LETTERS TO THE EDITOR

Cough – but is it asthma?

EDITOR,—Although the scientific content of Sheila McKenzie's recent review is impressive,[1] I do not agree with her conclusions. There is a group of children that one often sees in clinic, usually preschool children who have had a chronic persistent nocturnal cough that may wake them three or four times a night. Although there may be a personal history of eczema and a family history of atopy in general, there is often nothing to suggest personal wheeze. In view of their age it is often difficult to demonstrate airways lability scientifically. Dr McKenzie's approach seems to offer these children and their parents little except tea and sympathy.

It used to be my practice to offer this sort of child a trial of β agonists. It had a success rate of approximately zero. I have rationalised this that cough is due to airways inflammation, mucous, and oedema and therefore not likely to respond to bronchodilators. It is also likely that the time course of action of short acting β agonists make them ineffective at the most vulnerable time of the night.

My current practice is to start such children, after a very thorough history and examination, on a six week course of inhaled steroids. In my experience the success of such practice is something like 80% and although it may upset the scientific purists it certainly pleases the parents.

Clearly more research is required to elucidate this problem. I feel that in the absence of wheeze, however, that tests based on bronchial hyper-reactivity are not likely to be useful. Histological evidence of airways inflammation from direct bronchoscopy would be interesting but currently there is so little known about the early changes in childhood asthma that such an approach at present would not produce useful results. A double blind randomised trial of the use of inhaled steroids in this situation would be one way forward and the measurement of breath nitric oxide to help clarify the degree of airway inflammation would also be one interesting approach for the future.[2]

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1 McKenzie S. Cough – but is it asthma? *Arch Dis Child* 1994; **70:** 1–2.
2 Kharitonov SA, Yates D, Robbins RA, Logan Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. *Lancet* 1994; **343:** 133–5.

Dr McKenzie comments:

Antibiotics used to be prescribed for cough and sometimes still are. Parents often claim their benefit, as Dr Upton's parents do for steroids. Anecdote is no substitute for a good clinical trial.

Parents, of course, are pleased to be given a prescription and doctors are often delighted to write one, but sometimes parents are better pleased with an explanation. There is no proof that any medication is better than no medication for cough. I have to admit that my own practice of a two week trial of β agonists is far from satisfactory.

I agree with Dr Upton that treatment of cough with inhaled steroids needs proper evaluation. There is not much at present to support their empirical use. My main concern is that too many children could be labelled asthmatic because their cough improves while they are taking steroids. This could be purely coincidental or it could be that steroids affect non-specific cough by a mechanism different from that in asthma. I suspect the understanding and treatment of cough in children is likely to be one of the growth industries of the next decade.

Ethnicity and the sudden infant death syndrome: important clues from anthropology

EDITOR,—Davies and Gantley question a number of entrenched views on infant care practices.[1] The welcome fall in sudden infant death syndrome rates which has accompanied the reduction in the prone sleeping position of infants in several countries after 'risk reduction' campaigns suggests that apparently small changes in infant care practices may have profound effects upon infant well being and survival.

At birth the human infant is the least neurologically mature primate, with the longest and most intense postnatal dependence upon the mother. Infant monkeys separated from their mothers for brief periods experience adverse physiological consequences, including increased adrenocorticotrophic hormone concentrations, reduced body temperature, cardiac arrhythmias, and compromise of the immune system.[2]

In the home environment, mothers are able to achieve a thermoneutral environment for their sleeping infants with remarkable accuracy.[3] Studies of mothers and their 3 month old infants sleeping either in separate rooms or in the same bed ('co-sleeping') within a sleep laboratory on successive nights have shown the complexity of the mother-infant interactions during sleep.[4] Co-sleeping mothers and infants continually induce mutual small arousals, the infants breast feed more frequently than when sleeping separately, and mothers actively monitor and regulate their infant's thermal environment. The infants' inspired air commonly contains 0·5–1% carbon dioxide from the mother when co-sleeping. Co-sleeping babies spend less time in the deeper stages of sleep. Co-sleeping mothers almost always place their infants next to them in a supine position, close to their nipples, so that the infants can feed. The supine position is the only one in which infant manipulation, control, and breast feeding is facilitated.[5]

Infant sleep, breathing, arousal, and thermoregulation all evolved in the context of continuous parental contact, and no evidence has been produced on the benefits of solitary sleeping arrangements.

Western values favour early autonomy and individualism and researchers inadvertently may have overemphasised the infant's physiological independence from its caregivers, confusing the infant's preparedness to adapt with actual adaptation.[6]

Anthropological studies of parents and infants provide the basis for postulating that for some, possibly small subclass of potentially vulnerable infants, mother-infant contact throughout the night may be protective. Human evolutionary studies, cross cultural data on human behaviour, and studies of mother-infant interactions can give important insight into normal human development.

