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PATERNAL HYDROCARBON EXPOSURE IN PRADER-WILLI SYNDROME

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SIR,—A deletion of chromosome 15 has been found in 50% of individuals clinically diagnosed with Prader-Willi syndrome (PWS),^{1,2} and this deletion is almost always of paternal origin.^{1,3,4} In females, meiosis is arrested at the dictyotene stage of meiosis I during fetal life, whereas proliferation of gonial cells is continuous in the male. Thus, if the replication of chromosome 15 is sensitive to environmental effects, there might be increased risk for chromosomal deletions which involve breakage and reunion during paternal gametogenesis. Such environmental factors could include paternal drug use, occupational exposure, and irradiation. Pointers to such a possibility include an increase in abnormal metaphases with chromatid and chromosome aberrations in blood lymphocytes of workers with occupational lead exposure,⁵ an increased frequency of paternal occupational lead exposure in children with Wilm's tumour,⁶ and paternal hydrocarbon exposure of children with cancer.⁷ In 40 PWS families we¹ observed an apparent high frequency of fathers employed in hydrocarbon and/or lead related occupations. Subsequently we studied several PWS and control individuals for evidence of paternal hydrocarbon and lead exposure.

We compiled a list of 652 PWS patients, with their fathers' occupations at or about the time of conception, from the National Prader-Willi Syndrome Association. The average age of these fathers was 32, no different from the national average.⁸ To obtain controls With a genetic disease where paternal environmental exposure was an unlikely causative factor we chose fragile X syndrome (n = 66) and Down syndrome (n = 268). We classified occupations into twenty-three categories (table) derived from those used in similar studies.^{6,7} Twelve categories involve considerable occupational exposure to hydrocarbons and five to lead. The percentage of fathers with unknown occupations was much the same in our PWS group (7.1%) and our controls (7.5%) so these were excluded from statistical calculations.

Paternal occupational hydrocarbon exposure in the PWS group (20.8%) was greater than that in the controls (12.0%) ($p < 0.001$, two-tailed χ^2) but paternal lead exposure was not. 38 PWS patients were known to have chromosome 15 abnormalities and 9 (24%) of their fathers had occupational hydrocarbon exposure. These findings implicate paternal hydrocarbon exposure as a causative factor in PWS, probably by producing chromosomal aberrations during paternal gametogenesis.

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PATERNAL OCCUPATIONS OF PWS AND CONTROL INDIVIDUALS

Exposure/occupation	PWS (%)	Controls (%)
<i>Hydrocarbon:</i>		
Dentist	4 (0-6)	2 (0-6)
Chemist	10 (1-5)	0
Factory worker	47 (7-2)	7 (2-1)
Dyer, printer, painter	7 (1-1)	5 (1-5)
Oiler, refiner, distiller	8 (1-2)	1 (0-3)
Miner	1 (0-2)	1 (0-3)
Lumberman	11 (1-7)	0
Machinist	10 (1-5)	1 (0-3)
Cleaner	1 (0-2)	1 (0-3)
<i>Hydrocarbon and lead:</i>		
Driver, heavy machine operator	15 (2-3)	10 (3-0)
Mechanic	15 (2-3)	10 (3-0)
Service station attendant	5 (0-8)	2 (0-6)
<i>Lead:</i>		
Welder, solderer	3 (0-5)	4 (1-2)
Scrap metal worker, metallurgist	0	4 (1-2)
<i>Neither:</i>		
Professional, technical	104 (16-0)	73 (21-9)
Other white collar	174 (26-7)	96 (28-7)
Agricultural worker	25 (3-8)	4 (1-2)
Other craftsmen	24 (3-7)	20 (6-0)
Construction worker	25 (3-8)	13 (3-9)
Other blue collar	42 (6-4)	42 (12-6)
Armed services	46 (7-1)	7 (2-1)
Unemployed, student	29 (4-4)	6 (1-8)
<i>Unknown</i>	46 (7-1)	25 (7-5)