention to the adequacy of available methods for identification of low-dose exposures.

In 1980, Szklo (1) posed the question, "Are further epidemiologic studies of leukemia needed?" His answer was a qualified "yes", if attention is paid to refinement of disease definition so that less heterogeneous groupings of patients can be identified. Recent work involving the cytogenetic classification of leukemia patients suggests a promising avenue for making such refinements.

Most epidemiologic studies of leukemia have not distinguished between leukemia subtypes. Recent reports suggest that the leukemias represent a heterogeneous group of disorders with possibly differing risk factors. Inconsistent findings in different studies might, therefore, have resulted from differential cell type distributions. Even discrete clinical-pathologic categories of leukemia, such as acute lymphocytic or nonlymphocytic leukemia, appear to include heterogeneous subgroups. Differential prognosis and treatment response as well as new immunologic and cytogenetic assays suggest that acute nonlymphocytic and acute lymphocytic leukemias are each comprised of different diseases with similar appearance (1, 8–11). In past epidemiologic studies, the identification of risk factors may, therefore, have been limited by the inability to define precise subgroups of patients.

Recent improvements in laboratory techniques for cytogenetic analysis of banded chromosomal preparations have revealed

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nonrandom chromosome changes in the majority of patients with acute leukemia (8–12). Several recent observations suggest that for certain animal models and patient groups, the cytogenetic changes may have played a critical role in at least some of the steps leading to malignant transformation (13, 14). These include consistent cytogenetic changes in acute nonlymphocytic leukemia that are secondary to chemotherapy (13, 15), suggestions of similar changes in patients with prior occupational exposures (12, 13, 15, 16), and the strong concordance between the breakpoints observed for chromosome translocations and deletions and the location of cellular oncogenes (14). If true, these associations suggest that environmental or genetic factors may be more strongly associated with cases of leukemia with specific cytogenetic aberrations than with all cases of leukemia. The ability to classify leukemia patients by the presence or absence of specific chromosomal abnormalities may strengthen our ability to identify risk factors in epidemiologic studies.

Kessler and Lilienfeld (17) proposed in 1969 that large cohorts of individuals with chromosomal aberrations induced by specific exposures should be followed to determine the incidence of leukemia. They also proposed case-control studies in which leukemia cases and healthy population controls could be compared for the presence of specific chromosome aberrations. Such studies have not yet been feasible, but recent advances in cytogenetics may allow for progress in understanding the relation between exposures, chromosome changes, and leukemia risk. The development of techniques that can be used to classify patients by the presence of specific karyotypic abnormalities may make it easier to identify certain risk factors, although the etiologic significance of these changes is unknown.

The following review addresses the role played by chromosome changes and environmental exposures in the development of acute leukemia. The literature on occupational and environmental exposures, family disease histories, and associations between cytogenetic changes and both environmental exposures and leukemia risk will be discussed, and specific suggestions for future research directions will be made. The emphasis throughout will be on the acute leukemias, particularly the acute nonlymphocytic leukemias, because the evidence for an environmental etiology of this leukemia subtype is strongest. Unfortunately, it is not always possible to single out this subgroup in studies that have been reported. Therefore, relevant studies dealing with all leukemias combined will also be cited.

Incidence and time trends

The leukemias account for approximately 3 per cent of total cancer incidence and 4 per cent of cancer mortality in the United States. The average annual incidence of leukemia in the United States is 8 per 100,000 for females and 11 per 100,000 for males (18). Leukemia is more common among whites than among nonwhites and for most cell types is more common among males than females. In childhood, acute lymphocytic leukemia predominates. Acute lymphocytic leukemia is also seen in adults, but accounts for only a small percentage of cases (5 per cent of leukemias in adults over age 40 years). Acute nonlymphocytic leukemia, which is not often seen in childhood, accounts for approximately 30 per cent of all leukemias, and over 85 per cent of acute leukemias in persons over age 40 years. The acute nonlymphocytic leukemias include a varied group of bone marrow cancers with many clinical and epidemiologic similarities (3). Acute myeloblastic or myelocytic leukemia accounts for approximately 75 per cent of the acute nonlymphocytic leukemias. Other subtypes include acute promyelocytic, acute myelomonocytic, acute monocytic, and acute erythrocytic leukemia.

