CHAPTER - EIGHTEEN

EPIDEMIOLOGICAL STUDIES IN LEUKEMIA

Attempts to understand the nature of the disease process and to work out effective therapeutic measures are intimately linked with the better understanding of etiopathogenic factors. Although extensive experimental, clinical and epidemiological studies have greatly extended the horizon of our knowledge about various aspects, the pathogenesis of leukemia, like any other neoplastic disease, remains obscure. It may be recalled that it is after a long debate on the fundamental biological nature of leukemia that it is now generally accepted as essentially a neoplastic process.

The epidemiological studies of leukemia have yielded valuable indirect leads to the possible etiologic factors.
These have been particularly helpful in the identification of groups of individuals running a high risk of leukemia. This predisposition to leukemia may be acquired or environmental, congenital or genetic (Court Brown & Doll, 1959; Fraumeni & Miller, 1967a).

Official data on vital statistics in the USA and other countries have suggested a steady rise in mortality from leukemia over the years (William and Welter, 1953; Stewart and Hewitt, 1959). Although it has been contended that the recorded increase was partly due to improved diagnostic accuracy and disease certification, the magnitude of rising trend (Stewart and Hewitt, 1959), disproportionate increase in specific cytological types (Court Brown and Doll, 1959) and changing sex differentials (Fraumeni and Wegener, 1964) strongly favoured the conclusion that the increase was at least in part real and was possibly caused by increasing exposures of the population to leukemogenic factors such as chemicals and ionizing radiations.

The bone-marrow is susceptible to the toxic effects of a variety of chemical agents including benzene, chloramphenicol and phenylbutazone. Bass (1961) made experimental studies and convincingly demonstrated the myeloproliferative effect of benzene. Lignac (1932)
demonstrated chemically induced leukemia in mice. Clinical and haematological observations on industrial workers exposed to occupational hazards to benzene inhalation strongly suggested the leukemogenic potentiality of benzene in man (Mollory et al., 1939; Vigliani and Saita, 1964). It is of particular interest to note here that chromosomal studies in workers exposed to industrial benzene have revealed numerous abnormalities (Tough and Court Brown, 1965). A follow up survey of 151 patients suffering from marrow depression attributed to phenylbutazone and chloramphenicol revealed only one case with characteristics suggesting a casual relationship between drug intake and development of leukemia. Hence the fact that it might have been a mere coincidence cannot be ruled out (Fraumoni and Miller, 1967a). The potentially leukemogenic nature of benzene phenylbutazone lysergide and chloramphenicol causing chromosome damage has been reported.

The radiations seem to be playing a vital role in the etiology of leukemia. Since the first report by Weil (1925) of induction of leukemia in man by X-rays several experimental studies have confirmed the leukemogenic effect of ionizing radiations in a number of animal
species (Krebs et al., 1930; Furth and Furth, 1936).
A number of epidemiological surveys have strongly suggested the leukemogenic effect of radiations (Coloney and Lange, 1954; Simpson et al., 1955, 1957; Stewart et al., 1956; Coloney, 1959; Kemelmam, 1966; Messiah et al., 1966). Radiation has been considered an etiological factor in some cases of chronic granulocytic leukemia occurring four to twelve years after heavy exposure (Court Brown and Doll, 1957; Heyssel, 1960). Court Brown and Abbott (1953) and Court Brown & Doll (1957, 1959) showed a significant increase in the incidence of leukemia in individuals receiving therapeutic irradiation on the spine for the treatment of ankylosing spondylitis. Court Brown and Doll (1963) confirmed the finding on a long term follow up. Further, the earlier reports of leukemogenic effect of preconceptional and antenatal maternal radiation (Stewart et al., 1956; Macmohan and Levy, 1964; Graham et al., 1966) have not been confirmed by the large survey published by the atomic bombs casualty commission (Hoshino et al., 1965). The recent observations on the increased incidence of leukemia among the survivors of the atomic blast at Hiroshima and Nagasaki have not only established beyond doubt the role of radiation in leukemogenesis but have considerably clarified the existing confusion regarding
the types of leukemia, the latent period between exposure and rising incidence of leukemia and also the duration of radiation effect (Biazzozero et al., 1966). However, it has been suggested that chromosomal abnormalities may be a common pathway for induction of leukemia by a variety of agents including radiations (Coll and Nowell, 1965; Fialkow, 1967; DeGrouchy and DeNava, 1968). Because radiations also cause chromosomal aberrations, cytogenetic studies of such cases are of interest. It has been found that the patients of chronic myeloid leukemia, exposed to radiation, with a few exceptions, were Ph' positive and often had a greater proportion of autosomal cell lines in the chronic stage than were found in the patients who had not been exposed to radiation (Buckton et al., 1962a; Engel et al., 1964; Gavosto et al., 1965; Sandberg et al., 1962a; Tanaka et al., 1963; Tough, 1965; Tough et al., 1960, 1962).

