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Radiation, Genetics and Childhood Leukaemia

INTRODUCTION

THE most compelling epidemiological evidence to date that induced genetic mutations contribute to human hereditary disease comes from a study of workers at Sellafield, a nuclear plant in the U.K. [1]. An increased rate of leukaemia was seen among local residents under age 25 whose fathers were employed there. When occupational exposure histories of fathers of patients diagnosed between 1950 and 1985 were reviewed, 4 of 46 fathers were found to have received 10 mSv or more in the 6 months before conception. Fewer than 1 father of the cases was expected to be exposed to this degree.

If the excess leukaemias are due to mutagenic damage to developing spermatozoa then childhood leukaemia must be to some extent a genetic disease. If so, it may be that the type of germinal mutation induced by radiation and which causes leukaemia does not occur spontaneously and that the Sellafield phenomenon is unique. On the other hand, if the effect of radiation is to increase the existing background mutation rate, then the findings imply that some proportion of childhood leukaemia is due to spontaneous mutation.

A disease is hereditary if a predictable pattern of inheritance can be demonstrated or if it is associated with a specific chromosome abnormality. But not all diseases that are due to inherited mutations fall into one of these categories; a highly penetrant dominant disease that is lethal before reproduction must be a consequence of a new mutation and family clustering is not seen. Some genes may confer susceptibility to a disease, which is expressed only when modifying genes or environmental factors are present and in these cases family patterns may be detected only upon close inspection of several pedigrees. And perhaps most relevant for cancer, a large proportion of non-genetic cases may obscure a smaller hereditary fraction.

Only a few of the mutations causing disease in childhood are detectable cytogenetically. For most, the sequence of DNA that is changed is too small. But there are several approaches to infer heritability, and, to answer the question 'Is childhood leukaemia a genetic disease?', I review several of these. I then examine experimental and epidemiological evidence that pertains to a second question: 'Can pre-conceptual exposure to ionizing radiation induce genetic damage which is expressed as leukaemia in a later generation?'

GENETIC STUDIES OF CHILDHOOD LEUKAEMIA

Twin studies

For purely genetic diseases identical twins should either both be affected or both be well. With environmental as well as genetic determinants, an identical twin of an affected child is at greater risk than other siblings or non-relatives.

7 twin pairs were identified among 8350 children dying from leukaemia under 6 years of age in the U.S.A. [2]. The estimated risk was 1 in 6 that an identical twin would become affected when the onset of leukaemia was early, declining to the general sibling risk by the second decade. In the few cases that have been studied with cell markers, leukaemic cells in identical twins were from a common progenitor, which suggests that the disease is due to a shared foetal circulation [3].

Siblings

In general, epidemiological studies of the risk to siblings of leukaemia patients have not been rigorous. A common strategy is to count sibling pairs among a population-based series. This approach is limited because neither the size of the sibships nor the number of years that siblings are potentially at risk are known; these variables may be estimated from other sources. In the U.S.A. 1 in 1600 white children develops leukaemia before age 15 [4]. Based on this incidence, for sibships of size 3 the expected ratio of those with 1 case to those with 2 cases (assuming no increased sibling risk and follow-up to age 15) is 1600 to 1. For sibships of 2 the ratio is 3200:1 and for size 4, 1075:1. The observed number of sibships with 2 cases divided by this expected number is an estimate of the sibling relative risk (RR). Fraumeni *et al.* [5] found 2 sibships (non-twins) of 2 cases each among a series of 1263 childhood leukaemias. Assuming an average sibship size of 3, the expected number is 0.8. Draper *et al.* [6] used information on both the number of sibs at risk and the total number of years of sibling follow-up and estimated that the risk was increased 2.3 times.

An alternative approach is to identify a proband with leukaemia and to ascertain additional cases among sibs. Miller [7] reported 459 index cases for whom there were 5 affected sibs. 1 pair of these were male twins, 1 member of another pair had Down syndrome and in 2 pairs the proband had a major malformation (probably ataxia-telangiectasia). After removing cases of Down syndrome or malformation only 1 of roughly 1000 siblings was affected.

Overall, excluding cases with known genetic disease or major malformations and twins, a mildy elevated risk for leukaemia in siblings is a consistent finding [2, 6–9]. Sibling risk is, however, an insensitive indicator of genetic predisposition when the background risk of non-hereditary disease is significant.

