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INVITED EDITORIAL
One Fewer Worry for Survivors of Childhood Cancer

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Many treatments used for childhood cancer can produce reproductive toxicity. Well-known examples include the teratogenicity of both radiation therapy (Otake and Schull 1984; Brent et al. 1993) and methotrexate treatment (Milunsky et al. 1968; Warkany 1978) and the induction of oligospermia by treatment with cyclophosphamide (Watson et al. 1985; Meistrich et al. 1992).

Many of these treatments can also cause heritable genetic changes in mice and other laboratory animals (Sankaranarayanan 1991; Witt and Bishop 1996). Although human and other mammalian germ cells differ in their susceptibility to induced mutations, the processes of gametogenesis and mutagenesis in humans and in laboratory mammals are fundamentally similar (Favor 1993; Shelby 1994). It therefore seems likely that treatment of affected children with mutagenic agents could produce germ-cell mutations and consequent genetic disease in the next generation.

The question of greatest clinical importance, however, is not whether anticancer treatments can actually be shown to cause mutations in human germ cells but whether these therapies increase the frequency of genetic disease in the children of treated individuals. Clearly, potentially mutagenic treatments do not always cause germ-cell mutations that are transmitted to the next generation, and mutations that are transmitted do not always produce genetic disease in the offspring (Sankaranarayanan 1994; Shelby 1994). The paper by Byrne et al. (1998) in this issue of the *Journal* helps to answer this question.

Byrne et al. studied the frequency of congenital anomalies and genetic diseases among 2,198 children of individuals who survived a brain tumor or malignancy during childhood or adolescence. Their paper is remarkable for several reasons. The first is the large size of the study cohort, which provides sufficient statistical power to exclude a doubling of the overall rate of congenital anomalies. Previous investigations have involved far fewer children (Klein 1996; Dodds et al. 1993; Kenney et al. 1996; Green et al. 1997).

Second, Byrne et al. have carefully divided the congenital anomalies observed into those that are likely to have resulted from a germ-cell mutation and those that are not. Although this reduces the number of abnormal outcomes in each group, restricting the analysis to those most likely to have abnormalities resulting from new mutations may nevertheless increase the statistical power of the study (Friedman 1992). Congenital anomalies resulting from germ-cell mutations are uncommon compared with congenital anomalies resulting from other causes, and an effect restricted to the former may often be lost in the "background noise" of the latter if all congenital anomalies are considered together. Byrne et al. also distinguish between children whose parent survived cancer after receiving a potentially mutagenic treatment and children whose parent survived cancer without such treatment. It is only in the former group that a mutagenic effect on the germ cells would be expected.

This division of the data into subsets based on biological plausibility is most fully exploited by Byrne et al. in a nested case-control study within the cohort of children of cancer survivors. Neither this case-control study nor the full cohort study of children of cancer survivors provides any indication that cancer chemotherapy or radiotherapy measurably increases the risk of congenital anomalies in children who are subsequently conceived.

This good news is tempered by the fact that the data are partially out of date. Collection of data concluded in 1983, and cancer was diagnosed in the parents of members of the study cohort during 1945–1975. The inclusion criteria stipulate that a cancer survivor must have reached the age of 21 years between 1946 and 1980. Only the youngest members of this group are likely still to be having children.

Both therapy for childhood malignancy and the outcome of such treatment have come a long way since 1975. For example, very few of the survivors in this study had acute lymphoblastic leukemia, a disease that

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would account for a large proportion in any contemporary series of childhood-cancer survivors (Hammond 1997).

The only mutagenic drugs considered in the study were alkylating agents. These drugs are still widely used, but many additional cancer chemotherapeutic agents have been introduced in the intervening years (e.g., see Haskell 1980, 1995). Most of these newer drugs have been shown to be mutagenic in at least some test systems (Harrison 1996), and, in most instances, the mutagenesis occurs by a mechanism that is different from that of the alkylating agents (Perry 1996). As Byrne et al. point out, studies of the children of more-recent cohorts of childhood-cancer survivors will be necessary to determine the reproductive effects of contemporary cancer treatments.

Exposure to sufficiently high doses of ionizing radiation or mutagenic drugs *must* be capable of producing transmissible genetic alterations in the germ cells of humans. From a practical point of view, however, the risk of congenital anomalies among the children of cancer survivors does not appear to be measurably different from the risk of congenital anomalies among the general population. This is reassuring information for childhood-cancer survivors who would like to have children of their own.

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