LETTERS TO THE EDITOR

Respiratory rate and pneumonia in infancy

SIR,—Dr Berman *et al* have presented an interesting and comprehensive paper about the use of respiratory rate in infants in the diagnosis of pneumonia.¹ This is an important topic because counting respiratory rate is a critical aspect of the World Health Organisation acute respiratory illness programme.

One of the difficulties has been that the normal range of respiratory rate had not previously been defined. The object of our paper was to define the normal range of respiratory rate in infants when they were awake.² Berman *et al* suggested that our results (mean (SD) 61 (18)/minute) were too high because they do not compare with studies using electronic monitoring. Unfortunately, electronic monitoring is not a satisfactory gold standard for respiratory rate because studies in awake babies have movement artefact and the study of sleeping babies is not appropriate for routine clinical practice. Our range of respiratory rate for sleeping babies was similar to those in the published literature (42 (12)/minute).

They suggest that the use of a stethoscope or a hand on the chest for counting the respiratory rate in our study may have stimulated the infants to breathe faster than normal. Their own studies suggest this can result in a respiratory rate 14 breaths/minute higher than that obtained by observation. This may be possible, although it was not our observation. We used this technique simply because we found it very difficult to count respiratory rate by observation and wanted to use a technique that could easily be used in all babies regardless of their state. It was our experience that respiratory rate could be counted by observation accurately in sleeping or ill babies because they lie still and often have increased respiratory effort. It was surprisingly difficult in lively healthy babies because they move approximately once a second and also breathe shallowly and irregularly.

Berman *et al* compare our data with a study in which respiratory rate was counted by observation in a community in Peru. Unfortunately, even that data can not be considered to represent the respiratory rate range of normal infants because the children were selected for the study only if they had a cough.

Unfortunately, the authors make a common statistical mistake when calculating sensitivity, specificity, and predictive values for pneumonia using respiratory rate above or below 50 or 60 breaths/minute. Their data were collected only from selected children seen in hospital. In their Denver study the infants were only seen if they had a cough or congestion and in the Vellore study the infants presented with a runny nose or cough.

The authors had no data from normal infants. Sensitivity, specificity, and predictive values are accurate only for the populations from which the data were derived and cannot be extrapolated to infants in the community. Even using this selected data the sensitivity of a respiratory rate of 60 or more for lower respiratory infection was only 63% in Denver and 58% in Vellore. To be a useful screening

test for pneumonia, respiratory rate measurement must have a much higher sensitivity.

Before it can be claimed that respiratory rate is a useful screening test for pneumonia data must be presented using a simple technique of proved accuracy and repeatability from children with pneumonia and normal children in the communities where it will be used.

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- 1 Berman S, Simoes E, Lanata C. Respiratory rate and pneumonia in infancy. *Arch Dis Child* 1991;66:81-3.
- 2 Morley CJ, Thornton AJ, Fowler MA, *et al*. Respiratory rate and severity of illness in babies under 6 months old. *Arch Dis Child* 1990;65:834-7.

Drs Berman and Simoes comment:

We appreciate the opportunity to respond to Dr Morley's comments on our annotation. The issue of the usefulness of simple clinical signs to identify pneumonia is important and we agree that it is necessary to document the range of respiratory rate counts in infants with and without acute respiratory infections. Interpretation of studies is impaired by the use of different counting methods. Unfortunately there is no counting method that can be considered a gold standard. It is possible that differences in respiratory rates reported in studies may partially reflect the different methods used to obtain them. Our own study comparing simultaneous counts obtained by observation versus electronic pneumogram tracing documents differences between these methods.¹ Our annotation pointed out that counting with a stethoscope or by placing a hand on the abdomen may itself result in differences compared with obtaining counts by other methods. The use of a 15 second counting interval would also increase any consistent difference by a fourfold factor. We agree with Dr Morley that counting respiratory rates in very active 'lively' infants is difficult regardless of the counting method. Our recently completed study corroborates this finding.

The World Health Organisation (WHO) chose to develop respiratory rate thresholds based on data obtained using 60 second observed counts. This choice was made for operational reasons, based on the need to train community health workers to count respiratory rates without using a stethoscope.

The WHO respiratory rate thresholds have been designed to be used on subjects who have respiratory symptoms of cough or coryza. The case management guidelines are not relevant for healthy infants and children without respiratory symptoms. It is for this reason that sensitivity, specificity, and predictive value should be calculated on populations with respiratory symptoms. The predictive value of the respiratory rate threshold for pneumonia will vary with the prevalence of the pneumonia in the population with respiratory symptoms. It was not our intention to generalise sensitivity, specificity, and predictive value to the total population of children with and without respiratory symptoms.

We agree that the sensitivity and specificity of the WHO respiratory rate threshold applied to infants under 2 months of age is not as good as that in older infants and children. Further research is needed to evaluate the usefulness of

the threshold in association with other clinical signs to diagnose pneumonia in that age group. Studies are underway in the Gambia and the Philippines to clarify these issues.