An early steep rise in reported leukemia mortality from 1900 to 1940 has been followed by a lessening in the rate of rise. This is probably due to a leveling off in medical advances that would improve diagnostic

precision and to developments in treatment for some forms of leukemia (3). Recent US mortality data show very little change in leukemia death rates over time except for acute nonlymphocytic leukemia, which increased 20 per cent from 1969 to 1977 (19). The incidence of acute nonlymphocytic leukemia also increased over time. Some of the apparent increase can be explained by improved diagnostic precision and concurrent declines in incidence of acute unspecified leukemias (20–22). However, Swedish and US data demonstrate an increase in the incidence of acute nonlymphocytic leukemia for males but not for females, and show age-related differences in time trends (21, 22). Danish cancer incidence data also demonstrate a threefold increase in acute leukemias from 1943 to 1977 (23). The increased incidence was primarily due to acute myelocytic leukemia, but other forms of acute leukemia increased as well. In the United States, little change in overall acute lymphocytic leukemia incidence occurred between successive cancer incidence surveys in 1947–1948 and 1969–1971, but the incidence of acute myelocytic leukemia more than doubled (24). Data from the Connecticut Tumor Registry show that the incidence of acute lymphocytic as well as acute nonlymphocytic leukemia increased among males between 1935 and 1982 (22). Recent data from the Surveillance and End Results Program, however, suggest that incidence rates may no longer be increasing. Sex- and age-related differences in trends through at least 1980 suggest that some of the increased incidence may be real and possibly attributed to occupational or environmental exposures (21).

Genetic and familial factors

Chromosome disorders and familial susceptibility may be factors in the etiology of both acute nonlymphocytic and acute lymphocytic leukemia (2, 3, 17, 25). Studies have suggested increased leukemia risk for Eastern European Jews (26, 27) and decreased leukemia risk for Oriental populations (3, 17, 25). Other reports suggest increased risk for acute lymphocytic leukemia in genetically isolated populations where a high degree of consanguinity may be an important factor (28). There have been numerous reports of multiple cases of leukemia within families (29–31). Familial aggregation has been reported for both acute lymphocytic and acute myelocytic leukemia. The concordance for leukemia subtype suggests that such occurrences are not due to chance alone (3), but common exposures or undetected genetic syndromes cannot entirely be ruled out. Inbreeding may increase leukemia risk and has been reported to be a factor in some of the families with multiple leukemia cases (29, 32). Case-control studies have also shown that leukemia patients are more likely than others to have family members with leukemia, although most studies have had some methodological problems (3, 17, 25, 33). For example, in the study by Videbaek (33), the excess cancer incidence in families of leukemia patients was due to a lower than expected cancer incidence among control families, suggesting underreporting for controls.

Twin studies suggest increased concordance for childhood leukemia among monozygotic twins (3, 17, 34–36), although there may be a bias toward identifying and reporting concordant pairs. The selected nature of the twin populations studied and the shared pre- and postnatal environment of twins make interpretation of these reports difficult. Pre-conception chromosome abnormalities in parents passed on to their offspring might result in higher concordance for leukemia and other diseases among monozygous twins. Studies involving chromosome analysis of fraternal and identical twins with acute myelocytic leukemia and other acute leukemias, however, tend to support the hypothesis that a single leukemic transformation in utero leads to the establishment of a malignant clone in each twin via shared fetal circulation of monozygotic twins rather than an alternative hypothesis of increased genetic susceptibility for leukemia (37). Environmental ex-

posures may also be transmitted to monozygous twins via placental cross circulation. Studies in an adult twin population have not shown any concordance for the occurrence of leukemia (36).

Persons with certain chromosomal disorders, such as Down's syndrome or Klinefelter's syndrome, appear to be at increased risk for acute lymphocytic and acute nonlymphocytic leukemia (38). Down's syndrome is also more common in family members of leukemia cases (17, 39, 40). Persons with other disorders, such as Fanconi's anemia, ataxia-telangiectasia, or Bloom's syndrome, which are characterized by increased chromosome breakage, are also at increased risk of acute leukemia (3, 41–43). In these cases, leukemia may result from an interaction between chromosomal aberrations and environmental exposures (3).

Certain exposures, such as benzene (5, 44, 45), ionizing radiation (46), antineoplastic agents (47, 48), and other chemicals and drugs (49–51), are known to cause both chromosomal aberrations and leukemia. There are no data, however, to establish a causal sequence of events. Exposure to agents such as these may cause leukemia through chromosome changes, may cause both leukemia and chromosome changes which are unrelated, or may cause chromosome changes which increase an individual's susceptibility to effects from additional exposures.

