LETTERS TO THE EDITOR

Nitric oxide and severe sepsis

EDITOR,—Duke *et al* report changes in serum markers of nitric oxide (NO) production in children with severe sepsis.¹ Their findings provide additional data concerning activation of the L-arginine-NO pathway during systemic inflammation and also raise some important methodological issues.

The classical serum markers of NO production are nitrite and nitrate; these are also termed reactive nitrogen intermediates (RNIs) and are stable and easily measured in body fluids—see review in Feelisch and Stanler.² Levels of these markers in plasma, urine, and saliva are profoundly affected by dietary nitrate, especially ground water³ and nitrate rich food,^{2,4,5} where, after ingestion, levels of nitrate may increase 10-fold in healthy adults.⁶ In order to deplete the body of dietary nitrate and for serum nitrate and nitrite to accurately reflect total body NO production, at least 48 hours of a nitrate free diet is necessary.^{2,4,5}

In this study, Duke and colleagues used unselected emergency admissions of septic patients to an intensive care unit as study subjects, with elective cardiac surgery admissions as controls. It was therefore not possible to control for dietary confounders in either group. Moreover, cardiac failure results in induction of NO production.⁷ These factors might have contributed to the wide variation and the high levels of RNIs seen in both groups upon admission. This is one possible explanation why the authors only found a trend, rather than a significant increase, in RNIs in septic children with organ failure compared with those without. It is possible to circumvent the issue of dietary confounders in the measurement of NO production by measuring metabolites unaffected by diet. For example, one can measure hydroxyarginine,⁸ nitrosothiols,² nitrosohaemoglobin by electron spin resonance,² conversion of ¹⁵N-arginine to ¹⁵N-citrulline,⁴ and inducible NO synthase activity directly.⁵

Measurement of NO metabolites is also affected by renal function, as RNIs are retained in renal impairment, so it may be more accurate to express RNIs as an RNI:creatinine ratio.^{4,5} In addition, because RNI concentrations are affected by hydration state, NO formation may be overestimated in disease states characterised by dehydration,⁵ as may be the case in septic shock.

A further point concerns the production of NO by leucocytes. It would appear from the clinical details of the septic patients that a proportion were immunosuppressed, although this is not specifically mentioned. In sepsis, an important source of NO may be peripheral leucocytes. Septic neutropenic patients appear to produce less NO than septic patients with normal or raised neutrophil counts.⁹ If some of the study patients were neutropenic, this may result in a significant fall in the amount of NO produced by these children, thereby contributing to the wide range of serum values seen, and possibly acting as a confounder. It would therefore be

interesting to know whether the neutropenic septic patients were among those with the lowest serum RNI levels.

In conclusion we believe that studies investigating the production of NO in pathophysiological situations should take into account possible confounders, such as dietary nitrate, neutrophil count, renal function, and level of hydration.

DAVID BURGNER
Goroka Base Hospital,
PO Box 392, Goroka,
Papua New Guinea

KIRK ROCKETT
Department of Paediatrics, University of Oxford,
John Radcliffe Hospital,
Oxford OX3 9DU

Drs Duke and South comment:

Drs Burgner and Rockett make some important points regarding the interpretation of metabolites of NO in clinical studies. Currently there can only be a crude assessment of the role of NO in sepsis. We cannot infer from the measurement of serum nitrogen oxides, or any of the other measures suggested by the authors, the activity of NO in regional microcirculatory beds, or whether there is a causal relationship between NO production and sepsis morbidity. Even though we did find significantly higher levels of serum nitrogen oxides in children who developed organ system failure, we did not find a biological gradient between the numbers of organ failing and nitrogen oxide concentrations. Although variations in dietary intake of nitrates may partially account for this, there may be more important reasons. First, the cause of organ failure in sepsis will not be attributable solely to NO overproduction, or to any other individual cytokine. Second, there is likely to be a level of microcirculatory NO activity that is necessary to ensure tissue perfusion, and that is beneficial in sepsis. Third, our study had relatively small numbers of children with multiple organ failure, and low power to detect a difference.

We have analysed the data using the RNI:creatinine ratio and found no significant association between the ratio and mortality or organ system failure. The median (interquartile range) of area under the curve (AUC) RNI:AUC creatinine over the first 48 hours of intensive care unit admission was 957 (433–1268) for survivors, and 739 (335–791) for those who died (Wilcoxon rank sum test, $p=0.19$); and 990 (620–738) for those with no organ failure and 738 (338–1330) for those with one or more organ systems failing ($p=0.31$). In infants and children, age dependent differences in the normal range of serum creatinine make the interpretation of this suggested analysis additionally complicated.

There were four children with immunodeficiency causing neutropenia (numbers 8, 9, 17, and 18). These children did not have significantly lower serum nitrogen oxides than the other children with sepsis.

We agree that there are many confounding variables in the interpretation of NO metabolites. More importantly, despite the finding that overall NO is increased, many children with severe sepsis have low cardiac output, systemic vasoconstriction and pulmonary hypertension,¹⁰ and currently available agents that inhibit NO activity seem likely to reduce cardiac output,¹¹ worsen oxygen delivery and exacerbate pulmonary hypertension.¹²

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Sweat sodium is not sweat chloride

EDITOR,—We read the annotation on the diagnosis of cystic fibrosis with great interest.¹ However, some points about the sweat test that were made are potentially misleading and unfairly denigrate a valuable diagnostic tool.

