PRIMAL HEALTH RESEARCH

A NEW ERA IN HEALTH RESEARCH

Published quarterly by Primal Health Research Centre
59, Roderick Road, London NW3 2NP
Fax: +44 (0) 171 267 5123

Winter 1999 Vol 7. No.3

Towards an "Accordion method" for men?
About the concept of
MALE-MEDIATED DEVELOPMENTAL TOXICITY

When we originally designed our preconceptional programme, our priority was to minimise the effects of intrauterine pollution by fat soluble man made chemicals. For that reason, until now, only women made use of the "accordion method" in an attempt to renew their adipose tissues, where these chemicals are stored(1,2).

Data providing a basis for an emerging concept

The results of a recently published study from Montreal about childhood leukaemia is a reminder that men also might be invited to participate in our sessions. According to this report, when a man is more exposed than most men to pesticides and fertilisers, his children are at increased risk of acute lymphoblastic leukaemia, that is the most common form of cancer in childhood(3). The results are statistically very significant regarding pesticides in general, fungicides and fertilisers. It is noticeable that most of these fathers had been exposed to more than one category of the contaminants. It is therefore difficult to assess the specific effects of one particular contaminant and even of one particular category.

Although the underlying mechanisms cannot be explained from the epidemiological findings, the authors speculate on a mechanism of "genomic imprinting" that leads to the silencing of a gene in a "parent specific manner". The most attractive mechanism for abnormal imprinting in cancer is the alteration of DNA methylation. One must add that today the prenatal origin of acute lymphoblastic leukaemia is confirmed from a great variety of perspective. It seems that it is frequently initiated by a chromosome translocation event in utero(4).

We must give a great importance to the Montreal study because it offers a spectacular example of "male-mediated developmental toxicity". Furthermore it is the first time that the concept appears in a prestigious non specialised medical journal such as the Lancet. Until recently it was unknown outside a small number of highly specialised circles. In fact, as early as 1993, it was the title of an article in the "Annual Review of Public Health"(5), and, in 1995, of an article in "Epidemiology"(6).

Animal experiments have been instrumental in introducing and developing the concept. There

have been countless studies of alterations in offspring of experimental animals following paternal exposures to miscellaneous chemicals. The effects include decreased litter size and weight, increased stillbirth and neonatal death, birth defects, tumours, and behavioural abnormalities - some of these effects being transmitted to the second and third generations. A review article of such experimental studies came to the conclusion that paternal exposures may contribute to the incidence of a great variety of disorders in humans(7).

Among humans we are probably at the dawn of a new era of research inspired by this emerging concept. Most reports in that field are still semi-confidential. This is the case, for example, of a study of the reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry(8). The authors identified 19675 children (born between 1952 and 1988) of 9512 fathers who had worked at least one year in British Columbia sawmills where dioxin contaminated chlorophenates had been used. The controls were matched for year of birth and gender. The children of male sawmill workers were at increased risk for developing congenital anomalies of the eyes, particularly congenital cataracts; elevated risks for developing anencephaly or spina bifida and congenital anomalies of genital organs were shown according to specific windows of exposure.

Practical implications

What we learn from those men who are more exposed than others to synthetic fat soluble chemicals must be seriously taken into account because, whatever our occupation is, we all have in our body hundreds of such contaminants. The effects are just easier to detect when the levels of exposures are higher than average. The main lesson is that, in the current scientific context, men also should be encouraged to renew their stored fat in order to prepare for conception.

Male-mediated developmental toxicity is not the only reason for men to prepare for conception. Recent data suggest that paternal pesticide exposure tends to reduce the fertilizing ability of couples. 652 Dutch couples who sought in-vitro fertilisation treatment between 1991 and 1998 completed a questionnaire on occupational and life-style factors(9). 16 men were classified as occupationally exposed to pesticides (9 moderately exposed and 7 highly exposed). The association between pesticide exposure and fertilisation rate remained statistically very significant after adjustment for smoking habits, caffeine use, alcohol consumption and other occupational exposures.

