CANCER EPIDEMIOLOGY and PREVENTION

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CHAPTER FORTY-ONE

The Leukemias

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INTRODUCTION

The leukemias encompass a diverse group of malignancies that share in common merely the fact that all arise from cell systems that circulate in peripheral blood and that arise in large part from bone marrow. The differing cell origins of the leukemias require that different leukemic cell types be considered separately in terms of etiology, pathogenesis, therapy, and prevention. The convenience of the collective term "leukemia" frequently results in the leukemias being considered as a single entity. For general purposes, at least three separate types of leukemia should be distinguished: acute leukemia (AL), chronic granulocytic leukemia (CGL), and chronic lymphocytic leukemia (CLL).

Taken as a whole, the leukemias are not a particularly common form of human cancer, representing only about 5 per cent of total annual cancer incidence (Cutler and Young, 1975; Young et al, 1978). Despite being uncommon, however, the leukemias over the years have been studied more extensively than most other cancers. In part, this reflects the fact that these types of malignancy involve tissue systems (blood and marrow) that are easily accessible for diagnosis, for studies of pathogenetic mechanisms, and for monitoring therapeutic effects. In fact, not only are leukemic cells especially accessible for sampling, but they can be separated more readily from other tissue components than is possible for cancers involving solid tissues. The ability to examine and study relatively pure preparations of malignant cells is a distinct advantage for research studies.

Research concerning leukemia has also been greatly facilitated, in contrast to many more common human cancers, by the existence of several readily available animal models. As a consequence of these models and their availability for research, extensive information, especially with respect to etiologic mechanisms, has come from studies of leukemias as they occur in murine, avian, feline, bovine, and simian species.

Despite these practical advantages for research work, our understanding of leukemia etiology and pathogenesis has yet to produce effective methods for primary disease prevention, except perhaps for minimizing man-made exposures to ionizing radiation and to such marrow-toxic chemicals as benzene. This state of affairs stands in striking contrast to our obvious capacity, long recognized, for preventing most lung cancers through curtailment of cigarette smoking. This disparity in capacity for primary prevention underscores what may be a fundamental difference between tumors of mesothelial or mesenchymal origin (of which the leukemias are one class) and tumors of epithelial origin (such as lung cancer).

For epithelial types of cancer, it appears that environmental factors arise more generally from features of personal lifestyle (for example, diet, cigarette smoking, alcohol use, sexual behavior, and so on), while for nonepithelial cancers such etiologic influences appear to be less important. To the extent that we are capable of modifying lifestyle factors, this difference may be translatable into a greater capacity for prevention of epithelial tumors despite greater insight into the etiology and pathogenesis of mesothelial tumors such as the leukemias. The capacity to prevent disease by no means requires full understanding of disease causation.

This chapter contains a review of current

knowledge concerning the distribution and causes of human leukemias, with particular attention given to the implications such knowledge may have for preventive strategies. Since most of what we know concerning the etiology of human leukemias comes from epidemiologic studies, bolstered by experimental work in lower species, the emphasis here is on the epidemiology of leukemias. Since an earlier review summarized the medical literature published through 1973 (Heath, 1975), the present survey is designed to summarize current knowledge, with emphasis on work published more recently.

HISTORICAL PERSPECTIVE

Kelative standardization and specific ity of disease c lassification codes in the 19305, coupled with improved diagnostic capabilities through expanded use of bone marrow aspiralion in the 1940s, made effective epidemiologic studies of leukemia possible for the first time in the years following World War II. Prior to that time, etiologic observations consisted largely of c linical anecdotes, with considerable confusion existing between leukemias and infection-associated leukocytosis. Perhaps because of superficial diagnostic similarities between leukemia and leukocytosis, early theories of leukemia etiology heavily emphasized the possible role of infectious agents. As the medical uses of ionizing radiation increased, however, and as cases of leukemias began to appear in persons involved in such use (radiologists), radiation received greater attention as a cause of leukemia. This recognition, of course, was dramatically reinforced in the early 1950s when increased leukemia incidence first began to appear among Japanesesurvivors of atomic bomb radiation.

At the same time, great attention began to focus on the viral origins of animal cancers, particularly leukemia in mice. Such work recapitulated studies performed in the early 1900s that c learly identified the viral origin of chicken leukosis (Heath et al, 1975). Renewed animal experiments in this field were made possible by the development of inbred strains of mice, several of which showed marked susceptibility to leukemia. With the availability of such a c onvenient experimental tool, rapid advances were made in identifying animal leukemia viruses. In this setting, attention focused sharply during the 1960s on the possible viral origins of human leukemias. This was accompanied by increased interest in the possible genetic origins of leukemia, partly since animal models suggested that vertical transmission of leukemia virus from generation to generation might be an underlying mechanism for familial tendencies in the disease.