Environmental risk factors

High-dose exposure to ionizing radiation and occupational exposure to chemical solvents, such as benzene, have been shown to be risk factors for leukemias including acute leukemias. High-dose exposures, however, are likely to account for only a small number of cases, and there remains some uncertainty over whether low-dose exposures also increase leukemia risk. Other factors, such as exposure to pesticides and insecticides, exposure to other petroleum products, and specific medications, have all been linked with leukemia risk, but further studies are needed. Evidence for some of these exposures (radiation, chemicals, and cigarette smoke) is reviewed briefly below. Much of the data comes from case reports or ecologic studies which provide only indirect evidence of an association, or from studies of specific occupational cohorts where only a small number of leukemia cases are seen after extensive follow-up. Other studies have been limited to cases under age 20 years, and it is not necessarily possible to generalize findings from these studies to other age groups. With only a few exceptions, case-control studies have included only small numbers of cases with specific leukemia subtypes or have not differentiated between subtypes in reporting findings. Many occupational exposures that have been linked with leukemia risk are also found in other settings (2), but risk from household exposure to some of these chemicals has not been studied. Furthermore, only a small number of occupational chemical exposures have been evaluated, yet it is likely that many more are potential leukemogens (2, 3).

Radiation

Studies of populations exposed to ionizing radiation clearly demonstrate increased acute leukemia risk associated with moderate to high doses, but effects from low-dose exposures are less certain (4). Much of the evidence linking radiation exposure with leukemia risk comes from studies of Japanese survivors of the atomic bomb (4, 52–54). These studies demonstrated a relatively short latency of 5–21 years between exposure and leukemia, but increased risks for exposed survivors continued to be apparent through the late 1970s (52, 54). Cell-type and extent of risk tended to vary with age at exposure, dose, and type of bomb used (53). Acute myelocytic leukemia was more common among those exposed in Nagasaki to primarily gamma radiation. Individuals exposed in childhood were at increased risk of acute lymphocytic leukemia through the late 1950s. Other studies that demonstrate increased leukemia risk in-

clude studies of radium workers with significant lifetime exposures to radium isotopes (55), studies of patients irradiated for ankylosing spondylitis (4, 56), studies of patients irradiated for other benign conditions, e.g., menorrhagia (57), early studies of radiologists (58), and studies of patients receiving ^{32}P for polycythemia vera (59).

Not all studies of these groups have been positive, however (60–62). Findings are least consistent for low-dose exposures. A study of military personnel exposed during nuclear test explosions demonstrated an increased incidence of acute myelocytic leukemia for those exposed (63), but no leukemia excess was seen for workers at a nuclear facility (64) or nuclear shipyard (65).

Excess leukemia has also been reported in some studies of persons receiving therapeutic irradiation of the head and neck. Pochin (66) reported a slight excess for patients who received ^{131}I treatment for thyroid cancer, although large follow-up studies of patients treated with ^{131}I for hyperthyroidism have generally been negative (67). Excess leukemia incidence has also been reported for individuals treated in childhood for benign head and neck conditions such as tinea capitis (68), and thymic enlargement (69). Predominantly acute leukemias were reported. Other studies of head and neck irradiation have been negative (70).

Studies of very low doses, such as those from diagnostic irradiation, are also inconclusive. Incidence of acute leukemia was increased for patients who received diagnostic x-rays involving thorotrast (71), but because the half-life of thorotrast is quite long, these patients probably received significant lifetime radiation exposure. In the Tristate Leukemia Study (72), adult males with acute myelocytic leukemia were more likely than controls to have had multiple diagnostic x-rays. Results were not comparable for female cases, but the quality of data for females was questionable. Gunz and Atkinson (73) also found a significant association between diagnostic x-ray and acute myelocytic leukemia. The question of leukemia risk from diagnostic x-ray remains controversial (74). A recent study by Linos et al. (75), which included 54 cases with acute myelocytic leukemia among 138 total cases, was negative, but may have been too small to detect a risk.

Background radiation has also been suggested to cause acute leukemia. In a study of 42 deceased patients with acute myelocytic leukemia and 244 controls, Flodin (76) found a twofold increase in leukemia risk associated with a high background gamma irradiation score. Although not statistically significant, there was even a trend of increasing risk with increasing score. A subsequent study (77) with living cases and controls confirmed this finding.

