LETTERS

Rejoinder to Eigenmann PA, Haenggeli CA, Food colourings and preservatives—allergy and hyperactivity (Lancet 2004;364:823–4) and an erratum

Eigennmann and Haenggeli have commented on a paper we recently published (Haenggeli CA, Airport DJ, School of Psychology, University of Southampton, UK; Lancet 2004;364:823–4). This commentary gives a seriously misleading account of the findings of the study. Eigenmann and Haenggeli claim that “the term hyperactivity seems to be used synonymously to ADHD”. We deliberately did not use the term ADHD as a criterion for inclusion in the study. In this diagnostic term requires a set of explicit criteria to be met and is of doubtful value when applied to 3 year olds. The definition of hyperactivity which we used for this study was one based on the risk of subsequent behavioural difficulties in middle childhood which we had established previously in a longitudinal study of an epidemiologically ascertainment sample of 3 year olds.

The study used screens for atopy (AT) and for hyperactivity (HA) applied to a total population sample to identify cases for the following design: “Children were entered into the four group randomised, placebo controlled, double blind, crossover challenge study. The four groups were in a 2 x 2 between group design with the following groups: HA/AT, non-HA/AT, HA/non-AT, and non-HA/non-AT.”

Eigenmann and Haenggeli observe that “…families interested in hyperactivity seem to be over-represented” and on this basis conclude that “…results from this study should not lead to recommendations for the general population”. The presence of hyperactivity was one of the inclusion criteria of the food challenge phase of the study and consequently occurs in about half of the cases. A substantial proportion of children were included in the food challenge phase by design. Full details of participant flow were given in a diagram (fig 1 in our paper) as recommended in the CONSORT statement for reporting randomised trials.

The separate issue of sample attrition through each of the stages of the study was considered carefully and we concluded that the findings from the group completing the food challenge phase would indeed hold for the general population.

The study found significantly greater increases in hyperactive behaviour reported by parents when the children were given the active compared to the placebo challenge. The statement by Eigenmann and Haenggeli that “parents’ observations can be easily explained by their expectations” is puzzling. The parents, children, and the person collecting the behaviour ratings were blind as to the food challenge being taken by the child over these periods. Consequently “expectations” cannot account for the effects we identified based on changes during the active and placebo periods. This does not hold for the reduction in hyperactivity we observed during the withdrawal phase which, as we discussed in the paper, was not blinded and was greater than that for the placebo versus active periods. This would be expected if the withdrawal effect alone was influenced by parental expectations.

The final part of the Eigenmann and Haenggeli commentary is concerned with the use of diet changes as treatments for hyperactivity. Our study showed that the effects of food colourings and the benzoate preservative were not restricted to or more strongly present for children with atopy or hyperactivity. Consequently our conclusions did not relate to the treatment of children with hyperactivity but rather to the preventive public health issue of whether food additives are having a general detrimental effect on children’s behaviour. The final conclusion from the paper was “…if additives have an effect at all, it is via a pharmacological effect which is best exemplified by the non-IgE dependent histamine release. We believe that this suggests that benefit would accrue for all children if artificial food colours and benzoate preservatives were removed from their diet. These findings are sufficiently strong to warrant attempts at replication in other general population samples and to examine whether similar benefits of the removal of artificial colourings and sodium benzoate from the diet could be identified in community samples at older ages.” We are now conducting just such a replication.

Erratum

While preparing this rejoinder, we have discovered an error in the reporting of the composition of the above mix in the paper. The sentence reads:

“The active drink included 20 mg in total of artificial food colourings (sunset yellow, tartrazine, carmoisine, and ponceau 4R; 5 mg of each) (Forrester Wood, Oldham, UK) and 45 mg of sodium benzoate (J Loveridge, Southampton, UK).”

should have read:

“The active drink included 20 mg in total of artificial food colourings (sunset yellow 5 mg, tartrazine 7.5 mg, carmoisine 2.5 mg, and ponceau 4R 5 mg) (Forrester Wood, Oldham, UK) and 45 mg of sodium benzoate (J Loveridge, Southampton, UK).”

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Competing interests: none declared

References


Developmental delay versus developmental impairment

The use of the term delay should be replaced by impairment because of parental perception of the meaning of delay as applied to development. We would like to draw attention to my experience of parents’ perception of delay and possibly re-educating our profession to the term delay. It is common practice to refer to children who are detected to be significantly behind in achieving developmental milestones to be developmentally delayed. In talking to prospective adoptive parents I have become aware of how misleading this phrase is in describing to prospective adopters what we mean.

The general population has a perception of delay to mean something that will get there in the end, rather like a train being delayed, but reaching its destination eventually. It has taught me to use the term impairment rather than delay so that I do transmit to prospective adopters the true meaning of what I am trying to describe.

I wonder if as a profession we would consider examining our use of this term delay and possibly re-educating our profession to use the term impairment because it does not suggest that the child will be normal eventually.