Identification of human leukemia viruses, however, has proven to he an elusive task, and so, in the past decade, etiologic theories regarding leukemogenesis have given more and more recognition to multiple causation, with special emphasis on environmental causes, particularly possible chemical exposures. The latter trend follows closely the recent tendency to emphasize theories of environmental carcinogenesis in the entire cancer field. A broad historic view of etiologic thinking with regard to the leukcmias, however, would suggest that, both for these particular types of cancer and for cancers as a whole, a balance of interactive causative factors, some arising in the environment and some in the host itself, rather than any one form of causation, comprises the proper perspective in studies of cancer etiology.

PATHOLOGIC CHARACTERISTICS

As emphasized initially, the leukemias constitute a collection of quite different diseases. Cases are basically classified according to cytology of leukemic cells coupled with certain histologic, cytochemical, and immunologic characteristics. Much of the clinical and pathologic variation described among the leukemias, however, either is primarily of concern for predicting prognosis and response to therapy or is of rather uncertain significance. For the purpose of understanding current epidemiologic data, it seems sufficient to recognize three basic types of leukemia (AL, CGL, and CLL) and to be aware of the fact that often the lymphocytic varieties of leukemia are closely related to lymphomas. In the latter circumstance, occasional cases, especially cases of CLL, either may have progressed from what previously had been diagnosed as lymphoma or niay differ clinically from lymphoma only by the fact that bone marrow is found to be infiltrated with lymphocytes. This diagnostic overlap between lymphomas and lymphocytic leukemias suggests that for some varieties of leukemia, considerations of epidemiology and disease pievention should involve both categories of cancer together. At the same time, certain rare forms of leukemia (plasma cell leukemia, for instance) might for epidemiologic purposes more appropriately be considered in other diagnostic categories (multiple myeloma).

Of the three basic forms of leukemia men-

tioned, the greatest clinicopathologic variety is encountered for AL. Here a wide range of cell types can be seen. The variety is generally greater in adult than in childhood cases, acute lymphocytic leukemias (ALL) and acute undifferentiated (stem cell) leukemia accounting for the great majority of childhood cases. Overall, acute granulocytic leukemia (AGL), ALL, and acute undifferentiated leukemias are the varieties of AL most commonly cited. Two not uncommon cytologic varieties, however, especially among adults, are acute monocytic leukemia and acute myelomonocytic leukemia. The latter form in particular is considered by many hematologists to be a variety of AGL. True acute monocytic leukemia, on the other hand, may have its origins in the monocyte or histiocyte rather than in the granulocytic cell series.

Commonly, cases of granulocytic leukemia may exhibit disordered red cell proliferation in marrow, with occasional abnormal nucleated red cells appearing in peripheral blood. Such cases, especially when the red cell abnormalities are pronounced, are commonly termed erythroleukemia or diGuglielmo's disease or syndrome. Whatever terminology is used, however, clinically and epidemiologically such cases seem likely to belong under the classification of ACL.

Cytogenetic studies have been widely used in studies of leukemia cell variations. Despite extensive investigations, however, the only cytogenetic finding of consistent value in distinguishing among cases has been the Philadelphia (Ph^1) chromosome, which characterizes marrow cells in most cases of typical CGL. Occasional cases of CGL that do not display this cytogenetic characteristic appear to be a distinctly separate pathologic group with different clinical characteristics and different responses to therapy. Cases of CGL ambng children, although not a common occurrence, are more usually of the Ph^1-negative variety, whereas the reverse holds true in adult cases.

EPIDEMIOLOGIC CHARACTERISTICS

The descriptive epidemiology of the leukemias can be considered in terms of (1) secular trends, (2) geographic distribution, and (3) age, sex, and race or ethnic group patterns. Although detailed cancer incidence data have recently become more widely available (Cutler and Young, 1975; Waterhouse et al, 1976; Young et al, 1978), much of our knowledge concerning the time, place, and person distribution of leukemias still depends on mortality statistics, While such data can provide a fairly accurate reflection of incidence for acute fornis of leukemia, variable survival times and inaccuracies in death registration limit the value of mortality information.

