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CAUSES OF CHILDHOOD CANCER NEWSLETTER

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Vol 17 No 2

(website: <http://www.cancer.umn.edu/page/risk/c3main.html>)

April 2006

Robert W. Miller, M.D., Ph.D.

C³ notes with great sadness the death of Dr. Robert W. Miller, who was one of the founding fathers of childhood cancer epidemiology. Bob was the Chief of the Clinical Epidemiology Branch at the NCI for almost 20 years. He was a pediatrician by training and headed childhood investigations for the Atomic Bomb Casualty Commission, showing health effects on unborn children secondary to external radiation. He was also one of the first individuals to describe a link between aniridia and Wilms' tumor; and retinoblastoma and secondary malignancies. Bob epitomized what can still be learned today from astute observation at the bedside and beyond.

For many years Bob published the "Childhood Cancer Etiology Newsletter" which ran through the mid-1980s: His Newsletter was the inspiration for C³, which dedicated its first issue in August 1990 to him. Please see an obituary published in the 29 March, 2006, edition of the *New York Times* for more details of Dr. Miller's illustrious career. We send our sincerest sympathies to his family and colleagues, and note that many current investigators making seminal discoveries in childhood cancer causation are "standing on Bob's shoulders". William G. Woods

How Very KRAS

Noonan syndrome (NS) is characterized by short stature, facial dysmorphism and cardiac defects (typically peripheral pulmonary stenosis). Oncologists are becoming more familiar with NS since it was recognized that these children have increased susceptibility to juvenile myelomonocytic leukemia (JMML). Children with NS and JMML often have an excellent outcome with spontaneous regression of the disease without aggressive therapy. Fifty percent of children with NS carry a heterozygous mutation in PTPN11, which encodes SHP-2, a phosphatase that relays signals from activated receptor complexes to downstream effectors including Ras. In addition, some children with JMML (around 35%) have acquired (not germline) PTPN11 mutations [Tartaglia *et al*, *Nature Genetics* 2003; 34: 148-150]. In a new report, Schubert *S et al* [*Nature Genetics*, 2006; 38:331-336] describe *de novo* germline mutations in the gene KRAS in 5 children with NS, one of whom presented with clinical

features of JMML at age 3 months. In a related article, Niihori *T et al* [*Nature Genetics* 2006; 38:294-296] describe germline mutations in KRAS or BRAF (a molecule downstream from RAS) in children with cardio-facio-cutaneous (CFC) syndrome. Children with CFC syndrome show phenotypic overlap with NS, having pulmonary stenosis, hypertrophic cardiomyopathy, ichthyosis and facial dysmorphism. Of interest, one of these children had ALL. An excess of malignancy has not previously been described in CFC syndrome, but accurate genetic diagnosis may reveal significant susceptibility as is seen in NS.

COMMENT: There seems to be a flurry of genes identified in children with cancer susceptibility syndromes. Identification of specific genetic abnormalities that confirm a diagnosis made sometimes on the basis of unclear phenotypic features can be helpful. In particular, for pediatric oncologists and transplanters, recognition of the subset of children with JMML who have NS is important, as these children should not be subjected to the aggressive therapies needed for other children with JMML. Stella M. Davies

Liver on the Edge of Transformation

We have reported previously that infant leukemia (diagnosed in the first year of life) has characteristics that distinguish it from leukemia in older children [see C³, Vol 16, No 6; Vol 12 No 2]. Infants with leukemia have a poor prognosis, are almost equally likely to have ALL or AML, and often have a genetic abnormality (*MLL* gene rearrangement) in their leukemia cells. Non-infants tend to have a good prognosis, are 4 times more likely to have ALL than AML, and rarely manifest *MLL* gene rearrangements in their leukemia cells. There is also strong molecular evidence that infant leukemias are initiated *in utero*. Because *MLL* gene rearrangements in therapy-related leukemias are associated with DNA topoisomerase II (TOPO2) inhibitor therapies, there is speculation that infant leukemias may result from maternal exposure to DNA TOPO2 inhibitors during pregnancy. There is a growing body of epidemiologic evidence that at least for some *MLL* positive infant leukemias, this might be the case [Spector *LG et al*. *Cancer Epi Bio Prev* 2005; 14:651-655; Alexander *F et*

al Cancer Research 2001; 61:2542-2546]. However, experimental studies are needed to address whether appropriate target cells can be affected by exposure to DNA TOPO2 inhibitors. **Money Penny CG et al [Carcinogenesis 2006, 27:874-881]** evaluated whether etoposide (a TOPO2 inhibitor) could induce *MLL* gene rearrangements in cultured hematopoietic stem cells (HSC) isolated from human fetal liver. Notably, the authors found a dose-dependent decrease in HSC viability with exposure to etoposide. DNA damage was observed at etoposide concentrations between 0.14 and 0.5 μ M, while *MLL* gene rearrangements were observed in cells exposed to levels between 0.5 and 1 μ M. Inhibition of DNA TOPO2 was noted with etoposide concentrations \geq 25 μ M, but was not observed at the lower concentrations associated with DNA damage. Interestingly, there was a significant increase in the mean percentage of HSC occupying lymphoid lineages with exposure to etoposide, whereas there was no effect on the composition of the myeloid lineage. The authors conclude that low acute doses of etoposide can cause DNA strand breaks and *MLL* gene rearrangements in human fetal HSC.