- 1 Simoes EAF, Roark R, Berman S, Esler LL, Murphy J. Respiratory rate: measurement of variability over time and accuracy at different counting periods. *Arch Dis Child* 1991 (in press).

Diagnosis of pneumothorax by echocardiography

SIR,—Over the last 18 months we have performed frequent echocardiograms on ventilated neonates as part of a study on haemodynamics.¹ Pneumothorax is common in this setting. We report three cases where pneumothorax was first suspected on echocardiography.

Case reports

CASE 1

This infant, born at 41 weeks' gestation weighing 2370 g, was ventilated after birth asphyxia and meconium aspiration. A chest x ray picture at 4 hours showed no air leak. At 22 hours the heart was difficult to see echocardiographically and was best seen from the right sternal edge. There was no clinical deterioration. Transillumination was negative. A further chest x ray picture showed a small left pneumothorax which was managed conservatively. Five hours later, radiography showed no air leak and echocardiographically the heart was easily seen and normally positioned.

CASE 2

This infant, born at 25 weeks' gestation weighing 785 g, was ventilated for hyaline membrane disease. There was no air leak on a chest x ray picture at 4 hours. At 16 hours, on echocardiography, the heart was difficult to see and displaced to the right. Transcutaneous carbon dioxide had risen from 4.5 to 6.9 kPa over the previous half hour. Transillumination showed left tension pneumothorax. After drainage, the heart was no longer displaced on echocardiography.

CASE 3

This infant, born at 27 weeks' gestation weighing 1040 g, was ventilated for hyaline membrane disease and birth asphyxia. A chest x ray picture at 10 hours showed no air leak. Echocardiography at 14 and 36 hours showed poor myocardial function. From 48 to 52 hours systolic blood pressure fell from 40 mm Hg to 32 mm Hg despite support. At 52 hours the heart was difficult to see echocardiographically but was displaced to the left with the apex tilted cranially. Transillumination showed right tension pneumothorax. After drainage the blood pressure rose to 58 mm Hg; echocardiography showed an easily seen, normally positioned heart.

The heart is normally easy to see echocardiographically in the neonate ventilated for hyaline membrane disease. In these three cases the heart was difficult to see from the left sternal edge, and was displaced laterally, away from the air leak; this was presumably due to a combination of mediastinal shift and interposing air, which is impervious to ultrasound.

Unilateral pulmonary interstitial emphysema has mimicked these findings, hyperinflated

lung lying in front of the heart. With other causes of mediastinal shift the heart should be easily seen unless there is air in front of it; in diaphragmatic hernia the heart should be visible in its displaced position² until bowel gas accumulates.

Ultrasound is therefore a new technique to diagnose pneumothorax, but it is clearly not the best, and any suspicion should be confirmed using conventional methods before treatment. Nevertheless, pneumothorax can be a catastrophic complication of hyaline membrane disease, and those performing echocardiography on sick, ventilated neonates should be aware of this, so if the heart is difficult to visualise, or is laterally displaced, the attending clinicians can be informed immediately.

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Dr J Skinner is supported by the National Heart Research Fund.

- 1 Skinner JR, Hunter S, Hey EN. Pulmonary artery pressure in hyaline membrane disease. *Pediatr Res* 1990;28:286.
- 2 Crawford DC, Wright VM, Drake DP, Allan LD. Fetal diaphragmatic hernia: the value of fetal echocardiography in the prediction of postnatal outcome. *Br J Obstet Gynaecol* 1989; 96:705-10.

Fluconazole in neonatal disseminated candidiasis

SIR,—We report the case of an infant, born at 28 weeks' gestation weighing 900 g, who on the 22nd day of life had thrombocytopenia and leukocytosis. Urine and blood cultures yielded *Candida albicans*. Amphotericin B was raised to 1.0 mg/kg/day by day 4 and on day 5, flucytosine 25 mg/kg every six hours was added and a broviac catheter inserted. Peripheral and central blood cultures on the 7th, 14th, and 18th days of treatment with amphotericin B continued to yield *C. albicans*, and cultures of abscesses on the forehead and arm yielded *C. albicans* on day 18. Ultrasound of the kidneys, head, and abdomen as well as an ophthalmologic evaluation, gallium scan, and culture of the cerebrospinal fluid were negative. Amphotericin B and flucytosine were discontinued after 18 and 12 days, respectively. The catheter was removed and intravenous fluconazole (6 mg/kg/day) initiated.¹ The catheter was replaced on day 4 of fluconazole. On day 5 of fluconazole peripheral and central blood cultures were

negative for *C. albicans*. Fluconazole was discontinued after 20 days with cultures remaining negative during four months of follow up.