Secular Trends

Leukemia incidence, as reflected in mortality data, increased dramatically from 1900 to the 1940s. While much of this rise undoubtedly reflected improved diagnosis and more accurate death registration, some at least can be presumed to reflect true increased occurrence, perhaps the result of increased exposure to radiation and chemicals in industrial societies. Since the 1940s the rate of increase has diminished, with most recent data suggesting a slight decline in rates, especially among whites. While this trend may well reflect improved control over leukemogenic environmental exposures in the last several decades, it might also be attributed to lengthening case survival *co*-incident with attainment of relatively complete case detection and reporting.

Geographic Distribution

For cancers overall, striking differences in frequency exist between different countries. This is considerably less true for the leukemias, however, than for most other forms of malignancy. This fact may well reflect underlying etiologic differences between epithelial and mesothelial tumors, whereby striking variations in lifestyle factors are mirrored in striking variations in incidence levels for epithelial cancers. For the leukemias, however, geographic differences rarely exceed the twofold level for countries with comparable reliability and accuracy in the reporting of mortality or incidence statistics. The most striking difference involves CLL, which is extraordinarily uncommon in Oriental countries. Since this difference in CLL frequency persists for persons of Oriental origin living in other countries, it seems likely that host or genetic factors are responsible (Heath, 1976). For other types of leukemia, differences in incidence are much less marked, and it is uncertain to what extent they reflect environmental as opposed to host factor variations.

Small variations in incidence levels have been described for regions within countries, notably the United States and Great Britain.

While these differences rarely exceed a 1.5-fold differential, they do appear to correlate with socioeconomic conditions, higher rates existing where income and physician density is higher. This is also reflected in a slight tendency for rates to be higher in urban as opposed to rural settings. Despite these findings, however, the overall picture is one of relative uniformity, especially when compared to geographic variations in other cancer types.

Age

As with all cancers, the leukemias vary widely in incidence by age. Overall annual incidence rises with age from a low of 1 to 2 cases per 100,000 in young adulthood to 30 or more cases per **100,000** over age 50. Unlike most other cancers, however, a distinct childhood peak exists, rising to about 5 cases per 100,000 at age 2 to 4 years and decreasing in later childhood. This peak has appeared especially to affect Western white populations, and in Great Britain it has been suggested that the childhood peak may not have existed prior to the **1920s.** While the cause of the peak is debatable, it is conceivable that it reflects changing environmental exposures in utero or in early infancy.

Different leukemic cell types display striking differences in age pattern. CLL is almost never seen before mid-adulthood and is common above age **50.** Ph¹-positive CGL is likewise an adult disease, although not uncommon in younger adults, and is occasionally even seen in children. As indicated previously, when CGL **does** appear in children, it more often is of a Ph¹-negative variety. At all ages, the most common variety of leukemia is AL, accounting for virtually all childhood and young adult cases and perhaps two-thirds of cases in older adults. In childhood, most cases of AL appear as ALL or undifferentiated or stem cell types. After puberty the great majority of AL cases, however, are AGl or a monocytic or myelomonocytic variety. The origins of these age differences are unknown.

Sex

Males in general are affected more often by leukemia than are females. Sex ratios, however, are to some extent a function of cell type: male predominance is greatest for CLL (2:1), while the sex distribution is closer *to* 1:1 for other types. Although some data have suggested an increasing male to female ratio over time, such a trend is not clear-cut. Since excess male incidence is commonly equated with possible occupational factors operating preferentially by sex, this general pattern for the leukemias may possibly reflect the influence of occupational environmental leukemogens.

Race and Ethnic Group

Racial and ethnic patterns of leukemia incidence show a consistent excess at all ages in whites over blacks and among Jewish populations. To what extent these differences reflect host or genetic factors as opposed to socioeconomic or environmental and lifestyle influences is not known. Among blacks, however, the leukemia deficit is particularly prominent in older age groups and may to some extent represent deficient case detection as a function of medical care availability. In contrast, the striking deficit of CLL in Oriental populations, as discussed previously, appears to arise primarily from genetic factors or some intrinsic race-related host characteristic governing leukemia susceptibility.

