**LETTERS TO THE EDITOR**

**EGC and echocardiographic diagnosis of pulmonary thromboembolism associated with central venous lines**

Erroneously, Pollard et al retrospectively studied 21 children with central venous lines for parenteral nutrition by electrocardiography and eight by echocardiography. They state that ventilation perfusion (V/Q) scanning has a low sensitivity for detection of major pulmonary emboli based on the PIOPED investigators' study of 933 adult patients.5 The echocardiogram (ECG) criteria used by Pollard et al were based on a study of 49 adult patients of whom half were diagnosed by V/Q scan alone.6 Pollard et al describe their ECG findings as diagnostic of embolism and dismiss use of the V/Q scan. Their ECG based method cannot be regarded as more accurate than the technique used to validate it.

The study of Pollard et al presents ECG criteria for right ventricular strain as diagnostic of embolism without any validation. Corroboration of the diagnosis is available in only two children who had emboli at necropsy. In addition ECG criteria based on adult normal values were applied to paediatric patients, for example the frontal QRS axis at 5–7 years is +11 to + 143 allowing a normal child to achieve a positive criterion. The V/Q scan has however been validated in paediatric population and also supports that the pulmonary angiogram is of limited usefulness in chronic microemboli, while most authorities regard it as the gold standard.4 Pollard et al assert that the echocardiogram is very sensitive in establishing the diagnosis of pulmonary embolism, whereas the originator of the echocardiographic criteria suggests that it is an initial investigative tool. Pollard et al's reference to our own study is inaccurate in stating that 12 of 34 children had thrombosis visualised on echocardiography. In fact of the 12 children who had thromboemboli four were diagnosed only by V/Q scan with unremarkable echocardiograms, while eight had echocardiograms showing right atrial thrombus or pulmonary hypertension; in five of the eight V/Q scans showed clots. In two patients with indirect echocardiographic evidence of pulmonary hypertension as the sole abnormality pulmonary embolism was diagnosed at necropsy.

Pulmonary embolism secondary to long term parenteral nutrition has been ignored for too long. An increased awareness of this complication will improve patient care but only if a clear diagnostic and management strategy is available. Pollard et al's study confirms this issue and has given inappropriate prominence to ECG and echocardiographic diagnosis. These are valuable initial investigations which should lead on to V/Q scanning and if necessary to pulmonary angiography.

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**Drs Pollard, Sreeram, Wright, Beach, Booth, and Kelly comments:**
We are pleased that Dollery et al found our paper so stimulating but are disappointed that they seemed to have missed the point and are left confused by the use of the ECG and echocardiogram. Dollery et al draw attention to an important study comparing the sensitivity of ventilation perfusion scanning (V/Q), ECG and ECHO.3 Further scrutiny of this paper revealed that while the V/Q scan correctly identified only 29 out of 49 patients with pulmonary embolism, ECG and echocardiogram may pick up more cases than a V/Q scan we used echocardiographic information to draw attention to the fact that pulmonary thromboembolism is common in children with long term indwelling central venous lines and to advocate evaluation of preventative strategies. This view is supported by work previously published by Dollery et al,8 although we found a greater incidence of pulmonary embolism. We are grateful for the clarification of their study.

We have not dismissed the use of V/Q scanning or pulmonary angiography as they suggest and it is our practice to use these techniques in the absence of ECG and echocardiographic information in appropriate clinical situations to establish a diagnosis of pulmonary thromboembolism. We think that the ECG and echocardiogram is helpful and possibly more sensitive than current 'gold standards' but there have been no prospective studies comparing these techniques with V/Q scanning and pulmonary angiography in children to confirm this. Without this information we were unable to make recommendations regarding the place of any of these tests in routine investigation of such cases. We suggest that Dollery et al should also await results of prospective comparative studies before pronouncing judgment on our observations.

We agree that ECG and echocardiographic diagnosis of pulmonary thromboembolism requires further validation in children and Dollery et al will find this clearly stated in our paper. We did use appropriate paediatric reference values for the analysis of ECGs and echocardiograms and again, this is stated in the methods. Use of adult normal values would have been inappropriate. Until prospective data are available, we believe that clinicians may well find information from these readily available, non-invasive investigations helpful.

