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.

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- 1 Abbas AK, Lichtman AH, Pober JS. Effector mechanisms of immunoglobulin E-initiated immune reactions. In: Abbas AK, Lichtman AH, Pober JS, eds. *Cellular and molecular immunology*. 2nd Ed. Philadelphia: WB Saunders, 1994: 279-92.
- 2 Brostoff J, Hall T. Hypersensitivity - type 1. In: Roitt I, Brostoff J, Male D, eds. *Immunology*. 3rd Ed. St Louis: Mosby Year Book, 1993: 19.1-22.
- 3 Tanaka T, Ben-Sasson SZ, Paul WE. IL-4 increases IL-2 production by T cells in response to an accessory cell independent stimuli. *J Immunol* 1991; **146**: 3831-5.
- 4 Maeda K, Sone S, Ohmoto Y, Ogura T. A novel differentiation antigen on human monocytes that is specifically induced by granulocyte-macrophage colony stimulating factor or IL-3. *J Immunol* 1991; **146**: 3779-84.
- 5 Lebedin YS, Raudla LA, Chuchalin AG. Serum levels of interleukin-4, interleukin-6 and interferon-gamma following in vivo isotype-specific activation of IgE synthesis in humans. *Int Arch Allergy Appl Immunol* 1991; **96**: 92-4.
- 6 Lawlor GJ, Tashkin DP, Asthma. In: Lawlor GJ, Fischer TJ, eds. *Manual of allergy and immunology*. 2nd Ed. Boston: Little Brown, 1988: 115-65.
- 7 Schauer U, Kohl I, Jager R, Becker H, Rieger CH. Coexpression of CD4 and CD8 on mitogen-activated peripheral blood T cells from children with asthma: possible involvement of interleukin-4. *Ann Allergy* 1992; **68**: 354-9.
- 8 Bruijnzeel PL, Rihs S, Virchow JC Jr, Warringa RA, Moser R, Walker C. Early activation or 'priming' of eosinophils in asthma. *Schweiz Med Wochenschr* 1992; **112**: 298-301.
- 9 Schleimer RP, Sterbinsky SA, Kaiser J, et al. IL-4 induces adherence of human eosinophils and basophils but not neutrophils to endothelium. Association with expression of VCAM-1. *J Immunol* 1992; **148**: 1086-92.

A judicial comment on temporary brittle bone disease

EDITOR.—A recent reported judgment by Mr Justice Wall¹ in the Family Division of the High Court is relevant to the debate on temporary brittle bone disease.² The use of this diagnosis to explain injuries in both child protection and criminal court proceedings is largely due to the work of Paterson.³ In the case reported he was asked how two earlier cases that had been before the courts had been treated in his research data. In one case there had been a criminal conviction and in the other there had been a finding of non-accidental injury by the Wardship Court. It is reported that Paterson replied that both cases were included in his research as proven cases of brittle bone disease. Indeed, when asked how he would log the case before the court (the baby had suffered brain injury and multiple fractures), should the judge make a specific finding of non-accidental injury, he replied that he would still regard the case as being one in which the child had suffered temporary brittle bone disease. In the words of the judge 'Whilst courts of course accept that there may be cases where there is a divergence between judicial and clinical findings, I regard as worrying in the extreme Dr Paterson's failure to record in his research material of cases of proven brittle bone disease judicial findings to the contrary. In my judgment this is a factor which must cast the gravest doubts on his findings'.

The judgment also reaffirms that the courtroom is no place to advance untested hypotheses⁴ and emphasises the need for expert witnesses to provide independent assistance to

the court and not omit to consider facts which detract from their concluded opinion. Attention is also drawn to an earlier judgment by Cazalet J,⁵ also involving brittle bone disease, which points out that a misleading opinion from an expert may well inhibit a full assessment by non-medical advisers, reinforce parental denial, and thereby put a child at risk.

For future cases coming before the High Court there will be awareness of previous judgments relating to evidence on temporary brittle bone disease, however, this may not be so in the Family Proceedings Court. As Mr Justice Wall comments: 'It is not difficult to imagine circumstances in which a non-accidentally abused child might be returned to abusing parents on the false premise that the child has not been abused. That in my judgment is just as much an injustice as a false finding that a parent has injured a child'.