ETIOLOGIC EVIDENCE

As is true of cancer generally, the probable causes of leukemia include a wide range of factors, acting singly or in combinations, some involving intrinsic host characteristics (genetic traits and immunologic mechanisms), and others reflecting environmental exposures (radiation, chemicals, and infectious agents). Information comes both from animal experiments and from epidemiologic studies of human populations. What follows *is* an overall synopsis of epidemiologic data, with emphasis on observations published since **1973.**

Genetic Factors

Various lines of evidence indicate the operation of host genetic factors in human leukemia etiology. Aside from differences among racial groups (especially the paucity of CLL among Oriental populations as noted previously), such evidence includes multiple cases in families and associations between leukemia occurrence and various genetic markers or genetically determined conditions (Heath, **1976; Zuelzer** and Cox, **1969).**

Familial Leukemia

Although occasional families have exhibited striking tendencies for multiple leukemia case occurrence (Kaur et al, 1972), such situations are much more the exception than the rule. Numerous surveys have examined the question of familial leukemia occurrence without consistent evidence that leukemia incidence is more than faintly increased in close relatives of leukemia patients. If a general tendency does exist, it would appear to involve CLL more often than other cell types. The existence of consanguinity in occasional multiple case families, however, together with an apparent tendency for increased consanguinity in Japanesefamilies with leukemic sib pairs (Kurita and Kaniei, 1969), strongly suggests that genetic factors can be important in human leukemia, much like aninial counterparts in which experimental inbreeding can dramatically affect frequency of leukemias and other cancers.

Particular attention has been given to twin studies with somewhat uncertain results. Although some observations in the United States have suggested strong concordance of childhood leukemia in like-sexed or monozygotic twins, evidence from Great Britain is uncertain (Draper et al, 1977). Given the fact that monozygotic twins share their placental circulation, it may be that some cases of concordant twin leukemia represent intrauterine leukemia "transplantation" from an affected twin to its mate rather than genetic predisposition alone (Chaganti et al, 1979; Falletta et al, 1973).

Associated Genetic Conditions

More striking evidence, perhaps, of a genetic factor in leukemia etiology involves association of leukemia cases with'chromosomal aberrations, increased incidence among individuals with known chromosomal disorders, and increased incidence in connection with certain immunologic diseases. Despite such clinical associations, no clear-cut or consistent genetic markers (e.g., ABO blood group and HLA histocompatibility type4 have yet been discovered in connection with leukemia (Blattner et al, 1078).

Chromosomal abnormalities, however, an indirect indication perhaps of the fundamental relation of leukemia to the structure and function of genetic material, are commonly seen in leukemic bone marrow cell lines. These aberrations (increased chromosomal breakage and abnormal karyotype patterns) vary widely from case to case. Tn date, the only chromosomal abnormality specific to a particular leukemic cell type is the Ph' chromosome in niarrow cells from cases of CGL.

Beyond such chromosomal changes in individual cases, leukemia has long been known to occur with greatly increased frequency in Down syndrome (G trisomy) and probably in other varieties of meiotic nondisjunction (D13-15 trisomy and Klinefelter syndrome). Among persons with Down syndrome in particular, leukemia is about 20 times more common than in the general population. All ages are apparently affected, and all types of leukemia are probably involved. A further parallel between these two disorders is the fact that both Down syndrome and leukemia (at least among children) increase in frequency with mother's age at time of birth. These relationships, however, probahly operate independently of each other since, unlike Down syndrome, leukemias appear to decrease in frequency with increasing birth order. A further association is the apparent increased frequency of Down syndrome among sibs of leukemic children.

In addition to chromosomal aberrations in leukemia cases and the association between leukemia and nondisjunction syndromes, a further link to chromosomal disturbance is the fact that leukemias occur with increased frequency in various conditions themselves characterized by increased chromosomal breakage. Several of these conditions are hereditary in nature: Bloom syndrome and Fanconi anemia. Others reflect environmental exposures that induce chromosomal injury: populations exposed to ionizing radiation or to chemicals such as benzene. In fact, the one form of leukemia consistently marked by chromosomal alteration (CGL) not infrequently itself gives rise to fulminant acute leukemia with marrow blast cells arising by chromosomal alteration of the underlying Ph'-positive clone,

A final set of disorders also appears to predispose to leukemia, although not through mechanisms of overt chromosomal damage. These involve immunologic conditions; some of them are hereditary in nature (ataxia telangiectasia and Bruton-type X-linked agammaglobulinemia), and others represent particular familial situations (immunologic abnormalities in relatives of patients with various forms of lymphocytic leukemia or lymphoma) (Blattner et al, 1976). These particular observations seem confined to malignancies arising from lymphocytic cell lines and therefore strongly suggest that inherited propensities for immunologic malfunction may involve predisposition to lymphoid neoplasia as well.