We had hoped to stimulate interest in the prevention of pulmonary embolism in parenteral nutrition dependent children with small bowel failure as a goal we share with Clare Dollery and her colleagues.9

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**Persistent nocturnal cough in childhood: a population based study**

**EDITOR—**The study by Ninan et al accepts that 'it is now well established that in some cases isolated persistent cough may be the sole presenting manifestation of asthma.' This is a fact proved in two studies that the article refers to. However, at the same time Ninan et al try to discount isolated persistent nocturnal cough as a marker of asthma. We have shared the same concern and this has been defined as a condition that has been present for at least three months. Consequently those children with persistent nocturnal cough should have been defined as those who have had symptoms at least three months and not four weeks.

The second problem is relying on the parents' history of persistent nocturnal cough. This is simply unreliable in our experience and has been proved in the small study by Falconer et al. This means that the reported persistent nocturnal cough is underestimated and inevitably has biased the results.

As we have suggested the diagnosis of asthma is easier when cough is associated with wheeze, shortness of breath and tightness in the chest, although, in fact, none of these symptoms individually or collectively is specific for asthma. For example, cough, cyanosis, dyspnoea, bronchiectasis, tuberculosis, and other rare conditions may present in a similar way. Detailed history including type of cough may help in the differential diagnosis. For example, dry cough is more suggestive of asthma. Other studies have relied on diagnostic tests to confirm or refute the diagnosis of asthma rather than relying on history alone.

Unfortunately in this study no diagnostic tests were applied to those with reported persistent nocturnal cough. We also would have liked to know if the symptoms of the 12% of the 27 children with it had been controlled by the antiasthmatic medication. We therefore think it is rather misleading to discount persistent nocturnal cough as a marker of childhood asthma.

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**Drs Ninan and Russell comment:**
We thank Drs Madlom and colleagues for their comments. We would like to point out that the publication here is only a small part of a...
much larger epidemiological study looking at changes in prevalence of respiratory symptoms and atopic diagnosis in childhood over a 25 year period. Eliciting information on the duration of persistent nocturnal cough is a particularly thorny issue. Falconer et al.² confirm the observations of Archer and Simpson that parental recording of nocturnal cough is inaccurate. They found significant underreporting over a three month period and, by haphazard choice, we chose subjects who had at least three episodes of persistent nocturnal cough and each of these episodes lasted for at least one month. Recall for recent events in general is more accurate than distant events. We feel this may have minimised the bias towards under-reporting.

Over the last four decades, epidemiological studies have consistently used wheeze, compared with those who did not, as the main outcome, and tightness of chest as marker symptoms of asthma. Though uncommon medical conditions such as cystic fibrosis and bronchiectasis may present with similar symptoms, particularly that the numbers are small. All the children in the study were examined by a paediatrician (TKN) and none of these children had overt evidence of either cystic fibrosis or bronchiectasis.

Studies on a diagnostic test are hospital based whereas this was a cross sectional community based study and we had constraints on the type of investigations that could be carried out. Long term prospective studies are needed for assessing effectiveness of control. This was designed as a prevalence study. We therefore have no information on effectiveness of control of persistent nocturnal cough.

Finally, we would like to reiterate that persistent nocturnal cough in epidemiological studies is not a good marker for asthma. This is a different population of children when compared to those in hospital, where there is a greater tendency to diagnose asthma in this biased hospital population for very valid reasons.


**Sodium/glucose cotransporter activity in cystic fibrosis**

**Errors.**—Enhanced intestinal sodium dependent glucose transport has been suggested to contribute to glucose intolerance in cystic fibrosis.¹ Moreover, this increased absorption exacerbates the luminal dehydration that contributes to cystic fibrosis pathophysiology. In the airways of those with cystic fibrosis sodium absorption is also increased, and recent reports suggest that this arises from the failure of a direct inhibitory effect of the cystic fibrosis transmembrane conductance regulator (CFTR) on apical membrane sodium channels.²,³ Increased sodium/glucose absorption in cystic fibrosis intestine may therefore occur in a similar way, or could alternatively involve an intracellular mechanism. To distinguish between these possibilities glucose uptake by the human small intestine in children with and without cystic fibrosis has been measured using brush border membrane vesicles (BBMVs); this allows the study of membrane transport in isolation from intracellular components.