Goh (1966) found a small G group chromosome in man who had received total body radiation and discussed its possible relationship to the Ph' chromosome. It differed in being present in a much smaller population of the bone-marrow cells and was also found in lymphoid cells (Goh, 1968a). It is unlikely, therefore, to be associated.
with the development of chronic granulocytic leukemia.
The mechanism of leukemogenesis following irradiation is complex and no straightforward sequence of events has been put forth.

Chromosomal abnormalities similar to those seen following exposure to radiation and radiomimetic chemicals may occur in a variety of viral infections both in vitro and in vivo. There is no evidence that such changes which may be temporary leading to acute leukemia. More suggestive evidence for viral etiology comes from epidemiology and from analogy with animal leukemia and with Burkitt's lymphoma. Some Burkitt's lymphoma cells contain cytogenetic changes similar to those found in viral infected tissue culture cells but the significance of this is not yet clear. So the possibility that the virus can play a role in the genesis of human leukemia is being increasingly discussed, mostly on indirect and circumstantial evidence. Recently one form of human leukemia occurring in African children has been reported to have been successfully transmitted to monkeys (Epstein et al., 1964). Such reports, however, remain unconfirmed. The viral etiology of leukemia and lymphoma in mice and possibly in rats has been shown to be well established.
The possible pathway of neoplastic transformation caused by virus in animals has been suggested but so far as human leukemia is concerned any discussion on the subject is still very speculative.

The possibility that there may be a genetic predisposition to the development of leukemia is being increasingly entertained on consideration of the data available on animal leukemia as well as epidemiology of human leukemia. Increased frequency of spontaneous leukemia in certain strains of mice, increased susceptibility to leukemogenesis following exposures to radiations or by transmission of virus have been interpreted as evidence of importance of genetic factors in the development of leukemia (Kirschbaum and Mixer, 1947; Kirschbaum, 1951; Dameshek and Gunz, 1964).

Consideration of hereditary factors in human leukemia is much more complex because of the genetic heterogeneity of human population and rarity of leukemia among human ailments. Epidemiological surveys have been successful in identification of groups of individuals who run a high risk of development of leukemia with familial clusters or in association with certain genetic disorders. The evidences may be briefly summarized as follows:-
1. Familial concentration of cases of leukemia has been reported by a number of workers (Videbaek, 1947, 1958, 1966; Gross and Matte, 1948; Portman and Robinson, 1951; Jard et al., 1952; Gunz, 1961; McPhedran et al., 1963). As many as 5 members in the same family have been known to suffer from leukemia and several members of successive generations have been reported to have died of leukemia (Videbaek, 1966). A few other workers (Amiotti, 1953; Steinberg, 1957, 1960) found no significantly increased incidence of leukemia in families of a large number of patients when compared with an equal number of healthy people. It is, however, admitted that familial incidence of leukemia is greater in some cases of chronic lymphatic leukemia (Jelke, 1940; Gunz, 1957, 1961). However, the question of familial predisposition in chronic granulocytic leukemia and acute leukemia remains disputed.