Radiation

Radiation, at least of the ionizing sort, has long been known to cause leukemia. The earliest evidence came from cases arising in radiation workers soon after the discovery of x-rays. It subsequently has been shown that leukemia is particularly frequent among radiologists, although this excess risk is now decreasing, presumably as safeguards in radiation practice improve (Matanoski et al, 1975).

Considerable epidemiologic research has focused on radiation leukemogenesis. Information has come from three types of human exposure: nuclear reactions, medical therapy, and medical diagnosis. Whatever the source of information, three general features stand out. first, increased incidence seems directly related to radiation dose. Whether this relationship is entirely linear, particularly at low dose levels, and whether it involves any threshold dose below which leukemogenesis does not occur, remain matters of some uncertainty. Second, latent periods ranging from 2 or 3 years to 20 or more years can be expected between exposure and leukemia appearance. And third, mainly non-lymphocytic varieties of leukemia seem to arise from radiation exposure. A consistent feature in all sets of data is the absence of excess risk for CLL, although radiation exposure is associated with increased risk of ALL in young survivors of the atomic bomb.

Nuclear Reactions

Epidemiologic follow-up of Japanese populations surviving the 1945 atomic bomb explosions in Hiroshima and Nagasaki have clearly shown the leukemogenic potential of ionizing radiation (Beebe et al, 1978). All forms of leukemia except CLL increased in incidence, the earliest cases appearing about two years after the bombing. Peak excess was reached after 5 to 10 years, and incidence at 30 years post-bomb is still slightly greater than expected. latency has appeared to vary with age at exposure and with type of leukemia, shorter latencies being associated with CGL and younger ages. As person-years of follow-up accumulate in the Japanese experience, excess leukemia incidence has become discernible at total body dose levels in the range of 10 to 20 rem. The dose-response relationship appears linear for the most part, at least at higher dose levels.

In recent years, data suggesting excess leukeniia incidence have also been published for other population groups exposed to products of nuclear reactions: workers in the nuclear industry, military personnel present at atmospheric nuclear tests, and populations in areas especially prone to fallout from nrrclear tests. In no instance are the data entirely convincing, and further studies are in progress. In the case of persons employed in nuclear industries (Mancuso et al, 1977; Anderson, 1978) and in nuclear shipyards (Najarian and Colton, 1978; Evans et al, 1979), extensive dosimetry information makes it possible to make close comparisons between exposure levels and ultiniate health outcome. For nuclear test exposures, although some dosimetry information is available, records are incomplete, and questions exist concerning extent of internal radiation from ingested or inhaled radioactive material (Caldwell et al, 1980). Similar uncertainties surround the levels of radiation received by populations in Utah, Nevada, and Arizona through fallout from atmospheric nuclear testing in the 1950s and 1960s. A recently suggested excess of childhood leukemia in southwestern Utah, although not yet clearly established (Land, 1979), may well be compatible with human close-response data from other sources if cumulative fallout doses prove to be in the range of 5 to 10 reni (Lyon et al, 1979).

Medical Therapy

Strong evidence for radiation leukemogenesis comes from epidemiologic follow-up of persons receiving therapeutic radiation for various medical indications. Many studies have been conducted in this area, the oldest and most extensive of which is the British study of men receiving x-ray therapy for ankylosing spondylitis (Court Brown and Doll, 1965). In this particular set of data, follow-up has been sufficiently long and cohort size has been sufficiently large to permit estimates of dose-response patterns, at least for doses over 100 rem. As in other studies, no excess incidence has been seen for CLL. Excess leukemia incidence has also been observed in studies of patients receiving radiotherapy for thymic enlargement, menorrhagia (Smith, 1977), and polycythemia.

Medical Diagnosis

Evidence of increased leukemia incidence following diagnostic radiation exposures is contained largely in studies of childhood leukemia following prenatal x-rays. The increased sensitivity of rapidly dividing fetal cells is felt to account for leukemia induction at fetal whole

body dose levels in the range of 5 rem. Recent analyses of a large continuing British case-control study of childhood cancer reconfirm this relationship and indicate a distinct dose-rcsponse relationship based on numbers of x ray film exposures during pregnancy (Bithell and Stewart, 1975; Kneale and Stewart, 1976). Data from a similar American study suggesting that pre-conception radiation of parents may also increase risk of childhood cancer remains unconfirmed (Graham et al, 1966).