Cytogenetics

Apart from Down syndrome, which carries a 20-fold increased risk, it is not proven that constitutional chromosome anomalies confer an elevated risk for leukaemia. 1 child in 500 will be born with an abnormal number of sex chromosomes and 1 in 500 carries an autosomal translocation [10], half of which are Robertsonian translocations. In an early study of 25 children with acute leukaemia, 1 XXY boy and 1 with XYY were discovered [11]. An additional child had an elongated Y chromosome and another was mosaic for an extra group F chromosome. In 45 unselected patients with acute lymphocytic leukaemia (ALL), 1 carried a balanced Robertsonian translocation [12]. This association has been seen several times since: 2 of 330 patients with ALL [13], 2 of 660 patients with acute non-lymphocytic leukaemia (ANLL) [14] and 4 of approximately 1400 patients with leukaemia of all types [15] carried balanced Robertsonian translocations. Based on an expected frequency in newborn infants of 1 in 1000 [10] in the four series, 2.4 Robertsonian translocations would be expected ($P < 0.01$). Although individuals with constitutional chromosomal abnormalities and leukaemia have been reported the association has not appeared in more than 1 member of a family.

Paternal age

The total number of divisions of precursor cells leading to mature spermatozoa increases with age, whereas oocytes divided only once between puberty and fertilization [16]. Mutations in replicating cells should therefore accumulate in fathers but not in mothers. For several dominant genetic disorders of childhood, including achondroplasia and Apert syndrome, the risk to the child increases with paternal age. Most new mutations causing retinoblastoma [17] and neurofibromatosis [18] originate on the chromosome contributed by the father. Possible reasons for a paternal effect also include greater male exposure to mutagenic agents and a limited capability of DNA repair in mature sperm.

In Sellafield, a non-significant increase in risk for leukaemia was seen in fathers aged over 25 (RR = 1.42 for age $\geq$ 25 and 1.87 for $\geq$ 40) [1]. In a case-control study of leukaemia in Shanghai, paternal age was not higher among the 309 children with leukaemia than among controls [19] and Shaw *et al.* [20] reported no difference in the U.S.A.

Second cancers and cancer in offspring

Because cancer therapy is mutagenic to somatic cells, most second primary neoplasms in children are thought to be a late effect of treatment, but 1 in 4 second primary neoplasms are found in children with genetic disorders [21]. In particular, children with hereditary retinoblastoma are at high risk for a tumour at another site [22]—implying that the mutation is important in other tissues and is possibly the first of several mutations that accumulate in a single cell. In contrast, a second primary cancer is much less likely to occur after childhood leukaemia. Although leukaemia comprises one-third of childhood cancers, only 6.5% of second primaries follow an initial diagnosis of leukaemia [23]. Cancer in a child of a parent with cancer may reflect inherited susceptibility, but an alternative possibility is that mutagenic therapy induced a germinal mutation causing the second cancer. Leukaemia is not described among offspring of fathers treated with radiotherapy in the few cohort studies reported. Of 4 cases of leukaemia in children of treated parents [24], 3 were likely examples of the Li–Fraumeni syndrome.

Consanguinity

A genetic aetiology for a childhood disease is probable when a significantly higher rate of consanguinity is found among parents of affected children than among the population at random. In one Japanese study, a higher rate of consanguinous marriage (50%) was seen among the parents of 20 leukaemia sibships [25] compared with the parents of non-familial cases (4.5%) or the general population (4–5%). For the 7 leukaemia sibships with childhood onset, 5 marriages were consanguinous. However, the investigators combined several families already reported with those identified through a mailed questionnaire; it is not clear to what extent the collected pedigress are representative and these provocative findings have not been replicated.

RADIATION AND HEREDITARY LEUKAEMIA

Ultimately, evidence for environmental germinal mutagens must come from epidemiological studies of offspring of exposed parents, but any implied biological process needs to be interpreted in the light of current knowledge of induced germinal mutations in other species, of the known spectrum of mutagenic effects of radiation, and of the role of human somatic mutations in leukaemia and other cancers.

Animal studies

Mice have been used as a model to evaluate the mutagenic risks to germ cells of radiation and chemical carcinogens. Ideally, the effects of the induced mutations should be readily identifiable, highly penetrant and correspond to alterations of a known number of specific chromosomal loci. Dominant mutations causing cataract formation and seven specific recessive mutations affecting coat colour and other distinct features have been used [26, 27]. Ehling *et al.* [26] observed 6 *de novo* genetic cataracts among 5231 offspring of male mice treated with 9.1 Gy in divided doses, and predicted that 17–20 new mutations causing dominant disease would be induced per million children in the first generation by exposure of spermatogonial cells to 10 mSv of radiation.