We were interested in the statement that '10% of normal adolescents will have sweat salt concentrations greater than 60 mmol/l'. Although this may be the case for sweat sodium, we do not find this for sweat chloride concentrations, provided a cut off of greater than 70 mmol/l as suggested by the author is used rather than 60 mmol/l as quoted in the seventh paragraph. Sweat sodium concentrations do have a greater age dependency² and may be misleading or confusing if chloride is not measured. In our experience, interpretation of sweat electrolytes does not require particular 'correction for age' as the cut off for sweat chloride of >70 mmol/l that we use for neonates and infancy, is maintained for adults,³ providing excellent discrimination. Reviewing sweat tests performed here on 68 individuals with clinical suspicion of cystic fibrosis aged from 10 to over 40 years over the last five years, seven had clear increases of sodium and chloride consistent with cystic fibrosis. Of the remaining 61, 14 had a sweat sodium greater than 60 mmol/l (with the chloride varying from 36–69 mmol/l) but none had a chloride greater than 70 mmol/l. To our knowledge only one of these 61 patients has subsequently been classified clinically as having cystic fibrosis and was associated with a 'mild' genotype. We

have found the ratio of chloride to sodium to be a valuable interpretative tool which is demonstrated best in graphical format. When the ratio is used in conjunction with the chloride concentration, patients with and without cystic fibrosis very rarely overlap in any age group in our hands. The fludrocortisone suppression test was used in the investigation of adults in the days when sweat sodium was often measured in isolation and should now be considered unnecessary and out of date for all ages.

Repeating a sweat test to confirm a positive result is prudent, but performing it three times to avoid technical errors should not be necessary. Centres needing to do this must consider whether they should continue to offer the test at all.

Difficulties because of inadequate sweat should not arise in infancy, although inadequate sweat weights may be a little more commonplace in neonates.

In contrast to the author, we consider the sweat test to be very useful indeed in infancy in the diagnosis of cystic fibrosis. It is very unusual in our population in the West Midlands to come across normal sweat chlorides in children who are subsequently found to have cystic fibrosis. In the 1990s it is inappropriate to measure only sweat sodium. Moreover, sweat sodium and sweat chloride are not synonymous and must be differentiated—to discuss sweat 'salt' muddies the waters. We believe that the sweat test continues to provide valuable diagnostic information when interpreted correctly in the context of the clinical presentation—don't knock it out of the diagnostic repertoire.

S K HALL
S M KEFFLER
P WELLER*
A GREEN

*Clinical Chemistry Department and Department of
Respiratory Medicine and Cystic Fibrosis*,
Birmingham Children's Hospital,
Ladywood Middleway,
Ladywood, Birmingham B16 8ET*

Dr Wallis comments:

I am sorry that your correspondents feel that the sweat test got a bad press in the recent annotation. This was never intended and statements such as 'the sweat test remains the gold standard for the diagnosis of cystic fibrosis' and 'raised sweat electrolytes confirm most cases of cystic fibrosis' are strong confirmation of its importance. Far from knocking it I can only reconfirm its central place by again quoting from the article's 'golden rule' to perform 'the sweat test in a centre that undertakes the test regularly and measures both the sodium and chloride'.¹

Not all biochemistry departments measure both chloride and sodium levels in sweat routinely. Some believe that sodium levels have been well studied and provide robust information for varying sweat weights in childhood⁴ while others prefer to measure chloride. Most clinicians would like to have levels for both electrolytes in unusual clinical cases or after equivocal results in the initial testing. In these borderline cases—as with the small infant—I would have no problem in requesting a third sweat test.

I thank the correspondents for emphasising the importance and benefits of measuring and differentiating between both salts in the sweat test and for highlighting the specific value of chloride levels. But a normal sweat chloride, although rare, is well described in

cystic fibrosis. Beware the unusual phenotypes. They are out there.

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- 3 Hall SK, Stableforth DE, Green A. Sweat sodium and chloride concentrations—essential criteria for the diagnosis of cystic fibrosis in adults. *Ann Clin Biochem* 1990;27:318-20.
- 4 Hjelm M, Brown P, Briddon A. Sweat sodium related to amount of sweat after sweat test in children with and without cystic fibrosis. *Acta Paediatr Scand* 1986;75:652-6.

Diagnosing cystic fibrosis

EDITOR,—Colin Wallis' review of diagnostic criteria for cystic fibrosis gave an excellent overview of an increasingly complex subject.¹ No longer can cystic fibrosis be diagnosed on the basis of suggestive symptomatology confirmed by sweat testing. Mutation analysis has led to the identification of many pancreatic sufficient 'mild mutations', some of which, including the 3849+1 Okb C-T splicing mutation at intron 19² and the A455E mutation,³ are associated with normal sweat electrolytes. In other cases the phenotype can vary with the length of the polypyrimidine tract in the splice acceptor site in intron 8 (poly T variant).⁴ In many of these mild mutations functional cystic fibrosis transmembrane conductance regulator (CFTR) is produced but with reduced single channel kinetics.⁵

Quantitation of chloride channel dysfunction, derived from transepithelial current measurements,⁶ can provide a rapid and reliable method for confirming or excluding the diagnosis of cystic fibrosis.⁷ However, nasal potential difference measurements are far from straightforward, particularly in infants and young children. In such cases intestinal current measurements can prove helpful. Our own studies using jejunal biopsy tissue and similar work from Dutch colleagues using rectal biopsy tissue⁸ have shown abnormal intestinal chloride currents can be identified in patients with inconclusive sweat electrolyte concentrations or where genetic analysis has revealed only one CFTR mutation.