Diagnostic radiation exposures after hirth have yet to be firmly associated with excess lcukernia incidence. This is not surprising, of course, since cumulative dose levels are on the whole in the range of a few rads or less. Recent reanalysis of leukemia case-control data suggesting a substantial leukemogenic effect at these low levels (Bross et al, 1979) has been seriously questioned on grounds of methodology (Boice and Land, 1979). The one exception among studies of postnatal diagnostic radiation may be the follow-up of persons receiving thorotrast (radioactive thorium dioxide), among whom cumulative dose levels may well have been substantial and who appear to show a definite increase in leuhemia occurrence (da Silva t lorta et al, 1974).

Other Radiation Sources

Several investigations have sought correlations between background radiation levels and human cancer occurrence. To date, no such correlations have been found, whether for leukemia or for cancers generally. However, since annual background dose levels rarely exceed 100 to 200 mreni, it is not surprising that no cancer effect has been seen. Based on dose-response data from other sources, the linear response hypothesis would require investigation of exceedingly large population groups if excess incidence were to be seen in populations in Colorado exposed to uranium mine tailings (Mason et al, 1972). A recent study suggesting a correlation between childhood cancer and magnetic field radiation in Colorado (Wertheimer and Leeper, 1979) has not been confirmed in a similar study from Rhode Island (Fulton et al, 1980).

Chemicals

Various chemicals are known to be toxic for marrow cells, and it is not unlikely that many of these also possess leukemogenic potential. Evidence of leukemogenicity is strongest for benzene where recent occupational epidemiologic studies have suggested significant increases in leukemia incidence among workers with probable past exposure to benzene (McMichael et al, 1975; Infante et al, 1977). While not all such studies have shown increased leukemia incidence (Ott et al, 1978; Thorpe, 1974), the two studies suggesting an association between benzene and leukemia incidence support earlier anecdotal evidence from cases of leukemia for which strong histories of exposure to benzene can be documented (Vigliani and Forni, 1976). While most data suggest that leukemias induced by benzene exposure tend to be myelocytic in cell type, one study concerning rubber workers showed an excess in lymphocytic cases (McMichael et al, 1975). The latter study also suggested the possibility that organic solvents other than benzrne niight play a role in leukemogenesis. These observations, together with reports concrrning possible increased risk of leukemia in chemists (Olin, 1976) and possible increased marrow chromosome breakage in leukemia patients with histories suggesting occupational exposure to leukemogens (Mitelman et al, 1978; Lawler et al, 1979), point to a need for more epidemiologic investigations concerning the leukemogenic potential of work-related chemicals.

More indirect evidence of the potential leukemogenicity of organic hydrocarbons comes from a study showing excess leukemia mortality among Nebraska farmers (Blair and Thomas, 1979), thereby suggesting a possible link to exposure to chemicals used on farms. Data suggesting that leukemia and other cancers may be increased in children whose fathers work in hydrocarbon-related occupations (Fabia and Thuy, 1974) have not been confirmed in subsequent studies (Hakulinen et al, 1976; Zack et al, 1980). Chromosomal analyses, however, have raised the possibility of increased chromosome breakage both in chemical laboratory workers and in their children (Funes-Craviotoet al, 1977).

Increasing evidence has accumulated in recent years concerning the leukemogenic potential of various therapeutic chemicals. Early anecdotal reports suggested such sequelae after treatment with phenylbutazone and chloramphenicol. Later evidence focused strongly on the leukemogenic potential of alkylating agents such as melphalan used in cancer chemotherapy (Karchmer et al, 1974; Kyle et al, 1975; Coleman et al, 1977: Reimer et al, 1978; Bergsagel et al, 1979) and busulphan (Stott et al,

1977). Such reports underscore the need for clinicians to consider the risk of treatment-induced cancer as they prescribe cancer therapy. (See Chapter 62 for further discussion.)

Despite the relative paucity of positive epidemiologic findings with respect to chemical leukemogenesis in humans, it remains likely, based on general knowledge from experimental animals, that such exposures do contribute substantially to case occurrence. Low-level exposures to multiple chemicals, many of them with structural features similar to benzene, are frequent in modern life. Specific exposures and specific dose levels, however, are extraordinarily difficult to establish, and even when this may be possible, epidemiologic analyses are severely hampered by limitations in sample size and by inability to correct for competing risk factors In the absence of firm human data, therefore, it may be prudent to assume that, as with exposure to ionizing radiation, chemical exposures relate in a roughly linear nonthreshold manner to leukemogenesis and to plan preventive strategies accordingly.

