LETTERS TO THE EDITOR

Maternal smoking and blood pressure in 7.5 to 8 year old offspring

EDITOR,—Morley *et al* demonstrate convincingly that the systolic blood pressure of offspring of smoking when compared with non-smoking mothers was significantly lower if they were delivered before 33 weeks' gestation but significantly higher if they were born at 33 or more weeks'.¹ No direct mechanism for this finding is suggested.

Using unbiased methods, we determined the precise relationship between fetal renal nephron number and gestational age, confirming unequivocally that almost half of the total complement of glomeruli is generated during the last few weeks of normal nephrogenesis—that is, between week 32 and 36 of gestation.² We also documented that type II intrauterine growth retardation, such as is associated with maternal smoking and which was recorded in the >33 weeks' group of Morley's study, results in an irretrievable loss of 50% or more of glomeruli in most cases.³ In animals, neonatal unilateral nephrectomy has been shown to result in compensatory glomerular hypertrophy, increasing the filtration area available, but requiring increased glomerular perfusion and, in turn, a raised perfusion pressure.⁴

The finding of Morley *et al*, of a difference in the blood pressure of the offspring of smokers related to delivery before or after 33 weeks', may now be explained by hypothesising continued nephrogenesis ex utero between week 33 and 36 in the early delivered group, in contrast to a loss of up to 50% of nephrons in the post 33 week group as a result of continued intrauterine exposure to adverse circumstances. Indeed as infants delivered to smoking mothers before 33 weeks' in this study showed normal birthweight ratios, it is probable that a developmental deficit does not exist in this group. However, in the post 33 week group with low birthweight ratios, a glomerular deficit, requiring a compensatory raised blood pressure in later life, seems likely.

It is perhaps important to reiterate that although postnatal weight gain in growth retarded infants may approach the original genetic potential, the 'window of opportunity' nature of nephrogenesis precludes such recovery and compensatory mechanisms may develop with profound effects on morbidity and mortality in later life.

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1 Morley R, Leeson Payne C, Lister G, Lucas A. Maternal smoking and blood pressure in 7.5 to 8 year old offspring. *Arch Dis Child* 1995; 72: 120-4.

2 Hinchliffe SA, Sargent PH, Howard CV, Chan YF, Van Velzen D. Human intrauterine renal growth expressed in absolute number of

glomeruli assessed by the Disector method and Cavalieri principle. *Lab Invest* 1991; 64: 777-84.

3 Hinchliffe SA, Lynch MRJ, Sargent PH, Howard CV, Van Velzen D. The effect of intrauterine growth retardation on the development of renal nephrons. *Br J Obstet Gynaecol* 1992; 99: 296-301.

4 Seyer-Hansen K, Gundersen HJG, Osterby R. Stereology of the rat kidney during compensatory renal hypertrophy. *Acta Pathologica Microbiologica et Immunologica Scandinavica* 1985; 93: 9-12.

Dr Morley comments:

The data put forward by Hinchliffe, Howard and van Velzen do not entirely explain our findings.

We reported previously that in a cohort born up to 33 weeks of gestation¹ decreasing size at birth was not associated with the rise in later blood pressure reported in population studies² and hypothesised that the adverse influence of growth retardation on later blood pressure takes place later in gestation.

As a group, babies born preterm do not grow well in the neonatal period and often suffer severe growth retardation. If continued nephrogenesis depends on good nutrition we might expect that the children who grew best or received a nutrient enriched formula should have lower later blood pressures. This was not the case; neonatal ex utero growth failure did not influence later blood pressure.³ Further analyses have shown that in those children born before 33 weeks of gestation the degree of growth failure after delivery did not influence later blood pressure, whether or not they were born growth retarded.

If the cause of higher later blood pressure in children born growth retarded is reduced glomerular numbers, then from our data we could speculate that growth retardation only adversely influences glomerular numbers if it occurs in utero and either starts or continues after 33 weeks of gestation.

In the group born after 33 or more weeks of gestation (almost all of whom had birth weights below the 10th centile) we found an adverse influence of maternal smoking on later blood pressure, in contrast to population studies.² We speculated that maternal smoking is deleterious for later blood pressure only if the fetus is exposed to it late in gestation and in the presence of growth retardation.