Increased risk of leukemia, particularly acute myelocytic leukemia, has also been suggested for persons who receive exposure to non-ionizing forms of radiation. Risks are increased for men employed in a number of occupations that involve exposure to electrical currents (78). Increased risks for persons in electrical occupations could, however, be due to other exposures such as metal fumes or solvents rather than electrical currents. Leukemia incidence is also reported to be increased for children and adults living near high-intensity wires (79), but others have found no increased risk (80).

Cigarette smoke

Although cigarette smoke is not generally thought to be associated with increased leukemia risk (81), many studies have reported increased risk for leukemia among smokers. The relative risks for leukemia reported for smokers have generally been much smaller than those reported for other sites, which may account for the lack of interest in smoking and leukemia. Nonetheless, the population attributable risk (which measures the proportion of leukemia incidence that can be attributed to smoking) may be large because smoking is so prevalent. Small quantities of many potential leukemogens are present in cigarette smoke in

either the gas or particulate phase (82). These include benzene, urethane, naphthalene, nitrosamines, and radioactive compounds.

In two large cohort studies in the United States, smokers were shown to be at increased risk of leukemia (83, 84). The American Cancer Society assessed cancer risk associated with cigarette smoking in a study of more than one million men and women (83). After three years of follow-up, leukemia risk among male smokers compared with nonsmokers was increased 40 per cent at ages 45–64 years and 70 per cent at ages 65–79 years (83). For comparison, the relative risks for lung cancer in the same age-sex groups were 7.8 and 11.6, respectively. In a study of 293,000 insured US Veterans, smokers had a 50 per cent increase in risk of death from leukemia (84). There was a suggestion of a dose-response for mortality from all leukemias, myeloid leukemia, and monocytic leukemia. In contrast, in a 10-year follow-up study of 40,000 British physicians, leukemia mortality for smokers was lower than that for nonsmokers, and risks appeared to decrease with increasing numbers of cigarettes smoked (85).

A case-control interview study in which information on smoking was obtained was conducted as part of the Third National Cancer Survey (86). Smokers appeared to be at increased risk for myelocytic leukemias, although the dose-response for acute myelocytic leukemia was inconsistent, possibly because there were few cases included. This study is difficult to interpret because controls were other cancers that were considered at that time to be unrelated to smoking. These sites may in fact prove to be directly or inversely associated with smoking, thus diluting or magnifying the association with leukemia. For example, controls included patients with cancer of the pancreas, cervix, and colon. Cancers of the pancreas and possibly cervix are now considered to be smoking-related (82) and, in some surveys, older women who smoke have been shown to be at decreased risk for colon cancer (83).

Paffenbarger et al. (87) conducted a case-control study within a follow-up study of a cohort of men who attended college before 1950. Leukemia cases (27 lymphocytic, 41 myeloid) were compared with four times as many matched controls for the prevalence of cigarette smoking during college. Slightly elevated relative odds were seen for lymphocytic leukemias, and significantly increased relative odds were seen for myelocytic leukemias, with relative odds of 2.4 and 3.6 for all smokers and heavy smokers. Other small case-control studies of acute myelocytic leukemia found no association with cigarette smoking (76, 77). Increased leukemia risk has been reported for adults whose parents smoked when they were children (88). While the number of cases with any one cell type was small, there was a significant increase in risk for acute leukemias associated with smoking by the mother (relative risk = 8.8), and a nonsignificant increase in risk associated with smoking by the father (relative risk = 4.6) (88).

Cigarette smoke by-products have been measured in the blood, urine, and saliva of smokers and passive smokers (89). Increased mutagenicity of the urine of smokers and increases in the number of sister chromatid exchanges in lymphocytes of smokers suggest genotoxic effects from cigarette smoke exposure which could affect leukemia risk (90).

Chemicals

Chemicals form the largest class of known environmental leukemogens. Much of the available information concerns exposure to anti-neoplastic agents or other drugs, and occupational exposure to a variety of solvents and other chemicals.