Infection

It is highly likely that infectious agents play a major role in human leukemia etiology. The viral etiology of nonhuman leukemias has been repeatedly demonstrated. Lacking the opportunity, however, to do the same kinds of experimental studies in man as are possible in rodents, cats, monkeys, and cattle, we are forced to use indirect means to seek evidence of infectious etiology in human leukemias. Thus far, these efforts have yielded remarkably sparse results. The techniques currently available for such studies, however, are limited to standard epidemiologic approaches, successful enough for classical infectious diseases in which latent periods are short, infectivity is often high, and clinical illness is relatively common, but unlikely to be productive in studying infectious events that animal models predict will involve long latency, variable expression of infection, probable vertical transmission from generation to generation, and relatively infrequent clinical disease.

In the absence of a clear understanding of human viral oncogenesis, and even with laboratory tools for detecting viral activity (e.g. procedures for isolating and identifying infectious agents or for measuring antibody response levels), we must be content for the present with relatively crude epidemiologic observations. Pertinent evidence comes from a variety of sources, but in particular from (1) studies of leukemia occurrence in relation to known infectious agents and (2) studies of possible clustering among leukemia cases (or, in other words, the potential relation of leukemia to unknown infectious agents).

Infectious Agents

Numerous observations have been made concerning the potential relationship of human leukemias *to* prior infection by either human or animal infectious agents. Almost without exception these studies have produced negative results, whether exposure has been by direct contact with infected individuals or by inoculation with potentially infectious material such as vaccines.

Particular attention has been given to exposures in utero, under the hypothesis that the immature immunologic status of the fetus niay make it particularly susceptible to leukemogenic infection and hence may account, by a latent period of two to three years, for the inciclcnce peak that appears for childhood leukemia at about age 3. initial observations in Great Britain suggested that in **utero** exposure to influenza might have such an effect (Fedrick arid Alberman, 1972). Subsequent studies, however, have yielded conflicting findings, and it now seems unlikely that any consistent leukemogenic effect exists (Hakulinen et al, 1973; Randolph and Heath, 1974; MacKenzie and Houghton, 1974; Curnen et al, 1974; Austin et al, 1975; Shore et al, 1976). Similar suggestions have been made for varicella infection in pregnancy (Bithellet al, 1973; Vianna and Polan, 1976), but observations thus far seem too few for firm conclusions.

Considerable work has also been devoted to the proposition that animal leukemia viruses may be infectious for humans and thus may account **at** least partly for human leukemia occurrence. Animal tumor antibody studies in veterinarians arid in other persons particularly exposed to animals with malignancy (primarily cats and cows, but also rodents, primates, and other species) have been almost entirely negative (Heath et al, 1975). At present, therefore, there is little room to speculate that any significant animal-to-human tumor virus contagion exists, at least within the limits of current laboratory techniques. In a similar vein, the concept that infectious disease immunizations might lead to increased leukemia occurrence through transmission of animal tumor virus contami-

nants (SV-40 virus in killed poliovirus vaccine and avian leukosis virus in yellow fever vaccine) has not been supported by epidemiologic studies. Likewise, evidence concerning the possibility that BCG vaccination might protect against leukemia development has been largely negative (Rosenthal et al, 1972; Snider et al, 1978; Skegg, 1978).

Much speculation in the past has focused on infectious mononucleosis (IM), its cytologic similarities to leukemia, and the possibility that its etiologic agent, the Epstein-Barr (EB) herpes virus, might also induce leukemia. Studies relating to this hypothesis have been consistently negative, although the situation appears different for lymphomas; EB virus is likely to be a causative factor for Burkitt lymphoma, and Hodgkin's disease has been found to be significantly increased in persons with prior heterophii-positive IM (Rosdahl et al, 1974). The latter observation may well reflect altered immune responses following IM rather than simple infection by EB virus.

Case Clustering

An extraordinary amount of epidemiologic effort has been devoted over the past 20 years to the possibility that leukemia cases, if not cancer cases more generally, may tend to occur in clusters, thereby reflecting the underlying operation of infectious agents as yet unidentified. While much that has been published concerning this subject has consisted of anecdotal accounts of individual case clusters, a substantial number of studies have sought systematically to assess degrees of clustering among cases in defined populations (Caldwell and Heath, 1976; Smith, 1978). While some work has continued to focus on cases clustered simultaneously by time and place of occurrence (Alperovitch et al, 1974; Smith et al, 1976; Kraus et al, 1978), attention has tended to shift more recently to the concept of cases clustered by virtue of past person-to-person contact, "acquaintance networks" with or without cases coinciding in time, in place, or jointly in time and place (Pike and Smith, 1974; Schimpff et al, 1976; Zack et al, 1977; Greenwald et al, 1979).