It would be interesting to investigate whether smoking in late gestation influences glomerular numbers and whether there is any interaction with growth retardation.

1 Morley R, Leeson-Payne C, Lister G, Lucas A. Size at birth and later blood pressure. *Arch Dis Child* 1994; 70: 536-7.

2 Law BM, de Swiet M, Osmond C, *et al*. Initiation of hypertension in utero and its amplification throughout life. *BMJ* 1993; 306: 24-7.

3 Lucas A, Morley R. Does early nutrition in infants born before term programme later blood pressure? *BMJ* 1994; 309: 304-8.

Plasma interleukin-3 and interleukin-4 concentrations in Turkish asthmatic children

EDITOR,—Asthma comprises a clinical-pathological triad of intermittent and reversible airway obstruction, chronic bronchial inflammation with eosinophils, and bronchial smooth muscle cell hyper-reactivity to bronchoconstrictors, which may be initiated by mast cell activation in response to allergen binding to IgE.¹ Multiple, multifunctional cytokines are released as a result of IgE mediated mast cell activation.² Interleukin

(IL)-4 is a potent stimulant for T cell growth and development and acts independently of IL-2 induced T cell proliferation.³ IL-3 is a glycoprotein that not only induces proliferation and differentiation of haematopoietic progenitor cells, but also enhances the expression of class II MHC molecules, which play an important part in T cell mediated immune response.⁴

IL-3 and IL-4 may have significant autocrine effects on the mast cell itself and these cytokines may facilitate IgE production by B cells.² It is now generally accepted that IL-4, IL-6, and interferon gamma play the main parts in the regulation of human IgE synthesis.⁵ This concept is based mainly on in vitro data.⁵

We measured plasma IL-3 and IL-4 concentrations in 20 Turkish children with bronchial asthma, who were diagnosed according to Lawlor and Tashkin's criteria.⁶ There were 13 boys and seven girls ranging in age from 49 months to 14 years, with a mean (SD) age of 8.0 (3.1) years. Twelve patients received prophylaxis with ketotifen, eight with theophylline, and all the patients were given β adrenergic agonists during acute attacks. None of the patients were receiving immunotherapy. Twenty healthy children with a mean (SD) age of 9.1 (3.2) years were included in the study as a control group.

Plasma IL-3 and IL-4 concentrations were measured using enzyme linked immunosorbent assay (ELISA) with Amersham kits. The minimum detectable concentrations of plasma IL-3 and IL-4 by this method are 1.5 pg/ml and 0.6 pg/ml, respectively.

In the control group, IL-4 and IL-3 were not detectable. In contrast, all patients had detectable concentrations of IL-4, and 9/20 (45%) of patients had detectable IL-3. The values are shown in the table.

Mean (SEM) plasma IL-3 and IL-4 concentrations in asthmatic patients and control group

	Asthmatic patients (n=20)	Healthy controls (n=20)
IL-3 (pg/ml)	7.38 (2.49)	ND
IL-4 (pg/ml)	31.30 (1.64)	ND

ND: non-detectable. Minimum detectable concentrations were considered non-detectable.

None of the patients had received corticosteroids in the last six months which might block cytokine production. Ketotifen antagonises mainly IgE induced release of mediators.¹ β Adrenergic agents and theophylline raise cAMP in the bronchial smooth muscle cells and inhibit contraction.¹ Therefore, of the drugs used in treatment and prophylaxis only ketotifen may have influenced the results. However, no significant difference in plasma IL-3 and IL-4 concentrations was found between the patients receiving ketotifen and theophylline.

Schauer *et al* have reported an in vivo pre-activation of lymphocytes from asthmatic patients with increased concentrations of IL-4.⁷ Bruijnzeel *et al* have found that IL-3 and IL-5 are demonstrable in the circulation of asthmatic, but not normal, individuals.⁸ Schleimer *et al* have proposed that local release of IL-4 in vivo in allergic diseases may explain the enrichment of eosinophils and basophils observed in asthmatic patients.⁹ Our data have revealed additional in vivo evidence of increased concentrations and activities of IL-3 and IL-4 in extrinsic asthmatic children.