During investigation of suspected child abuse, even before legal action is considered, the possibility of temporary brittle bone disease may be raised and threaten to compromise or obstruct protection of a child or therapeutic work with their family. By being aware of and referring others to relevant law reports¹⁻⁵ paediatricians can help keep the issues in perspective.

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- 1 Wall J. Re AB (Child Abuse: Expert Evidence) [1995] 1 FLR 181.
- 2 Smith R. Osteogenesis imperfecta, non-accidental injury, and temporary brittle bone disease. *Arch Dis Child* 1995; **72**: 169-76.
- 3 Paterson CR, Burns J, McAllion SJ. Osteogenesis imperfecta: the distinction from child abuse and the recognition of a variant form. *Am J Med Genet* 1993; **45**: 187-92.
- 4 Williams C. Expert evidence in cases of child abuse. *Arch Dis Child* 1993; **68**: 712-4.
- 5 Cazalet J. Note Re R (A Minor) (Expert Evidence) [1991] 1 FLR 291.

Infant length measurements

EDITOR.—Dr Doull and colleagues presented a paper on the reliability of infant length measurements.¹ Hoorah! Some of us have for many years tried, without much success, to encourage the measurement of infant length. In many studies it is a better measurement of growth than weight and is a stable linear growth measure.

Why the unsucces? 'It's very difficult to do; it's unreliable; you need a special apparatus; it's impractical to do in the field'. It has been shown that none of these concerns is valid,^{2,3} but Dr Doull has done so in an up-to-date persuasive way including showing that you do not need two professionals but only one, mothers being excellent holders of their infants' heads.

For velocity growth in infancy it is an important measure and there are a growing number of reference values available.⁴

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- 1 Doull IJM, McCaughey ES, Bailey BJR, Betts PR. Reliability of infant length measurement. *Arch Dis Child* 1995; **72**: 520-1.
- 2 Falkner F. Office measurement of physical growth. *Pediatr Clin North Am* 1961; **8**: 13-7.
- 3 Falkner F. Recommendations for monitoring growth in childhood: a human growth foundation committee report. *International Child Health* 1995; **6**: 79-85.

- 4 Roche AF, Himes JH. Incremental growth charts. *Am J Clin Nutr* 1980; **33**: 2041-52.

AUTUMN BOOKS

Management of Pediatric Trauma. Edited by William L Buntain. (Pp 788; £142 hardback.) W B Saunders Company, 1994. ISBN 0-7216-6280-3.

This comprehensive book covers all aspects of trauma care. It starts with a historical review, discusses the philosophy and organisation of paediatric trauma management, describes the treatment of specific conditions, and looks to the future.

There are 85 contributors (mainly surgeons) three of whom are Australian, all the others being North American. The book was more than six years in gestation and the chief editor has done well to produce a book that reads so fluently.

There are six separate sections. The first covers the history of the subject, the biomechanics of trauma, injury prevention, organisation of services, and developing standards of care. The figures report the agencies involved in prevention and some of the legislative solutions suggested have an American slant. Nevertheless, the principles of aetiology and prevention are universal and well described.

The chapter on trauma care organisation is excellent. Care of the injured starts at the roadside or in the home and continues until tertiary care is reached and provided. The authors write with authority on the improvement in care following the introduction of a team approach to the injured child 'There is no place ... for competition amongst care providers'. The response teams are described. Resuscitation and stabilisation are orthodox and follow advanced paediatric life support and advanced trauma life support (ATLS, ATLS) teaching. There are some exceptions: for example, use of a trocar in introducing a chest drain is deplored as dangerous by most of us in emergency care. The radiological evaluation is clear and uncontroversial, but our anaesthetic colleagues may balk at the suggested use of ketamine in potentially hypotensive, cerebrally injured children.

In fairness, the author admits to differences of opinion over this. He is not dogmatic: 'No singular approach should be considered the only correct approach. Rather a protocol for trauma care that is attuned to the institution's geographic and urban demographics, the availability of surgical expertise and the physical limitations of the building itself is appropriate'.

Chapters are devoted to trauma scores, protocols, and blood products. There is detailed consideration of specific system injury and then to special situations such as falls, birth injuries, non-accidental trauma, farm and submersion injuries. My surgical colleagues assure me that the operative procedures described are standard. A conservative approach is taken to urinary tract injuries and liver damage, but a slightly more aggressive approach than ours to splenic injury. A