COMMENT: This is an important study as it investigated a target cell of interest, fetal liver HSC, that is likely important in infant leukemia. Because such small doses of etoposide affected these cells, **Money Penny et al** further speculate that nanomolar concentrations of other DNA TOPO2 inhibitors (including common exposures) may be relevant. It is interesting that they observed a shift toward lymphoid compartments in these cells, given that infant leukemia can equally manifest as AML. In contrast, the DNA TOPO2 therapy-related leukemias are almost always AML and not ALL. Our recent epidemiological study suggested that maternal exposure to dietary DNA TOPO2 inhibitors was associated with an increased risk of AML with *MLL* gene translocations but not ALL [**Spector from above**]. The authors plan to investigate potential inhibitors of DNA TOPO2 in their experimental model. It will be of interest to see whether these clues from various disciplines might all eventually fit together. Julie A. Ross

Empire State Study

The incidence rate of hepatoblastoma has doubled in the last thirty years. At the same time it has become apparent that children born with low birth weight have an increased risk of developing the disease. These observations have focused attention on a malignancy that affects only about ninety children each year in the United States [**see C3 Vol. 15, No. 2; Vol 14, No. 3**]. In the latest study, investigators linked the New York State Cancer Registry to state birth records [**McLaughlin C et al. Am J Epi 2006; 163: 818-828**], excluding cases born in New York City because of differences in birth data. Records were successfully linked for 58/67 (87%) hepatoblastoma cases diagnosed during 1985-2001. A total of 6,056 controls were randomly chosen from among state birth records, matched 2:1 to cases in a parent study of all childhood cancers during the study period. Birth variables were obtained from electronic records. Most variables, such as birth weight, were readily usable; the composite variable "presumptive use of infertility treatment" was formed by adding affirmative answers to "in vitro fertilization" or

"other fertilization" with birth as part of a triplet (about 80% of which are thought to be due to fertility treatment). Odds ratios (ORs) and 95% confidence intervals (CIs) describing the association of birth variables with hepatoblastoma were calculated using unconditional logistic regression. As expected, there was a drastic significantly increased risk of hepatoblastoma among children with the lowest birth weights (OR $<$ 1,000g vs. 2,500-3,499g = 56.9; 95% CI:24.0-130.7). Raised, but not significant, ORs of 5.0 (95% CI:0.3-25.5) and 1.6 (95% CI:0.5-4.3) were observed for children with birth weights of 1,000-1,499g and 1,500-2,499g, respectively. The association of hepatoblastoma with low birth weight was independent of gestational age. Other significant birth variables, adjusting for birth weight, were male sex (OR male vs. female=2.1; 95% CI:1.2-3.9), young maternal age (OR $<$ 20 years vs. 30-39 years=2.5; 95% CI:1.0-5.5), high maternal prepregnancy weight (175lbs vs. 125-149lbs=2.5; 95% CI:1.1-5.9), maternal hypertension (OR hypertension vs. none=0.2; 95% CI:0.0-0.9), maternal smoking while pregnant (OR smoking vs. none=2.1; 95% CI:1.0-4.2), and presumptive use of fertility treatment (OR yes vs. no=9.2; 95% CI:2.1-31.5). Interestingly, there was significant interaction ($p=0.039$) between maternal smoking and birthweight such that the OR for smoking was 2.7 (95% CI:1.4-25.1) among children with birth weight \geq 2,500g and 0.2 (95% CI: 0.0-1.3) among children who weighed $<$ 2,500g at birth.

COMMENT: The linkage of two population-based registries was a virtue of this study, as was the use of data recorded prior to development of disease. A minor concern is that some controls, having been ascertained at birth but not followed up, may have moved from New York. This study confirmed that the degree of risk conferred by birth weight on the lowest end of the scale is quite substantial. Three studies, including the present analysis, have found an association of parental smoking with hepatoblastoma, which is remarkably consistent for such a small literature. [**Sorahan T and Lancashire R.J. Br J Cancer 2004; 90:1016-1018; Pang D et al. Br J Cancer 2003; 88:373-381**]. It is notable that the association seems independent of low birth weight, in this study and others, even though smoking is known to restrict fetal growth. The observation that presumptive use of infertility treatment markedly increased the risk of hepatoblastoma is intriguing, notwithstanding the manifestly imperfect assessment of exposure. As we have recently noted [**see C3 Vol. 17, No. 1**], previous studies of assisted reproductive technology and childhood cancer have lacked the power to look at specific diagnoses, in particular at embryonal tumors such as hepatoblastoma, for which an association is most plausible. This finding requires further study with care taken to distinguish different sorts of treatment for infertility. Other significant associations in this study deserve follow up but may be chance findings or the result of an inability, due to a small number of cases, to perform multivariate analysis. The Children's Oncology Group is currently conducting a case-control study of hepatoblastoma which aims to interview the mothers of and collect DNA from 600 cases and 720 controls. This investigation will be well-placed to pursue the leads suggested by previous studies. Logan G. Spector