The results of secretagogue challenge performed on duodenal or jejunal biopsy tissue in 10 patients with chronic lung disease with or without poor weight gain and two patients with meconium ileus but normal immunoreactive trypsin values are given below. Seven were known to be heterozygous for the $\Delta F508$ mutation. Compared with 49 normal controls and four obligate heterozygotes, the secretory response induced by 10^{-3} M acetylcholine was significantly reduced in six patients supporting a diagnosis of cystic fibrosis (mean (SE) changes in short circuit current (Δ SCC): $4.3(1.4)$ $\mu A/cm^2$, controls $37.0(4.0)$ $\mu A/cm^2$; $p < 0.05$), three of whom subsequently had the diagnosis confirmed by genetic analysis ($\Delta F508/L88S$, $\Delta F508/3849+10kbC>T$, $15251G>A/1525-1G>A$). Six patients had basal and secretory responses within the normal or heterozygote range (mean (SE) Δ SCC after acetylcholine: $26.7(6.8)$ $\mu A/cm^2$, heterozygotes $17.4(4.9)$ $\mu A/cm^2$); none of these patients has been found to have two identifiable cystic fibrosis mutations despite extended genetic analysis ($2 \times \Delta F508/N$, $4 \times N/N$).

Neither Veeze's group nor our own has found false positive intestinal current meas-

urements in control subjects. Intestinal current measurement appears an accurate and reliable method of either confirming or excluding the diagnosis of cystic fibrosis, particularly in young children unsuitable for nasal potential difference measurements, symptomatic adults with negative sweat tests, and patients with false positive sweat tests and atypical sodium/chloride ratios.⁹

CHRISTOPHER J TAYLOR

*Department of Paediatrics, University of Sheffield,
Sheffield Children's Hospital,
Western Bank, Sheffield S10 2TH*

ANN DALTON

JACKIE HARDCASTLE*

PETER T HARDCASTLE*

STEVEN EVANS

*Department of Human Genetics and Department of
Biomedical Science*,
University of Sheffield*

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Immaturity of medullary cardiorespiratory neurones leading to inappropriate autonomic reactions as a likely cause of sudden death in Rett's syndrome

EDITOR,—Rett's syndrome is a cause of intellectual disability with frequent respiratory dysrhythmia. In a survey in Great Britain, we identified episodic hyperventilation in 75%, apnoeic attacks in 70%, non-seizure vacant spells in 77%, and epileptic seizures in 70% of 191 classic cases. Of all reported deaths from Rett's syndrome, 25% were sudden and unexpected. Certain groups of interacting neurones in the medulla perform autonomic and respiratory functions that can be measured non-invasively. With informed consent and the approval of the local ethics committee, we measured the autonomic reactions to hyperventilation in Rett's syndrome and age matched controls while monitoring their respiration to understand the interactions between medullary autonomic and respiratory neurones.

Breathing movements were monitored using a resistance plethysmograph tied around the chest. Sympathetic activity related to the mean arterial blood pressure (MAP)¹ was measured continuously and

non-invasively using the Finapres (Ohmeda). Cardiac vagal tone (CVT) was also measured continuously and non-invasively from the responses of heart rate to spontaneous baroreflex. These were converted into atropine derived units of a linear vagal scale (LVS),² by a machine, the NeuroScope. All measurements including heart rate were integrated and stored beat-by-beat into a micro-computer.

In eight control girls aged 4–11 years, mean (SEM) CVT was 10.5 (0.9) units in the LVS, MAP was 94.6 (6.4) mm Hg. During voluntary hyperventilation, vagal tone responded briskly and successfully corrected the raised MAP (fig 1). In six girls with Rett's syndrome of the same age group, MAP was 78 (4.33) mm Hg during quiet rest. Vagal tone was 3.6 (0.7) units in the LVS, 65% lower than in controls ($p < 0.001$, t test), but similar to the 3.0 (0.6) units previously reported in quiet neonates.³ During spontaneous hyperventilation, vagal tone responded briskly, but failed to correct a grossly raised MAP (fig 1). Vagal tone was invariably withdrawn at the height of sympathetic activity during hyperventilation. This sympathovagal imbalance bears the risk of cardiac arrhythmias in Rett's syndrome, a possible cause of sudden death.

We suggest that medullary cardioinhibition is immature in Rett's syndrome. Although neuropathological studies have shown immaturities in other areas of the brain,⁴ this is the first functional evidence of immaturity which is potentially useful for diagnosis and management of Rett's syndrome.

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P O O JULU
A M KERR*
S HANSEN
F APARTOPOULOS
G A JAMAL

Peripheral Nerve and Autonomic Unit, INS,
Southern General Hospital, Glasgow G51 4TF and
*Glasgow University Department of Psychological
Medicine,
Gartnavel Royal Hospital, Glasgow, Scotland

Figure 1 Continuous and concurrent records of mean arterial blood pressure (BP) and a measure of cardiac vagal tone expressed in units of a LVS. The upper pair of traces are examples obtained from a normal 8 year old girl to show the reaction to voluntary hyperventilation (H). The lower pair of traces are examples obtained from an 8 year old girl with Rett's syndrome to show the reaction to her spontaneous hyperventilation (H).

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Late development of IgA antiendomysial antibodies and small intestinal mucosal atrophy after insulin dependent diabetes mellitus onset

EDITOR,—Recent studies have demonstrated that coeliac disease can develop months or years after the clinical onset of insulin dependent diabetes mellitus (IDDM).¹ Over the last 10 years, 200 consecutive children with IDDM at the onset have been tested for IgG and IgA antigliadin antibodies (AGA) by indirect immunofluorescence² and for IgA antiendomysial antibodies (EmA) using monkey oesophagus and, more recently, human umbilical cord as substrate.³ An antibody follow up was also performed in 151 of these patients every 3–6 months. At initial testing six diabetic children (four girls and two boys, median age 9 years, range 2–13) were positive for both IgA EmA and IgA AGA (associated with IgG AGA in five cases). A flat duodenal mucosa consistent with a diagnosis of coeliac disease was found in five (2.5%), whereas the remaining child (a 9 year old girl), who was positive for both IgA EmA and AGA at high titre, showed a normal small intestinal mucosa. One year later, antibody tests were again positive and a second biopsy specimen revealed the appearance of a subtotal villous atrophy (table 1, case 1). During follow up a further four children (three boys and one girl, median age at IDDM onset 3.3 years; range 2.9–3.5) of those initially antibody negative became positive. Two of these patients with antibody appearance within 10 and 16 months respectively showed a flat mucosa (table 1, cases 2 and 3). The late development of small intestinal atrophy in these three IDDM cases added 2% to the prevalence of the disease, which resulted as a whole 4.5%. The other two patients who became antibody positive (one only for IgA EmA at low titre) 18 months and 4.5 years after IDDM onset showed a histological picture of non-specific duodenitis (table 1, cases 4 and 5). It is possible to speculate that flat mucosa will never develop in them (especially in the patient with 4.5 years of follow up), nevertheless a condition of potential coeliac disease which needs