****

That couples, rather than women, participate in our preconceptional sessions will have obvious advantages. The main one should be a shared and therefore a strengthened motivation. Let us recall that our programme is based on a series of short semi-fasting sessions, so that a fast weight loss is immediately followed by a fast weight recovery(10). Although our specially designed cocktail is deemed delicious, some women might be tempted to deviate from their objective if their companion does not participate in the programme and does not hesitate to finish his dinner with a most appetising chocolate ice cream.

PRENATAL POLLUTION

A review of preliminary warnings

We occasionally mentioned, in our previous newsletters, a certain number of probable long term consequences of what we called "intra-uterine pollution". After our comments on the preconceptional effects of toxic chemicals, particularly polychlorinated synthetic chemicals, the less precise term "prenatal pollution" seems to be more appropriate.

The documented medical and demographic effects of prenatal pollution should be interpreted as serious preliminary warnings. They can already be classified in several groups.

Effects on tooth development

Dentists from Finland have been studying how polychlorinated chemicals interfere with tooth development since the early 1980s. They noticed that many children had poorly developed molars, discoloured and soft. The normal hard enamel coating was missing, making the teeth subject to decay. They took into account the effects of an accidental exposure to dioxins in Taiwan(11). Children whose mothers were exposed while pregnant showed tooth problems similar to those of Finnish children. Taking this as a clue, the Finnish dentists demonstrated that experimental exposure of rats to the most toxic dioxin (TCDD) leads to developmental defects of dental hard tissues (12).

To find out whether teeth could be used as a biomarker of exposure to polychlorinated chemicals, they examined dentitions of 102 children aged 6-7 for the presence of hypomineralised enamel defects(13). The permanent first molars were the target teeth. The degree of early pollution was estimated by measuring concentrations of the most toxic polychlorinated dioxin/furan and 33 biphenyl congeners in milk samples collected when the child was aged 4 weeks. Hypomineralised enamel defects were seen in the first molars of 17 children (17%). Severity varied from chalky lesions to localised loss of enamel associated with affected dentin. Mineralisation defects occurred more often and were more severe in children who had been exposed to higher amount of polychlorinated chemicals than in those exposed to lower amounts.

The authors suggest that hypomineralised dental defects may be the best available indicator of dioxin exposure, because defects are seen after exposure to very low concentrations and because such defects can be diagnosed even after many years.

Neurological and intellectual development

In our newsletter about milk pollution we mentioned a Dutch study published in 1995 about the neurological development of 418 children at the age of 18 months(14). Half of them were breastfed (at least 6 months) and half of them were formula fed. PCBs concentrations in cord and maternal plasma were used as a measure of prenatal exposure. To evaluate postnatal exposure, PCBs and dioxins were measured in human milk and in formula milk (in formula milk it was "below detection limit"). After taking into account many associated factors, it appeared that exposure to PCBs during fetal life had a negative influence on the neurological condition at 18 months. On the other hand no negative effects of exposure to PCBs and dioxins through breast milk could be detected. On the contrary, breast milk had a significant positive effect on the fluency of movements. The results of such a study suggest that, where the neurological development is concerned, intra uterine pollution probably represents a more serious threat for the unborn generations than milk pollution.

Similar conclusions can be drawn from an American study of the intellectual functions of 11

year old children. The authors recruited originally 212 newborns born to mothers who had eaten Lake Michigan fish contaminated with PCBs(15). Concentrations of PCBs in maternal serum and milk at delivery were slightly higher than in the general population. Prenatal exposure was evaluated by measuring concentrations in umbilical-cord serum and by taking into account maternal serum and milk concentrations. When the children were 11 years of age, a battery of IQ and achievement tests was administered. Prenatal exposure to PCBs was associated with lower IQ scores after control for potential confounding variables such as socioeconomic status. The strongest effects related to memory and attention. The most highly exposed children were three times as likely to have low average scores and twice as likely to be at least two years behind in reading comprehension. Although larger quantities of PCBs are transferred by breastfeeding than in utero, there were only deficits in association with transplacental exposure.