There have been numerous reports of acute nonlymphocytic leukemia in patients with prior treatment with cancer chemotherapy (6, 7). Cases have reportedly developed after treatment with a variety of

alkylating agents. Reports have implicated procarbazine used in treatment of Hodgkin's disease (91), melphalan used for a variety of cancers (92), chlorambucil (93), cyclophosphamide (94), and other agents (94). Epidemiologic studies have shown increased risks for Hodgkin's disease patients treated with MOPP (mustine, vincristine, procarbazine, prednisone) (95), ovarian cancer patients treated with melphalan or chlorambucil (92, 96), colon cancer patients treated with semustine (methyl-CCNu) (97), and others (96, 98). Effects in humans are supported by animal studies, and are not entirely due to underlying risk of secondary malignancy in persons with certain primary cancers (2). Furthermore, recent studies demonstrate long-term cytogenetic changes in patients treated with chlorambucil, which would be consistent with increased leukemia risk (99).

There have been case reports of bone marrow toxicity and even acute nonlymphocytic leukemia following treatment with the antibiotic chloramphenicol (100). These results are not supported by experimental studies (2) or by follow-up of patients with chloramphenicol-induced bone marrow depression (101). Case reports have also linked the anti-inflammatory agent phenylbutazone with bone marrow toxicity and acute nonlymphocytic leukemia (102), but, again, animal studies and other reports have been negative (2, 103). A variety of other analgesic medications have recently been linked with increased risk for agranulocytosis and aplastic anemia, conditions which have a high propensity for malignant transformation (104). Other therapeutic and recreational drugs including chloroquine, methoxypsoralen, and lysergic acid diethylamide (LSD) have also been reported to cause leukemia (6).

Benzene is probably the best known and most widely occurring leukemogen for humans (2, 5). Case reports dating back to the 1920s link benzene exposure and acute leukemia (5, 105). One of the first cohort studies of workers exposed primarily to benzene found a 10-fold increase in nonlymphocytic leukemia among workers involved in the production of Pliofilm (106). Askoy et al. (107) and Askoy and Erdem (108) reported a twofold increase in all leukemias among shoe-leather workers exposed to benzene, and Vigliani and Saita (109) reported a 20-fold increase in risk for benzene-exposed workers in shoe factories or rotogravure plants. In both studies, the majority of cases were acute myelocytic leukemia.

Today, petroleum production and petroleum products are the major source of benzene exposure, although the level of exposure is quite low. Studies of petroleum workers have not uniformly reported increased leukemia risks. Thorpe (110) studied petroleum refining and petrochemical plant workers in eight European countries. There were fewer than expected leukemia deaths among workers, but this study has been strongly criticized for methodological weaknesses (5). Increased leukemia incidence has been reported for a number of US petroleum cohorts (5, 111–113). Risks for total leukemia or for acute nonlymphocytic leukemia have been reported, although at least one study reported a risk only for lymphocytic leukemias (5). In other studies, leukemia risk was elevated for cohorts of refinery workers, but the increased risks could not be directly attributed to either benzene exposure or specific job classifications (5, 112). Cell type was not specified in the study by Thomas et al. (111). Studies by Hanis et al. (114) and Austin and Schnatter (115), which were industry-sponsored, were negative, but a 40 per cent increase in leukemia mortality among petrochemical workers studied by the National Institute for Occupational Safety and Health was also not statistically significant (116).

Death certificate studies do not consistently find increased leukemia mortality associated with employment in occupations with potential exposure to hydrocarbons and other petroleum products (117, 118). However, in a case-control study of 50 pa-

tients with acute nonlymphocytic leukemia and three groups of controls, including 32 patients with chronic leukemia, 100 outpatients with allergic diseases, and 100 outpatients from an internal medicine clinic, Brandt et al. (119) found significantly more cases than controls employed as truck drivers, filling station attendants, etc. Other reports also suggest similar associations (120–122).

A number of cohort mortality studies and nested case-control studies have been conducted within the rubber industry. The rubber industry at one time was a major user of benzene. Recent cohorts are more likely to have been exposed to other solvents, although benzene exposure still occurs. Many of the studies were reviewed by Checkoway et al. (123). Benzene-associated relative risks for overall leukemia have generally ranged from 1.5 to 3.0. British and US studies support an increase in leukemia risk from benzene exposure, although the relative risks in the British studies tend to be lower than those in the US studies. Furthermore, while in the British studies the evidence is strongest for acute myeloid leukemia, several reports from the United States suggest increased risk for lymphocytic rather than myelocytic leukemias (124). Further analysis of exposures in the same US plants demonstrated that risks for lymphatic leukemias associated with other solvents such as carbon tetrachloride and carbon disulfide were greater than those associated with benzene exposure, with relative risks of 12.8 and 18.0 versus 1.6 (123). Differences in chemicals used and differences in demographic characteristics of the British and US cohorts may explain the different cell type-specific findings.