to be confirmed by immunohistochemical studies is very likely. From a clinical viewpoint all those with coeliac disease (including latent and potential cases) did not show gastrointestinal symptoms except one, diagnosed 12 months after IDDM onset, who presented a mild malabsorption syndrome (table 1, case 1).

Of the four (2%) IDDM patients, positive at onset only for IgG AGA, associated in one case with IgA AGA, three were biopsied and small intestinal findings were completely normal. Moreover, both IgG and IgA AGA disappeared in the sera of all these patients within six months, supporting the hypothesis that their fleeting positivity as well as that of non-organ specific and organ specific auto-antibodies is a facet of the immunological derangement observed at IDDM onset.⁴

Our results show that the whole prevalence of coeliac disease in IDDM after a 10 year follow up is 1:25 (1:20 including also potential cases) and the documented finding of late developing mucosal atrophy significantly concurs in determining this high rate. Therefore, antibody screening and biopsy of IDDM patients only at disease onset is not enough to exclude gluten sensitive enteropathy. Seroconversion of IgA antibodies after the manifestation of IDDM predicts coeliac disease, but it can occur also years before developing flat mucosa. In this view, IgA EmA should be preferred to AGA (both IgA and IgG) for their higher sensitivity and specificity.³ The increase of IgA EmA titre after their appearance may help in timing rebiopsy.

EMANUELE CACCIARI
FRANCESCO B BIANCHI*
SILVANA SALARDI
FRANCO BAZZOLI**
LUCIA DE FRANCESCHI*
UMBERTO VOLTA*

Paediatric Clinic 1,
Department of Internal Medicine*, Cardiology and
Hepatology and
Department of Gastroenterology**,
Università di Bologna,
Polyclinic S Orsola-Malpighi,
via Massarenti 9,
40138 Bologna, Italy

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Table 1 Late developing small intestinal mucosal atrophy in IDDM

Case	Sex	Age (years)	EmA IgA	IDDM onset			IDDM follow up					
				AGA			Months	EmA IgA	AGA		Biopsy	HLA
				IgA	IgG	Biopsy			IgA	IgG		
1	F	9	160	80	160	NM	12	160	80	80	SVA	DQ2
2	F	3.3	Neg	Neg	Neg	nd	10	160	40	80	SVA	DQ2
3	M	2.9	Neg	Neg	Neg	nd	16	80	40	80	SVA	DQ2
4	M	3.5	Neg	Neg	Neg	nd	53	40	Neg	Neg	NM	DQ3
5	M	3.3	Neg	Neg	Neg	nd	18	80	20	10	NM	DQ2

Neg: negative; NM: normal mucosa; SVA: subtotal villous atrophy; nd: not done.

Retinal haemorrhages and convulsions

EDITOR,—The paper by Sandramouli *et al* suggested that convulsions rarely, if ever, give rise to retinal haemorrhages.¹ This was based on a series of 33 patients with convulsions, none of whom would seem to have had retinal haemorrhages. The statistical analysis they undertook was based on Hanley's rule of 3.² Its use can be summarised by their statement 'It is a good estimate of the worst case that is compatible with the observed data'.

Applying the rule to the series of 33 patients reported, it gives a worst case that is compatible with the observed data of 3/33 (approximately 9.1%).

The most that can be said as a result of this series, is that convulsions do not commonly give rise to retinal haemorrhages. If the word rarely was taken to mean less than 1% of cases, then the series would have had to involve 300 children and if the phrase 'if ever' was to mean less than 1/1000, the series would have had to include 3000 children, none of whom had retinal haemorrhages associated with convulsions.

The conclusion that convulsions rarely (if ever) give rise to retinal haemorrhages is probably a good deal more memorable than it is useful.

J M O'DONOHUE
Leon Gillis Children's Centre,
Queen Mary's University Hospital,
Roehampton Lane, London SW15 5PN

Mr Willshaw comments:

We thank Dr O'Donohue for his observations on our statistical analysis of the study of 32 children (one child from the original group of 33 was excluded).

Unfortunately, the phrase 'none of whom would seem to have had retinal haemorrhages' seems cast some doubt on the observation. We would emphasise again that these children all receive detailed ophthalmological examination, including the use of an indirect ophthalmoscope, within 48 hours of admission. Categorically none of them had suffered retinal haemorrhages.

We would exactly concur with Dr O'Donohue's interpretation of Hanley's rule of 3, but would emphasise again that this gives a 95% confidence level in this study. Within the text of the article, this is described as indicating that 'the chance of a child having retinal haemorrhages solely on the basis of having a convulsion is unlikely' and later 'that retinal haemorrhages in children are rarely associated with convulsions'. We would still feel that both of these observations are entirely appropriate on the basis of this statistical analysis and Dr O'Donohue may be interested to know that a further 32 children have now been examined, all of whom were under the age of 24 months, and still, to date, there has been no incidence of retinal haemorrhage occurring within 48 hours of the convulsion.

