Academic paediatrics: Easter Island or Easter Sunday?

J Savill

Commentary on the paper by Levene and Olver (see page 450)

W hen the last tree on Easter Island was felled, the inhabi- 
tants belatedly realised that there was no escape from an eon of "groundhog days". Paediatrics, a disci- 
pine championed in the UK, faces a comparably monotonous future bereft of innovation and improvement. Levene 
and Olver present alarming data on staffing changes in UK academic pae-
diatrics between 1999 and 2004.1 Most worrying is a 26% reduction in the stock of 
clinical lecturers, the academic saplings crucial to the future health of the 
paediatric wood. Is there hope for this dying research discipline? Yes, but only 
if paediatrics joins the main forest of clinical academic medicine in pursuit of 
research excellence, the surest protection against research assessment exer-
cise (RAE) related tree felling—loss of identity. Young paediatricians will win 
coveted research training and clinician scientist fellowships if they are sup-
sported in spending time in major research centres working at critical mass 
(although academic medicine sorely needs more fellowships available, espe-
cially at the post-doctoral level).

Pyridoxine or pyridoxal phosphate for intractable seizures?

P Baxter

Commentary on the paper by Wang et al (see page 512)

T he short answer is pyridoxal phos-
phate, but before reaching for the 
 prescribe pad it’s worth looking 
at the context. Intractable seizures have 
no set definition.1 One practical approach is to review management 
when seizures continue despite the use of 
two appropriate anticonvulsants at 
maximum tolerated doses. Points to 
consider include whether the diagnosis 
is correct, as syncope and other non-
epileptic events can still mislead; the 
cause of the seizures, for example 
structural, chromosomal, neurodegen-
erative, or metabolic conditions; 
whether there is an avoidable precipi-
tant; whether the choice of drug and 
dose were correct, as for example 
carbamazepine can exacerbate some 
primary generalised epilepsies; and 
compliance.1 Treatment options include 
other anticonvulsants; drugs such as 
pyridoxal, pyridoxamine and their 5’-
phosphates. It is a co-factor in many 
 enzymatic reactions in the CNS and 
elsewhere, particularly amino acid 
transamination and decarboxylation. 
This includes the formation of biogenic 
amines such as noradrenaline and ser-
otonin.2 Pyridoxine from any source is 
usually rapidly phosphorylated to the 
active form, as shown by the “end of 
the needle” response in cases of pyridoxine 
dependency. However, two cases have 
been described where this process was 
defective. These children presented with 
a severe neonatal epileptic encephalopathy that only responded to pyridoxal 
phosphate.4

Wang et al restrict their study to 
children with seizures resistant to three 
or more conventional drugs given over a 
six month period.1 Despite excluding 
structural, chromosomal, infective, 
or metabolic disorders, including pyr-
doxine dependency, they have collected 
an impressive number of children. Their 
data suggest that pyridoxine, and even 
more so pyridoxal phosphate, is useful 
in this group.

This is particularly so in children with 
West syndrome where six of their 13 
cases achieved seizure control with 
pyridoxine or pyridoxal phosphate. In 
countries such as Japan or Germany 
these are used routinely as first line 
therapy for West syndrome. In four case 
series pyridoxine responders totalled
20% of idiopathic and 5% of symptomatic cases, while in two others pyridoxal phosphate responders numbered 25% of idiopathic and 10% of symptomatic cases. These series are difficult to compare as different doses regimens were used. Nonetheless they support the findings of Wang et al that pyridoxal phosphate is more effective than pyridoxine. Interestingly the outcome appears better in responders than non-responders.7 8 Obvious response rates for vigabatrin or steroids are much higher.9 To complicate matters, other authors have suggested that adding pyridoxal phosphate to steroids or sodium valproate can help achieve seizure control at lower doses of the latter drugs.6

Wang et al also report that 2/44 children with generalised and 3/37 with focal seizures achieved complete seizure control with pyridoxine or pyridoxal phosphate. All of these developed epilepsy before the age of 15 months. Six more had improved seizure control, although it is not reported what their ages of onset or seizure types were, and one had an exacerbation of seizures. Earlier studies using pyridoxine in children resistant to what are now considered the older anticonvulsants have not shown very impressive responses. Livingston and colleagues10 found no useful response in 31 children; Hagberg and colleagues11 reported two out of 26 who achieved complete seizure control and others with improved control; Hughes and colleagues12 found some improvement in four of ten patients, while Singh and Sinha13 in a large Indian series reported seizure control in two out of 120. Jiao and colleagues14 reported that adding pyridoxine to conventional treatment in acute symptomatic recurrent seizures of any cause improved outcome. Wang et al are the first to report using pyridoxal phosphate in this situation, again with rather better results in highly selected patients. Neonatal seizures and some cases of Ohtahara syndrome form other special groups where useful responses can occur.15 In all these situations pyridoxine or pyridoxal phosphate appear to have an anticonvulsant effect, rather than to be treating a metabolic disorder. It is notable that younger children appear more likely to respond. However, rare adult responders have also been described.15