Increased leukemia risk has been reported for a number of other industries and occupations involving chemical exposures. Numerous case-reports link leukemia and exposure to chlordane and heptachlor (125). Ott et al. (126) reported increased risk for all hematopoietic cancers in workers in arsenical pesticide formulating plants, but two studies of workers exposed to heptachlor and chlordane were negative (127, 128). Milham (129) found a small nonsignificant increase in leukemia deaths for aluminum reduction workers. Increased leukemia mortality was reported for female but not male pharmaceutical industry workers (130). Other studies suggest small increases in leukemia risk for painters (122, 131), embalmers (132), farmers potentially exposed to pesticides and insecticides (133–135), meat workers potentially exposed to fumes from wrapping materials (136), ethylene oxide workers (137), sawmill and other workers exposed to herbicides (138, 139), and automotive workers exposed to a variety of hazards (140).

Several case-control studies of acute myelocytic leukemia patients investigated occupations of patients. In a small study, Flodin et al. (76) reported a sixfold risk associated with occupational solvent exposure and a threefold risk associated with pesticide exposure. A subsequent study demonstrated a risk for exposure to styrene but no other solvents, as well as risk for exposure to medical x-rays, poultry, and electrical wiring (77). A larger registry study of 636 acute myelocytic leukemia patients did not observe the same associations (121). However, inclusion of a large number of patients with urinary tract cancers in the control group may have biased against finding an association with solvents. Forestry work was found to be more common among male acute myelocytic leukemia patients, and health care and food industry jobs were more common among female patients than among controls with other cancers. Forestry work may involve exposure to cyclic hydrocarbons including benzene and also herbicide exposure. Health care workers may be exposed to infectious diseases, drugs, and sterilizing agents. In another study, increased risk for acute myelocytic leukemia was observed for agriculture and forestry workers, and for meat workers (141).

Cytogenetic considerations

It has long been recognized that epidemiologic investigations of cancer etiology

could be more powerful if more precise measures for disease diagnosis could be utilized (1). Future epidemiologic studies, designed to examine associations between risk factors which also cause chromosome changes, such as radiation and chemicals, and leukemia subgroups with particular chromosome abnormalities, may help explain the mechanism by which a risk factor acts to cause the leukemia (3). Alternatively, such studies may be able to show that the chromosome abnormality may not be causally related but may be an independent outcome of exposure (3).

Cytogenetic analysis of acute leukemia with banding techniques such as quinacrine fluorescence and/or Giemsa stain has permitted detailed characterization of structural rearrangements within chromosomes. The Third International Workshop on Chromosomes in Leukemia found abnormalities using primarily direct marrow analysis in 66 per cent of 330 newly diagnosed acute lymphocytic leukemia patients (10, 142). Smaller, single institution studies have found abnormalities in upward of 80 per cent of patients (143, 144). A hierarchical classification system was devised by the Third International Workshop for use in describing cytogenetic abnormalities. When more than one abnormal clone was identified, the one with the simplest karyotype was used for classification purposes.

The Fourth International Workshop reviewed cytogenetic material from 660 patients with de novo acute nonlymphocytic leukemia and found 54 per cent had chromosome abnormalities (12). Even larger proportions with chromosome abnormalities are seen in other studies. Reports by Yunis et al. (8, 9) and others (145) suggest that chromosome abnormalities are present in more than 90 per cent of acute nonlymphocytic leukemia patients. A classification system similar to that for acute lymphocytic leukemia patients was used to describe the distribution of abnormalities in acute nonlymphocytic leukemia seen in the Workshop study (12).

As part of the Fourth International Workshop, cytogenetics for 56 patients with acute nonlymphocytic leukemia secondary to cytotoxic chemotherapy were reviewed; 75 per cent were abnormal, and, in contrast to the de novo group, abnormalities of chromosomes 5 and 7 were much more frequent in patients with secondary acute nonlymphocytic leukemia (45 per cent vs. 12 per cent of abnormalities seen). Rowley et al. (146) observed similar results in a separate series of patients with acute leukemia and dysmyelopoietic syndromes following treatment for prior malignant disease. Studies of de novo acute nonlymphocytic leukemia have also shown an association of abnormalities of chromosomes 5 and 7 with prior occupational exposure to chemicals, solvents, or other petroleum products (15, 16).