Increased prenatal vulnerability of the male

Disorders of the male genital tract are reported to have recently increased. Similar reports in different industrialised countries indicate that more and more boys have undescended testicles(16,17). A Spanish study compared the rate of undescended testicles (cryptorchidism) in the different regions of the province of Grenada(18). Since this birth defect is typically corrected surgically, it was easy to calculate the frequency of the specific operation ("cryptorchidopexy"). Fruit and vegetable crops in the province of Grenada are treated with 51% of the pesticides used in Spain. In much of the area along the Mediterranean coast, greenhouse crop farming under plastic-encased systems is widely spread. In the enclosed greenhouses, workers (including pregnant women) are exposed to high levels of pesticides. It was found that rates of operations for undescended testicles were significantly higher in districts where pesticide use was high. In these areas, the level of cases was 2.32 times the rate in other areas($P<.05$).

Hypospadias is also more frequent. A recent analysis in the United States showed that the rate of hypospadias had nearly doubled in all 4 regions of the United States from 1970 to 1993(19). During the same period, testicular cancer rates have also increased(20). Today it is commonly accepted that most cancers of the testicles are the long term effects of early developmental defects.

The spectacular fall of the average sperm counts since the middle of this century represents the most intriguing sign of the increased vulnerability of the male genital tract(21). The only plausible interpretation is that all the synthetic polychlorinated chemicals that we accumulate over the years in our adipose tissues are hormonal disruptors. They interfere in particular with the development of the testis at the very beginning of intrauterine life.

Rates of birth defects and premature births

According to an American study of 8-year data gathered by the Centers for Disease Control from 1989 through 1996 , the rates of birth defects are increasing. Furthermore, during the study period, preterm births rose 4.5% in single births in white women. Premature birth rates were even higher among African American women. The authors suggest that pollution is the most probable cause for these increased rates.

Rates of miscarriages

It is difficult to demonstrate that the rate of miscarriages is currently increasing. One must rely on indirect methods. We previously mentioned the evaluation by T. Hassold, according to which there are 132 abortions of males for 100 abortions of females(22). In other words male embryos are more at risk of dying at the stage of miscarriage than female embryos. This implies that if the rate of miscarriages is increasing, the ratio of male to female births should be decreasing. During the first half of the century, the sex ratio had been slightly increasing. This was explained by the reductions in stillbirths: stillbirths tend to occur more in male babies.

Reduced ratio of male to female births

Recent reports from industrial countries indicate that the proportion of males has declined significantly in the past 3 decades(23). The male proportion among newborns in Denmark (24) and the Netherlands (25) have both declined in a parallel manner from the 1950s to the 1990s. There were similar trends in Canada (26) and the USA (27) for the period 1970 to 1990. For Canada, during this period, there was a loss of 2.2 male births per 1000 live births. In the USA, there was a decrease of 1.0 male birth per 1000 live births. It has been observed that in some Latin American countries (28) the male proportion has also declined since the 1970s. Similar trends have been reported in Finland (29) and in Italy (30).

Although the explanations for this decline may be multifactorial, it is highly probable that prenatal pollution is the main cause. This interpretation is supported by the reports following the 1976 industrial accident at Seveso(Italy) which produced the highest documented community exposures to TCDD (one of the most toxic dioxins). Between 1977 and 1984, 48 girls but only 26 boys were born to parents exposed to TCDD(31).

****

This list of preliminary warnings will probably lengthen in the near future. Meanwhile we must offer to couples programmes of preconceptional preparation adapted to the current scientific context. Those who missed previous issues of our newsletter and need further details about the "accordion method" can telephone to:

0181 675 73 20
or 0171 485 00 95
or fax 0171 267 51 23
or e-mail <MOdent@aol.com>