2. The incidence of other neoplastic disorders among relatives of leukemic patients specially that of patients of chronic lymphocytic leukemia has been
reported to be much more common than in general population (Morganti and Cresseri, 1954; Videbæk, 1947, 1958).

3. High concordance of rates for leukemia in monozygotic twins has been a very consistent finding with many workers (Guasch, 1954; Gunz and Dameshek, 1956; MacMahon and Levy, 1964; Videbaek, 1966). Studies of twins concordant for acute leukemia are of special interest because the cytogenetic reports have been found to be similar for identical twins (Pearson et al., 1963; Hilton et al., 1969), but dissimilar in non-identical twins (Sandberg et al., 1966). More cases will have to be studied before any definite conclusion can be drawn but the findings suggest that a genetic factor is implicated since similar changes were found in identical and dissimilar changes in non-identical twins.

4. Incidence of cancer and leukemia is much more common in individuals with congenital anomalies than in general population. The commonest example is the high incidence of leukemia in Down's syndrome (Krivit and Good, 1956; Stewart et al., 1958; Sulow and Welsh, 1958; Wald, 1961; Kiossoglou et al., 1964).
Other autosomal anomalies with a possible predisposition to leukemia include the D trisomy syndrome. A statistical proof of such an association, however, will be very difficult since the average survival time of D trisomy patients is low. The only evidence is of Schade et al. (1962) who described a patient with both D trisomy and leukemia.

While the cause of the frequent occurrence of leukemia with major congenital malformation remains for the present obscure, it is noteworthy that in mongolism, as well as in chronic myeloid leukemia, the same chromosome G (21) is believed to be aberrant, and that the frequency of both childhood leukemia and mongolism increases with advancing maternal age (Stewart et al., 1958; Ford, 1961; McMohan and Newill, 1962).

Leukemia may occur with frequency in individuals with abnormal sex chromosome complements (Tough et al., 1961; Mamunes et al., 1961; Kemp et al., 1961; Lewis et al., 1963a; Bonsser and Tanzer, 1963) as well as their normal relatives (Miller et al., 1961; Baikie et al., 1961a). The occurrence of leukemia in patients with Klinefelter's syndrome has been reported in
several instances (Mamunes et al., 1961; Tough et al., 1962; Bousser and Panzer, 1963). A family with one sibling having an XY/XXY sex chromosome complement and 2 siblings with acute leukemia were also reported (Jaikie et al., 1961a). Another family included one XXXY male, one leukemic male and two G21 trisomic mongoloid females (Miller et al., 1961). An XO/XX mosanic patient with leukemia was seen by Lewis et al., (1963b). Mamunes et al. (1961) have suggested that cancer and leukemia are more common in individuals with chromosomal abnormalities. Miller (1966) has also renewed the evidence for an increased incidence of leukemias in individuals with cytogenetic abnormalities.

5. It is being increasingly appreciated that a number of immunological deficiency syndromes are associated with an increased risk of development of lymphoreticular malignancies (Peterson, 1965 a, b). It has been suggested that congenital disorders with cytogenetic defects such as Down's syndrome, Klinefelter's syndrome, Bloom's syndrome, Fanconi's syndrome are associated predominantly with a high risk of leukemia, whereas in heritable disorders of
immunological deficiencies such as congenital aglobulinaemia, ataxia telangiectasia and Wishkott Aldrich syndrome are related mainly to lymphoreticular malignancies (Miller, 1966; Fraumoni and Miller, 1967a). The inter-relationship between malignancies and genetic diseases, congenital malformations and immune deficiency states apparently remains to be elucidated in terms of their mutual pathogenesis.

It is uncertain if chromosomal abnormalities form a common pathway for these disorders to be linked casually to leukemias and malignancies.

Further the nature of association of leukemia with chromosomal abnormalities is not clear at present. It does not necessarily mean that leukemia is a direct result of the chromosomal aberration, although the presence of a chromosomal defect may signify a predisposition to the effect of an environmental agent that may evoke cancer.