Fluconazole serum concentrations three hours after the infusion and before the next dose on day 7 of treatment were 10.30 and 6.98 µg/ml. Amphotericin B concentrations were 0.21 µg/ml on day 14 of treatment and 0.12 µg/ml 30 days after discontinuation. A first order, one compartment model² resulted in the following pharmacokinetic parameters for fluconazole:

$$t_{1/2\beta} = 37.4 \text{ hours, } aV_d = 1.2 \text{ l/kg,}$$

$$CL = 0.02 \text{ l/kg/hour.}$$

(Where $t_{1/2\beta}$ is terminal elimination half life, aV_d is the apparent volume of distribution, and CL is clearance.) This indicates a larger aV_d and a longer $t_{1/2\beta}$ as compared with adults (0.7 (0.06) l/kg and 22 (3.5) hours).³

The activities of four antifungal drugs against the isolate of *C. albicans* from this patient are indicated in the table.⁴ These results do not necessarily reflect therapeutic efficacy. Because of the presence of amphotericin B during and after fluconazole, one could speculate that fluconazole and amphotericin B acted synergistically. Other factors may have also helped to eradicate *C. albicans*. Further studies of fluconazole's efficacy in immunocompromised adults with invasive fungal disease are needed before studies in neonates are considered.

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- 1 Viscoli C, Castagnola E, Corsini M, et al. Fluconazole therapy in an underweight infant. *Eur J Clin Microbiol Infect Dis* 1989;8:925-6.
- 2 Gibaldi M, Perrier D. Pharmacokinetics. 2nd Ed. New York: Marcel Dekker, 1982.
- 3 Humphrey MJ, Jevons S, Tarbit MH. Pharmacokinetic evaluation of UD-49,858, a metabolically stable triazole antifungal drug, in animals and humans. *Antimicrob Agents Chemother* 1985;28:648-53.
- 4 Rinaldi MG, Howell AW. Antifungal and antimycotic laboratory evaluation. In: Wentworth BB, ed. *Diagnostic procedures for mycotic and parasitic infections*. 7th Ed. Washington, DC: American Public Health Association, 1988: 325-56.

Chronic vitamin D overdosage: a reminder

SIR,—After the reported increased incidence of rickets in Asian children in the late 1970s there has been increased awareness of the need for vitamin D supplementation.¹ This is now being recommended by the Department of Health and usually given together with other vitamins in multivitamin preparations.

Parents are able to obtain their supply through their local child health clinics under the Welfare Food Scheme.² There are also many alternative preparations available without a prescription via other sources, however, including chemists and health shops. Therefore, self medication without professional supervision is a potential danger. Chronic poisoning as a result of inappropriate administration of vitamins is rarely reported now (there has been no case reported in the English language literature in the past 10 years) but we were recently presented with a case of gross hypercalcaemia due to vitamin D overdosage.

A 6 month old Indian boy was admitted with a six day history of vomiting, constipation, and increasing apathy. Examination revealed a drowsy, listless child with signs of 5-10% dehydration. Plasma electrolyte concentrations on admission showed a urea of 7.4 mmol/l, sodium 148 mmol/l, potassium 2.9 mmol/l, and a grossly raised calcium concentration of 5.86 mmol/l.

Subsequent investigations showed an appreciably increased vitamin D concentration (25-hydroxycholecalciferol) at 2226 nmol/l (normal 10-120 nmol/l) and undetectable parathyroid hormone. On close questioning, his parents admitted to administering a compound preparation of vitamins A, C, and D since the age of 4 months, and as he had refused to take these from the dropper, they poured the vitamin into his mouth directly from the bottle instead! They had obtained their vitamin supply from a chemist privately and had received no professional supervision of administration.

The baby was given intravenous fluids for five days and also commenced on a low calcium, low vitamin D diet. He was discharged home on day 12. His calcium returned to normal by day 19 but his vitamin D concentration remained raised for over six months. Follow up at one year showed moderate global developmental delay.

This case illustrates the dangers of unsupervised vitamin supplementation. To prevent further incidents, tighter control over availability of vitamins and improved public awareness of the potential dangers of vitamin overdosage would be helpful. Health professionals should also aim to improve supervision.

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- 1 Anonymous. Rickets in Asian children. *BMJ* 1979;i:1744.
- 2 Department of Health and Social Security. *Present day practice in infant feeding*. 3rd Report. London: DHSS, 1988: 35-6, 50.

The paediatric departmental library

SIR,—Dr Clayden is, I fear, somewhat over optimistic when he suggests that we are 'on the brink of a breakthrough in data retrieval' by which we will 'access original articles and learned reviews at the touch of a few buttons . . . so the medical library will pass into the mists of memory'.¹ Clearly this sort of thing is on the horizon. I already spend nearly as much time advising doctors on suitable

Minimum inhibitory concentration and minimum lethal concentration of four antifungal drugs (concentrations in µg/ml)

	Amphotericin B	Fluconazole	Itraconazole	Schering 39304
Minimum inhibitory concentration:				
24 hours	<0.01	<1.25	0.02	<0.63
48 hours	<0.29	5.00	0.02	2.50
Minimum lethal concentration:				
24 hours	0.58	>80.00	>10.00	>80.00
48 hours	2.31	>80.00	>10.00	>80.00