The potential for refinement of risk estimates in epidemiologic studies using more specific case definition is strikingly illustrated by recent case series which reported a high frequency of chemical exposure among acute nonlymphocytic leukemia patients with clonal chromosome abnormalities (12, 15, 16). After dividing leukemia patients into those exposed to chemicals and those without such exposure, chromosome abnormalities were found more often among exposed than among nonexposed patients with acute nonlymphocytic leukemia and the abnormalities seen for exposed patients differed from those seen for the nonexposed. Similar associations have not been examined for acute lymphocytic leukemia.

The relative odds of prior chemical exposure in acute nonlymphocytic leukemia patients with chromosome aberrations compared with those without such aberrations ranged from 2.0 to 17.0 (12, 15, 16). Not all studies have demonstrated significant associations (147). Such studies may actually underestimate the chemical-associated relative risk for cytogenetic changes in leukemia. "Controls" are leukemia patients for whom no cytogenetic abnormality was detected. It may be that as cytogenetic techniques improve, these patients may be found to have the same or similar changes. Relative risks may also be greater if com-

parison is made between patients with cytogenetic changes and healthy controls.

Exposure data in the studies of acute nonlymphocytic leukemia patients came from chart reviews or intake interviews, and were available for only a limited proportion of eligible patients. It is not clear if other biases exist. Wide variations in reported frequencies of chemical exposure suggest variation in how data were collected or recorded in charts and how exposure was determined. None of these studies obtained the information on the prevalence of chemical exposure among persons without leukemia that would be necessary to estimate relative risk. Furthermore, not all studies considered potential confounding factors, such as differences in sex ratios or age between chromosomally normal and abnormal cases. Nonetheless, these studies suggest promising avenues for future research.

Discussion

While much has been written about the leukemias, we have not learned a great deal from recent epidemiologic studies. This is not necessarily because epidemiologic methods are inappropriate to the task, but because of deficiencies in the studies that have been completed. Many of the studies are limited by inadequate sample sizes, imprecise case definition, or inadequate exposure measurement. Nonetheless, the literature does point in the direction of an environmental component to leukemia risk and suggests that cytogenetic changes may play some role in the causal chain of events.

This review has focused on familial and cytogenetic factors and on environmental exposures that are of a physical or chemical nature. Other environmental factors such as a potential viral etiology of leukemia were considered out of the scope of this review. A number of epidemiologic and experimental observations suggest a viral etiology for leukemia as well as the plausibility of an interaction between genetic factors and viral exposures (1, 3). Some of the epidemiologic evidence for a role of viruses includes reports of increased leukemia risk among farmers, agricultural workers, and meat workers potentially exposed to animal viruses. These studies are cited elsewhere in this review as possible evidence for occupational exposure to chemicals and pesticides.

A necessary first step in planning future studies is to insure adequate numbers of leukemia cases of any one specific cell-type so that independent analyses can be conducted. While risk factors may vary substantially with cell-type, some exposures may lead to more than one type of leukemia. Much can also be learned by simultaneously evaluating risk factors for different cell-types using similar research methods. Few studies have been large enough to compare risk factors between subgroups of leukemia patients.

Case-control studies may be the most appropriate design for obtaining large enough numbers of patients with one specific diagnosis, although multicenter studies may be necessary. Adequate numbers may also be feasible in occupational cohort studies if collaborative, multi-plant, or multi-industry studies are done. Cohort mortality studies of specific industrial groups continue to provide useful leads on potentially important leukemogens, but few isolated industries or factories employ large enough numbers of workers so that more than a handful of leukemia cases would be expected, making it unlikely that specific leukemia cell-types could be evaluated.

In cohort studies and in case-control studies where specific cell-types are not evaluated separately, the distribution of specific leukemia cell-types may vary from study to study. To the extent that risk factors may differ with cell-type, studies may report conflicting results because of differing case mix. The cell-type-specific incidence of leukemia varies with both age and latency, for example, and findings in cohort studies could differ simply because of differing lengths of follow-up or differing ages of the cohorts.