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Congenital total lipodystrophy and peripheral pulmonary artery stenosis

EDITOR,—We read with interest this report of peripheral pulmonary artery stenosis in congenital generalised lipodystrophy but query the physical findings, particularly in case 1.¹ Furthermore, the term 'pulmonary hypertension' is used imprecisely. Pulmonary hypertension implies a pulmonary artery pressure higher than normal but whether this is systolic, diastolic, or mean has different connotations. The intensity of the pulmonary component of the second heart sound depends primarily on the pulmonary artery diastolic pressure dependent in turn on pulmonary vascular resistance. In peripheral pulmonary artery stenosis, both are low, analogous to the situation after pulmonary artery banding to reduce pulmonary blood flow in certain congenital cardiac defects. If the pulmonary artery diastolic pressure is high, the pulmonary component of the second sound is likely to be accentuated. In case 1 of the above paper, the child is alleged to have both peripheral pulmonary artery stenosis and 'a loud pulmonary second heart sound'. This would indeed be unique. We would be interested to know the authors' explanation.

JULENE S CARVALHO
ELLIOT A SHINEBOURNE
Department of Paediatric Cardiology,
Royal Brompton Hospital,
Sydney Street, London SW3 6NP

Dr Uzun comments:

We were surprised at Drs Carvalho and Shinebourne's comments on clinical signs in patients with peripheral pulmonary stenosis—they state that pulmonary artery diastolic pressure is low in these patients and that the pulmonary component of the second heart sound is, therefore, not accentuated (as it was in one of our cases). This may indeed be the case in some patients with a limited number of discrete pulmonary artery stenoses (diastolic pressure being low because of flow occurring through the low resistance vessels which are unaffected by the disease). In contrast, when there are multiple severe peripheral pulmonary artery stenoses and a paucity of low resistance vessels remaining then diastolic pressure in the proximal pulmonary arteries rises and the pulmonary second sound may be accentuated, as described in our report¹ (our patient's pressure was 85/30 with mean of 55 mm Hg). These clinical findings are not unique and are clearly described in the highly regarded reference text² edited by Dr Shinebourne himself!

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Neoplastic diseases of childhood

EDITOR,—Correspondence provoked by book reviews is unusual, but perhaps opinions there should occasionally be challenged to prevent reviewers shelving their prize without risk of riposte. I write because I was stung by a comment from Mike Stevens in his review of Carl Pochedly's *Neoplastic Diseases of Childhood* where he says that '...a whole chapter on the "techniques of bone marrow

biopsy" seemed a bit over the top'.¹ I smart for the obvious reason that I authored the chapter in question, but also because I am disappointed that one of the few unique features of the publication (which, overall, I agree shows its age and does not stand well against its competitors) should be singled out for dismissal.

Bone marrow aspiration and trephine biopsy is a pivotal investigation in many childhood cancers. It is commonly carried out by paediatric oncologists, frequently by trainees with relatively little experience, and often badly. Training in the procedure is usually little more than the 'see one, do one, teach one' approach. While that may work for lumbar punctures or venepunctures where the adequacy or otherwise of the specimen is obvious, it serves less well for a procedure where (arguably) greater skill is needed not only to get a specimen but also to assess its sufficiency and to create fresh smears for microscopy. No amount of subsequent extra effort in the laboratory can compensate for poorly prepared or otherwise inadequate material.

I have had the privilege of reviewing the diagnostic and early response marrow aspirate smears from children in UK leukaemia trials for some years now and am still struck at the hugely variable quality of the material that passes before my eyes. Libel laws prevent me from saying more than that slides from different centres do show a consistent and considerable variability in quality. It was this, as much as anything, that encouraged me to write the offending chapter when invited to do so. I am not aware that any other textbook for paediatric oncologists has tackled the subject and I remain unrepentant.

J S LILLEYMAN
ICRF Children's Cancer Group,
St Bartholomew's Hospital,
London EC1A 7BE

- 1 Stevens MCG. Neoplastic diseases of childhood [book review]. *Arch Dis Child* 1997;76:387-8.

BOOK REVIEWS

Pediatric Endocrinology. Edited by Mark A Sperling. (Pp 614; £68 hardback.) W B Saunders, 1996. ISBN 0-7216-5522-X.

The practice of paediatric endocrinology is the struggle to maintain physiology and constancy of physical development, sexual maturation, metabolic rate, plasma electrolytes, serum calcium, and glucose concentrations. To some, the objectives may seem mundane, but their attainment can at times be extraordinarily difficult. Contemporary paediatric endocrinologists need to know the link between clinical syndromes and the underlying pathology in transcriptional, ligand/receptor or secondary, intracellular mechanisms. Thus, a textbook of paediatric endocrinology must address this and the aim of the editor is to do so. The opening chapters relating to endocrine physiology and molecular endocrinology are clear and provide an overview of many research

techniques. After reading this section, the clinical endocrinologist should have little difficulty digesting complex molecular biology, which is now prominent in endocrine research. The text has a symmetry with the last two chapters dealing with the methodology of clinical investigative techniques, again expressed both concisely and clearly. The pre-eminence of health economics in all developed countries has encouraged a direct and rational approach to investigative aspects of clinical practice and the chapter on medical imaging is refreshingly pragmatic. The intervening chapters are a mixture of system orientated and clinical problem orientated reviews. Regardless of orientation, each chapter covers the pertinent physiology, pathophysiology, clinical consequences, and treatment strategies well. The chapters on disorders of growth hormone and insulin-like growth factors and Turner's syndrome are particularly good.

There are two limitations to this text. Firstly, the authorship is entirely North American and their clinical dogma not universally practised. While this is not a problem for the reader in North America, it may be limiting elsewhere. The second problem is inherent to all textbooks—that of currency. Notwithstanding this, it is a little disappointing for a text published in 1996 not to include any mention of a topical endocrine issue such as the role of leptin in childhood obesity. However, this should be seen as a minor criticism. In summary, *Pediatric Endocrinology* is a comprehensive, readable text with an eminent authorship. It has achieved the editor's stated aim of bridging the gap between biomedical science and the clinical practice of paediatric endocrinology.