BBMVs were prepared from endoscopic or Crosby capsule biopsies (duodenum or jejunum) taken from 38 children presenting with non-specific gastrointestinal symptoms or failure to thrive. Each specimen was obtained from an individual child with control tissues divided on the basis of biopsy histology showing no significant abnormality (n=46) or partial or total villus atrophy (n=3). Cystic fibrosis tissues (n=9) were obtained from pancreatic insufficient patients (six AF508/ΔF508, two ΔF508/other, one unknown genotype) and they had normal mucosal morphology. BBMVs were incubated for 10 seconds at 20°C in 100 mM sodium thiosuccinate and 100 μM D-[3H]-glucose, and active sodium dependent glucose transport was calculated from the uptake differences in the presence or absence of phloretin (250 μM). Results were analysed by non-parametric one way analysis of variance. Active uptake was observed in control vesicles from biopsies with no significant abnormality, but not in BBMVs prepared from biopsy specimens showing villus atrophy (p < 0.05 v no significant abnormality; fig 1), demonstrating that this preparation is sensitive to changes in epithelial function. However, active glucose transport in BBMVs from those with cystic fibrosis was not significantly different from controls with no significant abnormality (p > 0.05). This contrasts with studies of intact cystic fibrosis biopsy specimens where the rate of active sodium/glucose transport was approximately doubled.

The fact that active glucose uptake is not enhanced in cystic fibrosis intestinal BBMVs where the intracellular machinery is absent, indicates that the membrane activity of the sodium/glucose cotransporter is not directly altered in this disease. If wild type CFTR does regulate intestinal sodium linked nutrient absorption, it must do so via a mechanism involving intracellular components.

**Figure 1 Mean active glucose uptake into BBMVs prepared from biopsy specimens showing no significant abnormality (NSA), villus atrophy, or cystic fibrosis (pancreatic insufficiency).**

**Haemoglobin values in venous and skin puncture blood**

**Errors.**—Emond et al report valuable data on the range of haemoglobin values found in healthy 6 month old infants from a puncture (capillary) blood samples.² They state that such samples produce lower haemoglobin values than venous samples, quoting the report of Dallman and Reeves.³ While there is support for this view, others have found either no difference in mean values between the two sample types,⁴ or higher haemoglobin values in skin puncture blood.⁵ It is well recognised that much higher packed cell volume and haemoglobin concentrations can be found in skin puncture samples in the neonatal period, especially in ill children.⁶ In our own study,⁷ skin puncture haemoglobin values were on average 3.5% higher than those in venous blood, and the skin puncture value was higher in 76% of paired samples. To determine if these findings apply to samples collected in routine practice, a retrospective study of haemoglobin values of paired samples analysed in this laboratory over a five year period was undertaken. Subjects were children, many of South Asian ethnic origin, in whom the skin puncture sample was the only sample. A venous sample was then requested to search for evidence of iron lack or thalassaemia trait. Skin puncture samples were taken by laboratory staff and venous samples by medical staff. A venous sample was limited to paired samples collected within a 14 day period. A total of 188 such pairs was found; in 137 (73%) the samples were collected within two days of each other. Children were aged 0.5–16.9 years, median 3.7 years. The results confirm our earlier findings. Skin puncture values were significantly higher in each group, with the greatest difference between the two sample types being seen in infants (table). Skin puncture haemoglobin values were higher than venous values in 132 children (70%), lower in 42 (22%), and identical in 14 (7%).

It is likely that the reason for conflicting reports on the relative concentrations of venous and skin puncture haemoglobin lies in variations in blood collection technique, and the methods of haemoglobin determination. These methods have been widely available for many years. For example, excessive use of a tourniquet may cause venous stasis and give rise to higher haemoglobin values, while warming the thumb or heel before sampling can reduce capillary stasis, and lead to lower values from this type of sample.

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