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1 Davies DP, Gantley M. Ethnicity and the aetiology of sudden infant death syndrome. *Arch Dis Child* 1994; **70:** 349–53.
2 Mckenna JJ. An anthropological perspective on the sudden infant death syndrome. The role of parental breathing cues and speech breathing adaptations. *Med Anthropol* 1986; **10:** 9–53.
3 Wigfield RE, Fleming PJ, Azaz Y, *et al.* How much bedding do babies need at night? *Arch Dis Child* 1993; **69:** 181–6.
4 Mckenna JJ, Thomson E, Anders TF, *et al.* Infant-parent co-sleeping in an evolutionary perspective: implications for understanding infant sleep development and the sudden infant death syndrome. *Sleep* 1993; **16:** 263–82.
5 Mosko S, Mckenna JJ, Dickel M, Hunt L. Parent-infant co-sleeping: the appropriate context for the study of infant sleep and implications for sudden infant death syndrome. *Research Journal of Behavioural Medicine* 1993; **16:** 589–610.
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Leucocyte adhesion deficiency syndromes

EDITOR,—El Habbal and S Strobel recently gave an interesting overview of what is known about the leucocyte adhesion deficiency (LAD) syndrome and the molecular basis of adhesive events that occur in the immune response.[1]

I would like to point out some details that need clarification. As the authors state the adhesion molecules can be subdivided into three superfamilies: the integrins, the selectins, and the members of the immunoglobulin superfamily. The tables of the review listing the adhesion molecules, their tissue distribution, and the supposed ligands contain a number of errors which might be misleading for the understanding of the regulation of adhesive interactions.

Members of the integrin family of adhesion molecules are heterodimers which are formed by the association of an α chain with a β chain. Neither VLA-4 (α4β1) nor the β6 integrins are identical with LPAM-1, the lymphocyte Peyer's patch adhesion molecule-1. LPAM-1 (α4β7) shares the α4 chain with VLA-4, however, the β chain is different (β7 versus β1 or β6) and therefore LPAM-1 belongs to the β7 integrins.[2] This is critical for the regulation of lymphocyte homing because LPAM-1 specifically mediates the binding of lymphocytes to the mucosa associated lymphoid tissue of the gut. LPAM-1 is expressed on T as well as on B lymphocytes and the ligand is not CD28 (here the β7 integrin has been mixed up with B7, one of the most important costimulatory molecules expressed on B lymphocytes and binding to CD28 and CTLA-4 on T cells). In contrast, the ligands so far identified for LPAM-1 are: MAdCAM-1, VCAM-1, and the extracellular matrix protein fibronectin.[3] VLA-4, however, is identical with LPAM-2, the lymphocyte Peyer's patch adhesion molecule-2, which has erroneously béen listed as being VLA-2.

VLA-4 or LPAM-2 participates, for example, in the inflammatory response in asthma but does only contribute to a minor extent if at all to the homing of lymphocytes to Peyer's patches.[2]

ICAM-3, a member of the immunoglobulin superfamily and constitutively expressed on lymphocytes and intradermal Langerhans' cells, should be added to the list of counter-receptors of LFA-1 since it has been cloned already in 1992.[4]

CD21, TAPA-1, Leu-13, and CD19 form a complex on the surface of B lymphocytes that upon crosslinking transmits signals into the cell but has not been identified to function as a ligand for β4 integrins in adhesive interactions.[5]

A recently described novel LAD syndrome termed LAD type 2 deserves being mentioned.[6] This complex syndrome is characterised by recurrent bacterial infections with high neutrophil counts, mental retardation, short stature, and the Bombay blood phenotype. The analysis at the molecular level revealed the lack of expression of Sialyl-Lewis X (sialylated form of CD15), the carbohydrate ligand of the leucocyte adhesion molecules E-selectin and P-selectin, on haemopoetic cells. Due to this defect neutrophils are no longer capable of adhering to endothelial cells using the E- and P-selectin pathway which initiates the transmigration of immunocompetent cells through the blood vessel. The underlying mechanism leading to the deficiency of Sialyl-Lewis X probably is a general defect in the fucosylation of glycoproteins and carbohydrates. The disturbance of the fucose metabolism would also explain the Bombay blood phenotype and may lead to the understanding of the other components of the syndrome as, for example, the mental retardation.

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1 El Habbal MH, Strobel S. Leucocyte adhesion deficiency. *Arch Dis Child* 1993; **69:** 463–6.
2 Hu MCT, Crowe DT, Weissman IL, Holzmann B. Cloning and expression of mouse integrin βp (β7): a functional role in Peyer's patch-specific lymphocyte homing. *Proc Natl Acad Sci USA* 1992; **89:** 8254–8.
3 Berlin C, Berg EL, Briskin MJ, *et al.* α4β7 integrin mediates lymphocyte binding to the mucosal vascular addressin MAdCAM-1. *Cell* 1993; **74:** 185–95.
4 Fawcett J, Holness CLL, Needham LA, *et al.* Molecular cloning of ICAM-3, a third ligand for LFA-1, constitutively expressed on resting leukocytes. *Nature* 1992; **360:** 481–4.
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6 Etzioni A, Frydman M, Pollack S, *et al.* Recurrent infections caused by a novel leukocyte adhesion deficiency. *N Engl J Med* 1992; **327:** 1789–92.