FERGUS CAMERON
Visiting registrar in endocrinology

RICHARD STANHOPE
Consultant paediatric endocrinologist

Pediatric Endocrinology: A Clinical Guide. 3rd Ed. Edited by Fima Lifshitz. (Pp 947; \$195 hardback.) Marcel Dekker, 1996. ISBN 0-8247-9369-2.

The publication of another major textbook reflects the continuing growth of this evolving subspecialty. Endocrinological aspects are common in general paediatrics so this book will be welcome by a large number of doctors, both specialists and non-specialists. Nevertheless, Fima Lifshitz's textbook, while providing excellent material, sometimes is too specialised for the general paediatrician. However, the needs of the paediatric endocrinologist in training, striving to keep pace with modern practice, are fully met.

Fima Lifshitz has assembled highly qualified contributions by a broad spectrum of experts from around the world. The book reflects the authors' distinctive approaches, and like many multi-author compendiums reads like a series of monographs, although in some cases authoritatively.

Nevertheless, it is not difficult to read large sections of the book as most chapters are concise, well organised, well referenced, and focused on practical problems. The structure of the book is indeed one of its major assets. Chapters are clustered in sections dealing with most of the main issues of paediatric endocrinology. Eleven chapters are added compared with the second edition, providing excellent updated material on the endocrine

logical aspects of HIV infection or endocrine tumours in children, among other topics which only reflect the changing approach of this paediatric subspecialty. Certain new additions, like chapters on metabolic bone disease in total parenteral nutrition, or paediatric magnesium disorders, which are not usually dealt with in such textbooks, are more than welcome. Basic coverage of molecular biology is given by most authors. Psychosocial and ethical aspects are dealt with. The scope of the book is indeed impressive, and with a strong clinical orientation it tends to provide practical information throughout. Nevertheless tables and figures are sometimes not as useful as one would expect, and in some cases it does not provide the necessary treatment and diagnostic algorithms for it to be a true clinical guide as the title suggests. A number of chapters are certainly first rate, and make it worth paying the price of the book. However, because of the large number of contributors, there are repetitions and inconsistencies both in form and style. However, the editor needs to be congratulated for offering such a useful tool for improving the understanding and management of such a rapidly changing subject.

M MORENO
Research fellow

R STANHOPE
Consultant paediatric endocrinologist

Cystic Fibrosis. Edited by Dennis J Shale. (Pp 162; £25 hardback.) BMJ Publishing Group, 1996. ISBN 0-7279-0826-X.

This compact volume aims to present both current clinical thinking and practice with more fundamental aspects relating to the pathophysiology of cystic fibrosis. The book is written for respiratory and primary physicians, paediatricians, and all medical professionals seeking knowledge of the condition. It is a tall order to achieve this goal in only 162 pages. There are clear chapters on mouse models and on the cystic fibrosis gene but the clinical chapters, with the exception of those on respiratory infection and transplantation, are lacking in detail and under referenced to a degree that limits their value as a practical guide to treatment. The size of the book perhaps determined the relatively superficial account of the current clinical management of children and adults but in addition to the brevity there are some important omissions, for example the East Anglian controlled trial of flucloxacillin in screened cystic fibrosis infants, recent references to the use of inhaled steroids, and no mention of the flutter device. Generally referencing is more uneven with only 18 references in the chapter on the clinical management of children but no less than 172 in the chapter on respiratory infection.

There are too few up-to-date references for an account of a condition where understanding and treatment are constantly changing. There are none to exercise later than 1982; only two of 68 on lung injury are later than 1991. The social and psychological section (22 pages) is nearly twice the length of the key chapter on management in children (13 pages) and largely deals with the importance of the role of the clinical nurse specialist. Although few would question the important role of the nurse specialist, many paediatricians and physicians would be reluctant to admit that this member of the cystic fibrosis team was alone able to consider the patient as

a whole and ensure high quality care is delivered. The book is well produced with helpful tables of drug doses and key points but the photographs are of poor quality.

Students of this challenging condition with its continually changing clinical expectations, methods of treatment, and prognosis will read this book with interest and learn much from it. However, those looking for a balanced, detailed account of cystic fibrosis in 1997 to help in clinical management will need to search elsewhere for more detailed information. Also, although all would agree that cystic fibrosis remains a very serious life threatening disorder, the clinical chapters of this book convey a degree of pessimism that is not entirely appropriate nowadays.

J M LITTLEWOOD
Consultant paediatrician

This Battle Which I Must Fight. Cancer in Canada's Children and Teenagers. By S Huchcroft, A Clarke, Y Mao, et al. (Pp 110; paperback.) Supply and Services Canada, 1996. ISBN 0-662-24310-2. (The book can be obtained free from: Cancer Bureau, Laboratory Centre for Disease Control, Health Protection Branch, Health Canada, Ottawa K1A 0L2, Canada; fax 00 1 613 941 5497.)

In addition to coping with the emotional impact of learning their child has cancer, parents have to contend with a bewildering amount of new information. Well written and easy to understand literature is an essential adjunct to the initial consultation. This is useful both for parents themselves and anyone involved in the care of the child, such as extended family members and teachers. Indeed, most parents quite quickly become 'experts' on their own child's disease and its treatment, and often find themselves frustrated by the continual need to dispense sometimes painful information to everyone from the latest new senior house officer or locum GP to the school dinner lady.

Parents of children diagnosed with malignant disease in the UK are usually offered the information booklets produced by the Leukaemia Research Fund and the United Kingdom Children's Cancer Study Group. *This Battle Which I Must Fight* is a useful addition to these. It contains more detailed and complicated information than some families might require at diagnosis. However, despite my initial misgivings about this, parents and non-medical personnel who kindly read some of it for me found the text straightforward and easy to understand. The 'vignettes' provided by the children themselves are, as always, moving. I found these the most instructive aspects of the book. I have used some of the insights to help communicate with adolescents in particular.