Mutations predisposing to leukaemia in mice have not been well characterized. After treating male mice with 0.36–5.04 Gy of X-rays, Nomura [28] found a higher frequency of tumours, including lymphocytic leukaemia, among offspring (10.0%) than among controls (5.3%, $P < 0.01$). Induced cancers were not associated with chromosomal translocations. Congenital anomalies were also seen, but less frequently than tumours (2.2%). Data from four generations of mice show a persistently elevated leukaemia frequency of about 2%.

Radiation and sperm abnormalities

The frequency of numerical and structural chromosomal abnormalities in spermatozoa increases after radiotherapy, and the rise persists at least five years post-treatment. Among men receiving a testicular dose of 0.4–5 Gy the aberration rate reached 21%. For unexposed controls the rate was 8.5% [29]. The much lower rate of chromosome aberrations seen among newborn infants (0.6%) [10] attests to the efficiency of the process of selection against chromosomally abnormal conceptuses during embryogenesis.

Somatic mutation

50% of patients presenting with ANLL have clonal chromosomal abnormalities in the bone marrow [30]. Among patients with treatment-related leukaemia (following chemotherapy and/or radiotherapy) the most consistent abnormalities are losses and deletions of chromosomes 5 and 7 [31], which suggests that these changes may be markers of past leukaemogenic exposures. Although similar lesions have been seen in patients exposed to the atomic bomb blast [32] and benzene [33], cytogenetic studies of bone marrow of possible cases of occupational leukaemia show little consistency in the types of chromosomal lesions present or in the specific occupational groups at risk [34–36].

Mutations in the germline due to single DNA base changes are characteristic of hereditary retinoblastoma but a counterpart to the retinoblastoma gene has not been identified for leukaemia. A point mutation is frequently found in a member of the *ras* oncogene family in a range of human tumours, including a few ALL cases [37] but germinal transmission of *ras* mutations has not been verified. (A *ras* mutation may relate to the type of mutagenic exposure or to the tissue exposed; breast tumours induced in rats by methylnitrosurea generally carry different *ras* mutations than those induced by dimethylbenz[a]anthracene [38].) *Ras* mutations are more common in human melanomas in sites usually exposed to sunlight [39] and there may be a correlation between *ras* mutations in adenocarcinoma of the lung and smoking [40].

Paternal preconceptual radiation

In the Shanghai study, a fourfold greater risk was seen for all types of childhood leukaemia for fathers who had experienced 11 or more diagnostic X-rays (determined by household interview) ($P < 0.01$) [19]. No association was found with paternal occu-

pational radiation exposure in 126 children with leukaemia [41]. More striking, there were no excess leukaemias among children of Japanese men who survived the atomic bomb blasts (and who received a mean radiation dose of 492 mSv) [42].

In utero *radiation*

The results of a well-known report [43], which identified obstetric diagnostic radiation as increasing the risk of childhood leukaemia by roughly one-half, have been replicated [44], but there have been negative reports as well [19]. One argument against a causal association is that childhood leukaemia was not seen among children exposed *in utero* to the atomic bomb blast [45]. It is puzzling that in several studies diagnostic X-rays do not specifically relate to the type of tumour seen, in contrast with radiation-induced tumours in adults. The excess leukaemias appear to cluster in various age groups in different studies and the risk of leukaemia does not increase with the number of prenatal X-rays or the intensity of the exposure.

DISCUSSION

There are several genetic diseases associated with leukaemia, including Down syndrome, neurofibromatosis, immunodeficiencies, (ataxia-telangiectasia, Wiskott–Aldrich syndrome, severe combined immunodeficiency), chromosome instability syndromes (Bloom syndrome, Fanconi anaemia) and Li–Fraumeni syndrome, which together account for roughly 3% of the childhood leukaemias. To date, isolated case reports remain the best evidence that a genetic mutation or polymorphism may increase the risk for leukaemia on its own. Anderson [46] described a sibship with 5 children dying of acute leukaemia before age 7. In one remarkable family, 13 cases were seen in three generations, including 7 in children under age 15 (3 acute myeloblastic and 4 unspecified acute) [47].