Many relevant exposures, such as solvents, are widely used in different indus-

tries and are available for use in the home for routine household tasks or for specific hobbies or home-based industries. By examining exposures across industries rather than focusing on specific job categories within a specific industry, studies of leukemia subgroups and studies of women, who are underrepresented in most industry studies, become more feasible. In addition, this approach to evaluating occupational exposures will expand the usefulness of case-control studies. While case-control studies offer the advantage of easier access to large enough numbers of cases of any one cell-type, they are traditionally cited as having the disadvantage of including too few individuals with any one job history to adequately evaluate occupational exposures. With exposures such as solvents, which occur in a variety of occupational situations, the frequency of exposure among controls in case-control studies may be high enough to make such studies more attractive for this purpose.

Further refinement of case definition through parameters such as specific cytogenetic changes may make risk factor identification in epidemiologic studies more likely. Although standardized cytogenetic evaluation of large numbers of patients is not widely available, cytogenetic evaluation of bone marrow is being done more frequently for leukemia patients treated in a research setting. Leukemia patients often receive a bone marrow biopsy for routine diagnostic purposes as do patients with other diagnoses. Standardized cytogenetic evaluations added on to these procedures, while costly, might prove useful for etiologic studies. Other parameters, such as immunologic phenotype or description of cell morphology according to guidelines such as those proposed by the French, American, and British (FAB) Co-operative Group (148), may be more widely available and could also be used to refine case definition. Studies of HLA type in patients with acute lymphocytic leukemia and their parents and in patients with acute myelocytic leukemia have been suggestive of nonrandom differences between leukemia patients and others that may play an etiologic role (3). Further research in this area may prove worthwhile.

The clonal chromosome changes seen in bone marrow of leukemia patients have not been reported in persons without leukemia. While use of cytogenetic classification schemes such as those developed in the International Workshops on Chromosomes and Leukemia (10, 12, 142) may strengthen risk factor identification, studies in which cytogenetic evaluations of controls are not available will fall short of delineating a causal sequence of events. Chromosome changes may reflect underlying genetic differences in persons at risk for leukemia, may result from prior exposure to substances which cause genetic damage, or may be a consequence of the disease process. However, studies showing nonrandom chromosome changes in patients with certain exposures (12–16) and a recent report showing geographic heterogeneity in the specific chromosome aberrations seen in patients with acute nonlymphocytic leukemia (149) suggest the first two explanations may be more likely than the third.

Because the opportunity for studies in which chromosome analysis of bone marrow is done for both cases and controls is quite limited, studies are needed which correlate chromosome changes in bone marrow with changes seen in lymphocytes or other more readily available specimens. In addition, studies which evaluate the correlation between clonal chromosome changes and non-clonal changes such as sister chromatid exchanges or chromosome breaks might provide information that would increase the possibilities for cytogenetic evaluations within epidemiologic studies. Finally, studies that evaluate the persistence of specific chromosome changes following genotoxic exposures will also help in interpreting findings from case-control studies which incorporate some measure of genotoxic damage into the study design.

A number of small occupational cohorts or portions of cohorts have been evaluated

for specific cytogenetic changes such as sister chromatid exchanges or simple breaks. Registries of individuals included in these studies could be established, and to the extent that exposures and cytogenetic methodologies are similar, leukemia risks in relation to specific exposures with and without chromosome damage might be evaluable in the future. Where feasible, such studies should include serial testing so that leukemia risk in workers who first develop chromosome abnormalities as a result of some occupational exposure can be singled out. Additional studies of leukemia risk in persons with underlying chromosome abnormalities that are unrelated to environmental exposures are also warranted.

Many of the studies proposed in 1969 by Kessler and Lilienfield (17) are still not technologically feasible, but recent advances in cytogenetics and biochemical epidemiology have made studies that can accomplish some of the proposed goals feasible. Continued collaboration between epidemiologists and laboratory scientists will be necessary to fully understand the role played by environmental exposures and cytogenetic changes in the etiology of the acute leukemias in adults.

The emphasis in this discussion has been on refinement of case definition. Better case-definition alone will not be sufficient to identify risks from specific exposures. Attention also needs to be paid to development of more precise exposure measures that are suitable for use in large-scale studies. This should include refinement and validation of questionnaire methodology as well as development of biochemical measures of exposure and biologic response that are easy and inexpensive to apply.

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