There are excellent sections on the causes of cancer, trials (including what phase I, II, and III trials mean), and unproved treatments. The emotional and psychological impact of the disease are particularly well dealt with. One of the parents to whom I showed the book found the section about the effect on siblings as particularly helpful. I thought the section 'how to help', aimed at relatives and friends, was sensitive and practical.

The emphasis on Canadian data was slightly disorientating, but was presumably

because the book was produced as part of a Canadian government funded health initiative. I found many of the tables and graphs superfluous and parents found them complicated. Another irritation was the title. 'Battle' is always a word I dislike in the context of childhood cancer. It is all too often used in tabloid newspaper reports and can leave families with an inappropriate sense of personal responsibility. One mother of a child with relapsed disease commented that the title to her suggested that 'you lose the battle if you relapse'.

However, these are minor points and overall I think many parents would find this book helpful. The book can be read in an evening, and I would certainly recommend it to GPs and other medical and nursing staff who may only see children with cancer occasionally.

ANNE DAVIDSON

Senior registrar in haematology and oncology

Services for Young People with Chronic Disorders in their Transition from Childhood to Adult Life. Edited by Zarrina Kurtz and Anthony Hopkins. (Pp 155; £13.50 paperback.) Royal College of Physicians of London, 1996. ISBN 1-86016-033-6.

If you came across an advertisement in the 'lonely hearts' column of your local paper which read 'Various, seriously concerned, extremely well intentioned and experienced professionals seek meaningful relationships with confused, anarchic, independence and self identity seeking adolescents with chronic disorders.....' you might be justified in wondering what the chances were of there being an even reasonable long term outcome.

However if you then read on from the same advert '.....in order to help them form further meaningful relationships with other various, seriously concerned, extremely well intentioned.....' would you (a) ring your local MP and complain about the perverted adverts which were allowed into the papers nowadays (b) read an excellent and extremely helpful book on this vital subject entitled *Services for young people with chronic disorders.....* (c) develop your own set of guidelines to help them find salvation?

If you did (b) and read this informative book—especially the guidelines on pages 144 to 152, and then did (c)—the guidelines that you might come up with would be something like: 'remember they are human and adolescents first and foremost way, way ahead of any health problem; remember how well or badly you did with your own adolescents/adolescence; prepare the ground for transition well ahead of time; let the adolescent/their carer take the lead; remain human and empathise; stick with what you are good at and don't try and pretend to be competent at everything—you're not; form mutual support groups; and finally listen, listen, listen'.

This area of work, combining as it does, the transition for the adolescent to adulthood and the transition of medical, social, educational, and voluntary services for the adolescent from one set of professionals to another, is as difficult as it comes. One very clear message however, from some of the quotes from young people 'with special needs' in the book, is that the doctor should be absolutely up to date and skilled in her/his specialist medical knowledge (for example about cystic fibrosis, sickle cell anaemia,

epilepsy, diabetes, cerebral palsy, etc) before attempting anything more fancy.

So good luck with those relationships, this book will help you but, if occasionally you fail, stay human and remember that meaningful (and other) relationships are not made in heaven but have to be worked at hard. So you knew that already? OK nothing personal but then why were you reading the lonely hearts column?

AIDAN MACFARLANE

Consultant in public health and health policy

VIDEO REVIEW

Nephrotic Syndrome. £45. Obtainable from Audiovisual and Educational Services, University of Nottingham, Kidney Unit, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB.

Our son was diagnosed as having nephrotic syndrome five years ago. Luckily for him, and for us as parents, he is clinically managed at a small general hospital by a generalist paediatrician, which has meant that information is readily accessible and our questions are answered directly. This was particularly helpful in the early days of the syndrome because, with correct parental and clinical management life is virtually normal for both patient and family—even though our son suffers frequent relapses. Larger inner city hospitals may find this sort of management very difficult, if not impossible, to deliver for a variety of very good reasons.

This video is obviously targeted at the parents of newly diagnosed children and could be a vital tool in families' understanding and acceptance of the illness. It runs for about 12 minutes but during this short time it takes all the initial information given by a doctor and breaks it down. Simple language and diagrams are used to underline, clarify and reassure, and we experience it all by watching real children receiving treatment and being supported by their families. This leads into a more in-depth account of some of the detail of the management of this condition—steroid treatment and the possible side effects, relapses, keeping a diary, carrying out home urine tests, and includes the type of ongoing support that is received and readily available.

Possible complications are dealt with in just the right amount of detail so that families know what to expect but are not alarmed.

It would however be unjust to consider this video as useful only in briefing newly diagnosed families as its relevance is far broader. Indeed, since this syndrome is more prevalent in Asian children, I can only hope and suggest that copies are made in the appropriate languages. With some Asian parents, particularly mothers, having a poor command of English and often relying heavily on their secondary schoolchildren to act as interpreters, any device which can inform and clarify must be welcomed by clinicians, patients, and families. Equally valid would be its use in the education and understanding of the disease for some of its sufferers. Simon, our 10 year old son, who has the syndrome, found the video answered some of his questions, was enjoyable to watch, and gave

him a better understanding of his illness and treatment.

At £45 per copy the video will not be bought by many individual families. However, hospitals, libraries, and general practitioner surgeries should find it a very useful reference resource (for lending?).

I have referred in this review to the video's suitability for 'newly diagnosed families'. The diagnosis of a child as having a rare and potentially dangerous condition can feel to families like the end of a normal life. The gently and accessibly factual content in this video amply addresses the danger and will enable families to carry on their lives normally and safely.