There is limited evidence for a hereditary basis for a small proportion of leukaemias in children not known to be affected with other genetic disease. A doubling of leukaemia risk in siblings of patients is consistent with most reports but this may reflect the shared environment as well as genetic factors. HLA Cw3 and Cw4 are associated with roughly twofold elevations in the incidence of ALL [48], but RRs of this magnitude would have a negligible effect on siblings. Constitutional chromosomal abnormalities other than trisomy 21 probably have little impact on overall leukaemia risk, although the question of a predisposition among carriers of Robertsonian translocations warrants further attention. Concordance among identical twins may be better explained by a common foetal environment than by shared genes. Japanese findings on high consanguinity rates have yet to be confirmed, and the risk for second cancers following leukaemia and the risk to offspring of leukaemia patients have not yet been shown to be unusually high.

When the effects of ionizing radiation on human somatic cells and spermatozoa and on the germ cells of mice are reviewed, the biological basis for extrapolation to human germ cells appears sound. Irradiation of somatic cells is an established risk factor for leukaemia and induced cases are associated with particular chromosomal abnormalities in the marrow. Men undergoing radiotherapy have an increased frequency of chromosomal abnormalities in spermatozoa. In male mice, preconceptual radiation has been followed by an increase in leukaemia in offspring. It would appear that the Sellafield findings might have been predicted.

But despite the apparent consistency, if we accept that low-dose paternal irradiation may increase leukaemia rates in offspring by several times, we are compelled to reject the assumptions upon which genetic risk assessments have been based so far. In their 1988 report, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) implicitly assumed that there is one gene responsible for each of the dominant genetic diseases of man and that susceptibility to mutation at each locus is more or less equal [49]. Because recessive and multifactorial diseases are believed to be less dependent on the introduction of new mutations, the risk for inducing these conditions for a given dose of radiation are assumed to be less than for dominant diseases.

In the high-dose group of Sellafield fathers there were 4 cases of leukaemia when less than 1 was expected. The hypothesis that 3 of 4 cases were attributable to germinal mutations is consistent with either a rare mutation in the children of high-risk fathers that carries a high risk of cancer or a common mutation with a low risk. 1 in 1400 persons in England and Wales develop leukaemia before age 25. If we suppose that carriers of the susceptibility gene have a 1% risk of leukaemia to age 25 (i.e. RR = 14), the mutation must be present in 23% of children of high-risk fathers (assuming a population attributable risk of 75%; mutation prevalence equals 3 divided by [RR − 1]). Similarly, a penetrance of 50% corresponds to a RR of 700 and a carrier frequency of 1 in 200. Based on complete penetrance, a minimum of 1 germ cell in 1000 carries the leukaemia susceptibility gene. In comparison, the spontaneous germ cell mutation rate for retinoblastoma is 6×10^{-6} [50]. The hypothetical Sellafield figure for leukaemia alone is 50 times higher than the total incidence of dominant disease expected from 10 mSv extrapolated from animal studies [26]. If the harmful Sellafield exposure is actually the gonadal accumulation of ingested radionuclides, then risk predictions based on dose–response relations for externally radiated animals are unsound, but the estimated frequency of leukaemia mutations in the population will not be altered.

There are over 4000 single gene disorders referred to in the 8th edition of McKusick's *Mendelian Disorders in Man*. If the leukaemia mutation is representative of hereditary diseases, the total genetic burden at Sellafield should be proportionately higher. Therefore, on statistical grounds, a mutagenic basis for the Sellafield cluster appears unlikely—unless radiation effects are somehow restricted to leukaemia or there are abundant leukaemia loci in the human genome. A non-specific means whereby chronic low-dose radiation might affect spermatozoa and lead to leukaemia in offspring is more consistent with the observations, but as yet has no known biological basis. Children with unbalanced rearrangements involving any of the 22 autosomes are at risk for mental retardation, poor growth and developmental delay; possibly these and other non-specific endpoints should be included in further studies of radiation effects. Epigenetic methods of inducing hereditary disease are a matter for speculation—the activation of latent viruses, suppression of immune response, damage to the centromere or to other nuclear structures and interference with normal imprinting mechanisms might be candidates for consideration.

The findings at Sellafield are important because of the implications about the health effects of low-dose radiation on nuclear workers and their descendants. A mutagenic explanation for the cluster of childhood leukaemia is unlikely.

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