One bonus of pyridoxine or pyridoxal phosphate therapy is the relative lack of side effects. In pyridoxine dependency, even when given orally, pyridoxine can cause serious acute effects including apnoea in neonates, but not in older children. With very high doses in West syndrome, side effects of either preparation can include loss of appetite, restlessness and screaming, vomiting and diarrhoea, apathy and drowsiness. In adults taking very high doses for periods of months, a largely reversible sensory neuropathy (dorsal root ganglionopathy) can occur, but this has only rarely occurred in children.1 In West syndrome in particular, this seems important as both vigabatrin and steroids, while more effective, may have much more significant side effects. Pyridoxal phosphate is more expensive: in the UK, 50 mg tablets of pyridoxine and pyridoxal phosphate cost approximately 2 and 12 pence, respectively. In


Health care

Success in tackling deafness with multi-faceted interventions

A R Gatrad, A Sheikh

Commentary on the paper by Yoong et al (see page 454)

The interface between ethnicity, health, and health care delivery is complex, and studying this area is known to throw up somewhat paradoxical findings. In this issue, Yoong and colleagues raise two important observations that we wish to comment on, namely the persistence of consanguineous marriage patterns in British Pakistani Muslim families and, in those families with children with deafness, their access to relevant health care services. We consider each of these issues—the first predictable and the second unexpected—in turn.

It is now well known among health professionals that consanguineous kinship patterns increase the risk of recessively inherited disorders such as congenital deafness. It is estimated that the birth prevalence of infants with recessively inherited disorders rises by about 7 per 1000 for every 0.01 increase in the coefficient of consanguinity (F). Among British Muslim Pakistanis, F is estimated at 0.0431 compared with 0.003 for most North European populations. But despite this knowledge being widespread within professionals, it is our impression that a large proportion of Britain’s Pakistani Muslim population remain unaware of the relation between consanguinity and adverse outcomes. This may go some way to explaining why consanguinity persists as a social practice in this community.

Our belief that the process of acculturation (whereby immigrant minorities begin to take on the characteristics of the host population) would rapidly lead to the demise of the acceptable kinship pattern has not as yet been realised. On the contrary our experience suggests that consanguinity is alive and well and is, if anything, on the increase. Given the significant increased risk of death and serious disability associated with consanguinity it is pertinent here to consider why this might be so.

It is certainly true that more needs to be done to make information on the risks of familial marriage patterns available to the target populations, and in this vein there is also a need for health services to think more creatively about how best to disseminate this information. The burgeoning Asian and Muslim print, online, and audio/visual media outlets, for example, offer new and exciting opportunities to engage meaningfully with these communities. Importantly, this use of specialist media outlets should be viewed as additional to the more traditional approaches, and not as an alternative to other outlets, as both are likely to help reach different sections of these increasingly heterogeneous communities.

There is also a need for health professionals to develop a far more sophisticated appreciation of why consanguinity exists as a social phenomenon, recognising that it offers several important advantages that cannot be dismissed lightly. Briefly, these benefits include a secure mechanism to retain family wealth and property within a confined group, as has been used to considerable effect by British aristocracy and the royalty. More important perhaps, in the British Muslim context, is the belief that marriage of a son or daughter to a blood tie offers greater prospect of security for ageing parents than that which can be expected of someone who marries outside the family.

In order to have credibility among target populations, it is thus important that any health promotional interventions, aiming to reduce consanguinity, accurately reflect the potential advantages and risks associated with consanguinity and present this information in a non-judgemental fashion. The aim of such interventions must thus always enable families to make their own informed decisions in the light of accurate and unbiased information.

Even in cases where families do wish to move away from traditional marriage patterns (on account of an awareness of the health risks or for other reasons), this may not always be possible. This is because migration has, in the short term at least, fractured many social networks and therefore made it difficult to find suitable partners for offspring from outside the extended family. This may also in part explain the observed increases in consanguineous marriages that consanguinity is alive and well and is, if anything, on the increase.

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Taken together, these factors suggest that the proportion of British Pakistani Muslims in consanguineous relationships may continue to increase in the short term. However, as the message of the risk of adverse outcomes in children becomes increasingly appreciated and, furthermore, as these communities develop established social infrastructures, it is likely that there will then be a rapid transition to less introverted marriage patterns. The emergence of Muslim nursing homes and marriage agencies is, we believe, indicative of this future trend.