PENNY PRICE
Parent

WESTMINSTER BRIEFING

The following items are from *Children & Parliament*, Summer 1997. *Children & Parliament* is an abstracting service based on *Hansard* and produced by the National Children's Bureau. It covers all parliamentary business affecting children and is available on subscription via the internet. The *Children & Parliament* website provides direct links to full text *Hansard*, government department sites, the sites of the Office for National Statistics, Ofsted, and other relevant organisations. For further details contact Lisa Payne, Editor, *Children & Parliament*, National Children's Bureau, 8 Wakley Street, London EC1V 7QE (tel: +44(0)171 843 6000; fax: +44(0)171 278 9512). (The *Hansard* reference is given first followed by the date of *Children & Parliament*).

- The government intends to strengthen support for the International Labour Organisation's efforts to end hazardous and exploitative child labour in developing countries and to promote universal primary education. The World Trade Organisation's call for a human rights clause banning access to the most privileged terms of trade to countries where there is child labour (among other things) will also receive government support.

(21/22 May 97, Col 697-698, 93, 133; 03.06.97)

- The number of 5, 6, and 7 year olds in the UK is set to fall by about 142 000 by the year 2001, from 2.367 million to 2.225 million.

(22 May 1997, Col 119; 03.06.97)

- A ministerial group set up by the Home Secretary will look into the problem of alcoholic drinks which are directed at children. Alcohol levels of up to 4.5% have been found in 'freezerpops'. The government wants the industry to take action but is prepared to act itself if the industry response is not satisfactory.

(5 Jun 97, Col 552; 9 Jun 97, Col 326; 12 Jun 97, Col 513; all 24.06.97)

- In moving responsibility for disability issues from the Department of Social Security to the Department of Education and Employment the government wishes to emphasise the point that people with disability

should be thought of as able and willing to take advantage of education and employment opportunities and not as recipients of benefit. The minister for employment and disability rights will coordinate disability issues across government departments.
(3 Jun 97, Col 133-134; 24.06.97)

- The government plans to introduce a bill incorporating the main provisions of the European Convention on Human Rights into UK law, thus strengthening the rights of disabled people.
(9 Jun 97, Col 297; 24.06.97)

- A headcount of people sleeping rough in London on a single night in November 1996 produced a figure of 449. Under a Rough Sleepers Initiative over £17 million has been granted to voluntary organisations and housing associations in 12 towns and cities in England.
(11 Jun 97, Col 85-86 and 5 Jun 97, Col 224-225; 24.06.97)

- In England and Wales around 2% of live births are at home; in Scotland it is less than 1%.
(27 Jun 97, Col 661; 08.07.97)

- If a Bill amending present law goes through, local authorities will no longer be able to refuse services needed by chronically sick or disabled people on the grounds of lack of resources.
(17 Jun 97, Col 1111; 08.07.97)

- The proportion of gross domestic product spent on the NHS was around 3 to 4% in the 1950s and 60s, 4 to 5% in the 1970s, 5 to 5.5% in the 1980s and around 6% in the 1990s.
(25 June 97, Col 178-180; 08.07.97)

- The Office for National Statistics gets data from the National Congenital Anomaly System which has been in place since 1964. Between 1986 and 1995 the annual number of cases of Erb's palsy notified in England and Wales varied between 21 and 37, giving a rate of 0.3 to 0.5 affected babies per 10 000 live and stillbirths.
(7 Jul 97, Col 319; 22.07.97)

- Data collected from general practice give a mean weekly incidence of newly diagnosed asthma in children under 15 in England of 58.6 per 100 000 population in 1979, rising to 242.8 by 1993 but falling back to 168.4 by 1996.
(21 Jul 97, Col 415-416; 05.08.97)

- In 1991 there were some 583 000 prescriptions for lotions for head lice. In 1996 there were 2 161 000. There have been 23 'yellow card' reports involving malathion, 19 concerning children.
(16 Jul 97, Col 214-215; 05.08.97)

- A new government funded post of 'Drug Csar' has been advertised and 790 local projects have been funded recently under the drugs challenge fund.
(30 Jul 97, Col 39-40, 281-282; 19.08.97)

- Total NHS spending in 1978-9 was £6525 million (equivalent to £20 067 million in 1996-7 terms). For 1997-8 it is expected to be £35 948 million.
(28 Jul 97, Col 91-92; 19.08.97)

- The number of households for which local authorities in England undertook to find accommodation because of homelessness was 55 500 in 1979, 80 500 in 1984, 122 000 in 1989, 122 500 in 1994, and 117 000 in 1996.
(28 Jul 97, Col 44-46; 19.08.97)

- The proportion of young people in Great Britain going on to full time undergraduate education was 23% in 1991-2, 30% in 1993-4, and 32% in 1995-6. For those with parents in the professions the proportions in each of these years were 55, 73, and 79% and for those with partly skilled or unskilled parents 11, 14, and 16%.
(31 Jul 97, Col 499-502; 19.08.97)

- Over the last five years or so the proportion of children in England who have had a first dose of MMR vaccine by their second birthday has run at 91-92%. Uptake figures for the preschool booster dose, recommended since October 1996, are not yet available.
(30 Jul 97, Col 65-66; 19.08.97)

Archives of Disease in Childhood—[http:// www.archdischild.com](http://www.archdischild.com)

Visitors to the world wide web can now access the *Archives of Disease in Childhood* either through the BMJ Publishing Group's home page (<http://www.bmjpg.com>) or directly by using its individual URL (<http://www.archdischild.com>). There they will find the following:

- Current contents list for the journal
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The web site is at a preliminary stage and there are plans to develop it into a more sophisticated site. Suggestions from visitors about features they would like to see are welcomed. They can be left via the opening page of the BMJ Publishing Group site or, alternatively, via the journal page, through 'about this site'.