References

1- Primal Health Research newsletter. Spring 1999. Vol 6. No.4
2- Primal Health Research newsletter. Autumn 1999. Vol 7. No.2
3- Infante-Rivard C, Sinnett D. Preconceptional paternal expusure to pesticides and increased risk of childhood leukemia. Lancet 1999; 354: 1819 (letter).
4- Wiemmels JL, Gazzaniga G, et al. Prenatal origin of acute lymphoblastic leukemia in children. Lancet 1999; 354: 1499-503
5- Olshan AF, Faustman EM. Male mediated developmental toxicity. Annual Rev Public Health 1993; 14: 159-81
6- Sever LE. Male mediated developmental toxicity. Epidemiology 1995; 6: 573-4
7- Nelson BK, Moorman WL, Shrader SM. Review of experimental male-mediated behavioral and neurochemical disorders. Neurotoxicol Teratol 1996; 18 (6): 611-16
8- Dimich-Ward H, Hertzman C, et al. Reproductive effects of paternal exposure to chlorophenate wood preservatives in the sawmill industry. Scand J Work Environ Health 1998; 24 (5):416
9- Tielemans E, Van Kooij R, et al. Pesticide exposure and decreased fertilisation rates in vitro. Lancet 1999; 354: 484-5
10- Primal Health Research newsletter. Autumn 1999. Vol 7. No,2
11- Alaluusua S, Lukinmaa P-L, et al. Polychlorinated dibenzo-p-dioxins and dibenzofurans via mother's milk may cause developmental defects in the child's teeth. Environ Toxicol Pharmacol 1996; 1:193-97
12- Alaluusua S, Lukinmaa P-L, et al. Exposure to 2,3,7,8-tetrachlorodibenzo-para-dioxin leads to defective dentin formation and pulpal perforation in rat incisor tooth. Toxicology 1993; 8: 1-13
13- Alaluusua S, Lukinmaa P-L, et al. Developing teeth as biomarker of dioxin exposure. Lancet 1999 (16 jan); 353: 206 (research letter)
14- HuismanM, Koopman-Esseboom C, et al. Neurological condition in 18-month-old children perinatally exposed to polychlorinated biphenyls and dioxins. Early Human Development 1995; 43: 165-76.
15- Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 1996; 335(11):783-9
16- Jackson MB. John Radcliffe Hospital cryptorchidism research group. The epidemiology of cryptorchidism. Horm Res 1988; 30: 153-56.
17- Sharpe RM, Skakkebaek NE. Are estrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet 1993; 341: 1392-95
18- Garcia-Rodriguez J, Garcia-Martin M, et al. Exposure to pesticides and cryptorchidism: geographical evidence of a possible association. Environ Health Perspect 1996; 104: 394-99
19- Paulozzi LJ, Erickson D, Jackson RJ. Hypospadias trends in two US surveillance systems. Pediatrics 1997; 100: 831
20- Forman D, Moller H. Testicular cancer. Cancer Surv 1994; 19-20:323-41
21- Auger J, Kunstmann JM, Czyglik F, Jouannet P. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 1995; 332: 281-5
22- Hassold T. Sex ratio in spontaneous abortions. Ann Hum Genet 1983; 47: 39-47
23- Davis DL, Gottlieb MB, Stampnitzky JR. Reduced ratio of male to female births in several industrial countries. A sentinel health indicator? JAMA 1998; 279: 1018-1023
24- Moller H. Change in male - female ratio among newborn infants in Denmark. Lancet 1996; 348: 828-29
25- van der Pal-de Bruin KM. Change in male-female ratio among newborn babies in Netherlands, Lancet 1997; 349: 62
26- Allan BB, Brant R, Seidel JE, Jarrel JF. Declining sex ratios in Canada. Can Med Assoc J 1997; 156: 37-41
27- Marcus M, Kiely J, McGeehin M, Sinks T. Changing sex ratio in the United States, 1969-1995. Fertil Steril 1998; 70 (2): 270-3
28- Feitosa MF, Krieger H. Demography of the human sex ratio in some Latin American countries, 1967-1986. Hum Biol 1992; 64:523-530
29- Vartiainen T, Kartovaara L, Tuomisto J. Environmental chemicals and changes in sex ratio: analysis over 250 years in Finland. Environ Health Perspect 1999; 107:813-5
30- Astolfi P, Zonta LA. Hum Reprod 1999; 14(12): 3116-3119
31- Mocarelli P, Brambilla P, et al. Change in sex ratio with exposure to dioxin. Lancet 1996; 348: 409
32- Odent M Primal Health. Century-Hutchinson. London 1986 (out of print)
33- Seymour-Reichlin. Neuroendocrine - immune interaction. New Engl J Med 1993; 329:1246-53