Improving access to health care and ensuring equitable access for all sections of the population are national priorities for the NHS. While many research teams have highlighted the problems of poor access in relation to minority ethnic communities, there have been relatively few reports of success in ensuring delivery of high quality care to these communities, who are typically those most in need. There have furthermore been a number of reports of difficulties in delivering genetics counselling to affected families. The paper by Yoong et al is as far as we are aware the first to show equitable access to paediatric audiology and genetics services for Pakistani Muslims, and therefore makes welcome reading about a problem that was highlighted as far back as 1980. Importantly, it underscores the message that, with concerted effort and resources, it is possible to develop services that meet the needs of diverse population groups.

The main barriers to equitable provision of care are structural, reflecting the fact that the NHS was originally developed to serve a relatively homogeneous population. The increasing ethnic, religious, and cultural diversity of British society has therefore posed a considerable challenge to those involved with planning and delivering care, although as shown by the Stephen Lawrence enquiry, this problem is not exclusive to the NHS. Attempts at overcoming these barriers have hitherto often been misguided and/or simplistic with the risk of (unintentionally) alienating the intended recipients of improved care.

Overcoming barriers to facilitating access to care therefore requires an in-depth appreciation of the sociocultural context in which strategic interventions are framed. According to Kai, over 7% of the NHS workforce is from minority groups. If this group was empowered to reflect on their expertise, standards of health care for this vulnerable population could be improved. Cultural competence is an evolving process that depends on self-reflection, self-awareness, and acceptance of differences. Success in this programme has been
New bacteria in cystic fibrosis

In recent years new, or relatively new, bacterial isolates have been obtained from patients with cystic fibrosis (CF). They include Burkholderia cepacia, Stenotrophomonas maltophilia, Achromobacter xylosidans, and Mycobacterium avium complex. Three papers in Thorax have added to knowledge about the occurrence and clinical significance of the first two of these organisms.

S maltophilia (previously known as Pseudomonas, or Xanthomonas, maltophilia) is a Gram-negative, non-fermenting rod found in the airways of CF patients and with widespread antibiotic resistance. Its importance as a pathogen has been unclear. A cohort study based on the US CF Foundation National Patient Registry (CH Goss and colleagues. Thorax 2004;59:955–9) has shown no correlation between S maltophilia colonisation and progression of lung disease. Among 20 755 patients aged 6 years or older (median age at entry 13.8 years) 2739 (13%) had at least one positive culture for S maltophilia. Patients colonised with the organism had worse lung function (FEV1 adjusted for sex, height, and age) but S maltophilia positivity did not influence the rate of decline in lung function after adjustment for confounding factors. The effect of treatment for S maltophilia needs to be assessed.

Organisms of the Burkholderia cepacia complex can cause serious lung infection in CF patients. There are nine B cepacia complex species, the commonest of which is B cenocepacia. The ET12 strain of B cenocepacia has been isolated from patients in Canada and the UK but the PHDC strain has been confined to the USA. Now workers in Ghent, Belgium (T Coenye and colleagues. Thorax 2004 59:952–4) have examined 796 B cenocepacia isolates and found that on randomly amplified polymorphic DNA (RAPD) typing, 19 European isolates were similar to 14 US reference isolates for the PHDC strain. Rep-PCR using the BOX-A1R primer (BOX-PCR) confirmed that the European isolates (from eighteen recent clinical samples from CF patients in France and Italy and one urine sample in the UK from 1964) were of the same clone as the PHDC strain. The PHDC strain is present on both sides of the Atlantic ocean.

Researchers at a Manchester centre for adults with CF (AM Jones and colleagues. Thorax 2004;59:948–51) have studied the two most common species (genomovars) of the B cepacia complex—B cenocepacia and B multivorans. Forty-nine patients had been infected with either B cenocepacia (33) or B multivorans (16). Chronic infection ensued in 31/33 and 8/16 respectively. One-year survival among patients chronically infected with B cenocepacia was reduced compared with their Pseudomonas aeruginosa-infected controls (80% vs 100%) whereas among patients infected with B multivorans survival was the same as among their P aeruginosa-infected controls (100%). The rates of 5-year survival were 67% vs 85% (B cenocepacia vs P aeruginosa) and 75% vs 75% (B multivorans vs P aeruginosa).

S maltophilia is not associated with more rapid decline in lung function; B cenocepacia strain PHDC has crossed the Atlantic; and B cenocepacia, but not B multivorans, is associated with reduced survival compared with P aeruginosa.