Dr El Habbal and Professor Strobel comment:
We thank Dr Wagner for his interesting comments on our review on leucocyte adhesion deficiency (LAD) which focused on clinical presentation and management.[1] We did not intend to discuss extensively the interspecies homology of adhesion molecules and, for example, did not include the cadherins[2] as a fourth family of adhesion molecules.

Our review was based on 'consensus' data published, and single reports, however interesting in their own right, were not included and ICAM-3 and the recently described novel 'LAD type 2' were consequently not discussed. We did not associate LPAM-1 with CD28 as Dr Wagner states. It is B7 (CD80) (and not β7 as erroneously printed in our table 1) which associates with CD28. We apologise for this misprint. His comments on LPAM-1 and LPAM-2 are correct, but they apply to mouse integrins only.

VLA-4 is *not* recognised to be abnormal in LAD. The VLA family of integrins are expressed as heterodimers, composed of a variable α (CD49a, b, c, d, e, f) and a constant β chain (CD29). Human VLA-4 (CD49d) is known to be 'promiscuous' and known to associate with either β1 and β7 integrin subunits. In the mouse CD49d can pair with β7 or β1 chains to generate LPAM-1 and LPAM-2. In humans, LPAM-1 shares homologies with β1 and β6 integrins, as stated.[3]

Dr Wagner's remarks on P-selectins and E-selectins, as well as his comments on a signal transduction complex (CD21, TAPA-1, Leu-13, CD19) are interesting but not relevant to the topic of our review.

LAD is a key example where astute clinical observations (combined with basic research) have led to an exponential increase in our understanding of the role of cellular adhesion pathways in innate and adaptive immunity (*'copora non agunt nisi fixata'*, Paul Ehrlich).

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Migration of fine bore Silastic catheter to pulmonary artery

EDITOR,—We wish to report a serious complication that arose during insertion of a long line, which was to be used to administer intravenous antibiotics to a 12 year old boy with cystic fibrosis. A fine bore Silastic neonatal catheter (Epicutaneo-Cava-Catheter model No 2184, Vygon) was used. This model has a detachable Silastic indwelling catheter that is inserted through a supplied 19 gauge needle. The proximal end of the catheter contains a short metal rod that is anchored within the distal end of the external supply line to prevent migration once sited. After venepuncture of the left basilic vein the catheter, unattached to the supply line, was threaded through the needle. The catheter was almost fully advanced so that the distal end might lie in a satisfactory position within the great veins. The needle was then removed from the vein and disengaged from the catheter by threading it over the proximal end. At this point the catheter was lost to vision and when the needle was fully removed, the proximal end was still not visible. Chest radiography revealed the metal proximal tip of the catheter to be lying in the right pulmonary artery. The catheter itself was radiolucent. We presume that dynamic venous flow and negative intrathoracic pressure caused aspiration of the whole catheter into the circulation. Subsequently, the patient underwent general anaesthetic and cardiac catheterisation. The catheter was successfully removed intact using a snare wire during a difficult and lengthy procedure.

We have used this type of line successfully for a number of years. The manufacturers inform us that this complication has occurred once before worldwide. They also stated that adherence to the instructions included with the line, updated in April 1992, should prevent this complication. The instructions state that, after advancing the catheter through the needle to the desired position, 'the catheter should then be fixed in its final position by applying slight pressure beneath the needle tip and the needle is then withdrawn ...'. However, there is no warning in the instruction leaflet of the potential complication reported here, although we gather that this will be highlighted in future.

The use of short and long indwelling venous catheters is known to carry a small risk of embolism to the heart and great vessels and has in the past led to both serious morbidity and mortality due to thrombus formation, infection, and perforation.[1] For these reasons, attempted removal of embolised catheters or fragments is recommended. This has been achieved by thoractomy[2 3] or by cardiac catheterisation.[4 5]

Embolism has been more commonly reported with use of the 'catheter in needle' cannula where during insertion the needle shears off the distal part of the catheter.[1 6] This complication has led to widespread use of 'needle in catheter' forms of cannulas, although these are not free from risk of fracture and embolism.[7] Embolism due to disconnection of the catheter from the supply line has also been described[1 7] and most catheters now in use have undetachable external hubs to prevent this problem. The catheter used in this reported case has neither of the above safety features. For such lines to be used safely, it is necessary to ensure that throughout insertion the line is at all times both visible and held externally.

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1 Wellmann KF, Reinhard A, Salazar EP. Polyethylene catheter embolism. Review of the literature and report of a case with associated fatal tricuspid and systemic candidiasis. *Circulation* 1968; **37:** 380–92.
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Prophylaxis or modification of varicella by oral acyclovir after household exposure

EDITOR,—In his commentary on our paper Dr Conway raised several concerns about the use of oral acyclovir in varicella infection.[1] We do believe that varicella should be