In both instances (time-place and interpersonal contact clustering), results have suggested little if any tendency for cases to come in clusters beyond what chance would predict. Several studies, nonetheless, using a variety of statistical approaches, have suggested a weak degree of time-space clustering among childhood leukemia cases (Caldwell and Heath, 1976). Studies of interpersonal contact clustering, while focusing primarily on Hodgkin's disease and related lymphomas, have yielded variable and as yet inconclusive results with respect to leukemias and to lymphomas.

Other types of case clustering have also been sought without success. Leukemia occurrence appears to follow no consistent seasonal patterns. Likewise, no tendencies exist for leukemias to occur with undue frequency in spouses of leukemic persons, in children born to leukemic mothers, or in persons who receive blood transfusions from individuals who later develop leukemia (Greenwald et al, 1976). Orie recent retrospective study suggesting increased frequency of hospital-related exposures among patients with leukemia is as yet unconfirmed (Timonen and Ilvonen, 1978).

Despite this mass of generally negative or inconclusive inforniation, one should not decide too quickly that infection is not of etiologic importance for leukemia. For many known infectious diseases, if statistical tests for clustering alone were to be applied, it is unlikely that evidence would emerge to suggest clustering or infectivity. In the absence of specific biologic tests (molecular markers, virus isolation techniques, antibody measurements) arising from knowledge of actual leukemogenic mechanisms, it seems unlikely that the crude epidemiologic techniques currently available will be able to provide greater insights into leukemia causation thaq are presently at hand.

PROSPECTS FOR PREVENTION

As indicated in the introduction to this chapter, immediate prospects are not good for preventing the occurrence of leukemias to any substantial degree. Despite extensive research regarding pathogenesis and causative factors, our understanding of the origins of the leukemias does not yet have the depth necessary for devising primary prevention measures.

Two areas in which preventive programs may be successful, however, involve curtailment of human exposures to man-made sources of ionizing radiation and to various environmental chemicals with leukemogenic potential. In either case, we would act in the tradition of John Snow whereby a preventive program does not require precise knowledge of the etiology and pathogenesis of a disease. (The example is overdrawn, of course, since Snow removed the offending pump handle after the cholera epi-

demic was nearly spent.) For ionizing radiation, this primarily means programs for controlling the medical and dental uses of radiation, since such exposures account for about 70 per cent of man-made and hence controllable radiation. For chemicals, prevention will need to focus on benzene, a common solvent and gasoline additive, and perhaps other related compounds. Occupational exposures will need particular attention, although the accumulated total population impact of chemical exposures is primarily a nonoccupational matter.

Direct measurement of the success of such exposure-control programs will unfortunately not be possible. Since the leukemias, like cancers generally, are of multifactorial etiology, it is impossible to know which particular case results from which particular cause or set of causes. Nonetheless, a decline in non-CLL leukemias at an appropriate interval after instituting control of radiation and chemical exposures might be presumptive evidence of success. In the interval, achievement of documented reductions in exposure levels would need to suffice as a nieasure of success. Considerable progress may already have been made, of course, at least with respect to ionizing radiation, through improvement in radiologic technology and medical practice. Unfortunately, improvements in leukemia diagnosis and reporting at the same time that potential exposure to radiation may be occurring may have obscured true declines in incidence. The variable latent periods involved and the effects of treatment in widening the gap between incidence and mortality will also tend to confuse the issue.

In the meantime, the ultimate possibility of some form of preventive strategy based on the underlying viral or immunologic nature of human leukemias should remain a long-term goal. It seems unlikely that this possibility can be achieved, however, without sustained efforts in basic research concerning cell processes and oncogenic mechanisms on a broad multispecies basis. A fundamental recommendation, therefore, for prevention of leukemias is to maintain strong support for etiologic research.

SUMMARY

The leukemias account for a relatively small proportion of total cancer incidence but have received an exceptional amount of etiologic and epidemiologic research attention. Although specific cellular and molecular mechanisms of leukemogenesis remain unclear, the etiology of the leukemias can be characterized broadly in terms of genetic factors, exposure to ionizing radiation and chemicals such as benzene, and the potential influence of infectious agents. While long-range possibilities for primary prevention of the leukemias depend greatly on sustained basic research, particularly with respect to viral and host susceptibility factors, some immediate success seems possible through improved control over population exposures to man-made ionizing radiation and to marrow-toxic chemicals.

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