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Palivizumab prophylaxis in haemodynamically significant congenital heart disease

Patients with congenital heart disease (CHD) have been reported by many authors to have high rates of hospitalisation, morbidity, and mortality associated with respiratory syncytial virus (RSV) lower respiratory tract illness. However, in a recent paper in Archives of Disease in Childhood, Duppenthaler et al reported a substantially lower incidence of...
RSV hospitalisation in patients with “haemodynamically significant” CHD. 1

They suggest that the rate of hospitalisation in their population of patients from the Canton of Bern, Switzerland was as much as four times lower than rates previously reported in the United States. Based on these results they concluded that the unrestricted use of palivizumab to prevent RSV hospitalisation is not warranted. There are several possible methodological reasons for the disparity in RSV hospitalisation rates in the calculations of both the numerator and denominator. With respect to the denominator, Duppenthaler’s methods would miss all of the nosocomial RSV disease. Furthermore, ascertainning the true incidence of RSV hospitalisation would require that all CHD patients admitted to the hospital undergo RSV screening, as was done in the international multicentre trial, not just those with symptoms judged typical of RSV. 2

Finally, in a previous paper by the same authors in the first four years of the study (1997/98–2000/01), 12 of 497 patients studied aged <5 years were identified with CHD compared to 6 of 449 aged <2 years in this study. In the previous study encompassed children under the age of 5, the difference of six patients between the first study and this one would imply that children who were hospitalised were between the ages of 2 and 5 (making a strong case for palivizumab prophylaxis in that age group), or they were deemed to have haemodynamically insignificant heart disease (making a case for prophylaxis in this group or questioning the definition of haemodynamically significant heart disease). With respect to the denominator, the authors used the International Classification of Diseases (ICD) coding as a screen for patients with haemodynamically significant CHD for entry into the cardiology registry. However, the ICD system does not allow for severity adjustment and therefore does not distinguish between haemodynamically significant and insignificant disease. In our recent multicentre trial, we defined haemodynamically significant CHD as patients with cyanotic CHD, single ventricle physiology, or those with acyanotic CHD that required medical or surgical therapy. Over the period described in the present study, this would account for only about 35–40% of all the CHD patients. This would have significa-

antly reduced the number of patients in the denominator, increasing RSV hospitalisation incidence. Secondly, no attempt was made to verify the accuracy of screening utilizing the ICD system, which might have resulted in missed patients with CHD due to inaccurate and/or inconsistent coding. Third, the calculations of years of observation, as written, was assumed to equal the number of child-years. This would be true if every child were born on 1 July; however, if births are spread out over 12 months the number of child-years would be halved. Thus, if the numerator were increased (for the reasons stated above) by perhaps one and one-half to two times and the denominator were decreased by two times (even just to account for the incorrect child-years of observation), the actual calculated hospitalisation rate per 100 child-years would be between 3/5 and 4 times higher than the rates quoted in tables 3 and 4. These rates would then be incomparable to the rates calculated in the USA. 3

In support of this statement is a brief recalculation of their data. The total birth cohort observed over six years was 54 947. There were 813 RSV hospitalisations which would give a rate of 29.6 per 1000 children per year, similar to other developed countries. Finally, the calculation of relative risks for hospitalisation uses a referent group that is not low risk, but includes children with prematurity and chronic lung disease, that would unfairly bias the relative risk in a lower direction. An incorrect referent group would be the low risk group as was done by Boyce and colleagues. 1

We would agree with the authors that the unrestricted use of palivizumab in CHD patients is not warranted. The intention was never to use the drug indiscriminately in CHD patients as evidenced in the cardiac trial that restricted its use in truly haemodynamically significant young CHD patients. 4 We disagree with the use of an NNT analysis to justify this statement. An NNT analysis only factors in the cost from a single RSV hospitalisation. But the CHD infant with RSV is likely to incur additional morbidity and mortality related to future hospitalisations and/or treatment, especially when it comes to surgical correction, and thus raises the cost of care. 2 Also, NNT analysis takes only a payer’s perspective, and ignores the societal component of pharmacoeconomics. As healthcare providers, it is our responsibility to use costly drugs in a responsible manner, while also ensuring that these patients receive the treatment/prevention from which they would clearly benefit.

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References


Authors’ reply

We greatly appreciate the interest of Feltes and Simoes in our study, but we are somewhat surprised by the intensity of their allegations. The large number of unrelated flaws they claim to find in the methods we used suggests that Feltes and Simoes have a fundamentally different view of how RSV data should be interpreted. In our opinion, their critique is mostly unjustified and requires a firm rebuttal.

It is true that nosocomial infections were not included in our study. 1 We did not claim otherwise. However, adding for instance a 14% rate of nosocomial RSV infections as reported for the placebo arm in their study (9 of 63 cases), 1 would not translate into a major change in the calculated RSV hospitalisation incidence. It is also correct that RSV tests were not conducted in CHD patients admitted for reasons other than respiratory tract disease, but this direct to claim that RSV testing was performed only in patients with typical RSV symptoms. Symptoms and signs leading to RSV testing are detailed in the method section of our paper 1 and encompass the vast majority of presentations caused by RSV. Furthermore, it is unclear why Feltes and Simoes here compare our observational study with their randomised controlled trial (RCT), 2 which we used as the comparator study. In this study, however, only 6% of cases were specifically coded as RSV infection; 94% were coded as “bronchiolitis”. 2 Thus, it appears obvious that our case catchment was not inappropriately insensitive. It is also worth mentioning here that our method of diagnosing RSV had undergone in-house validation. 1

In our previous study, 1 we did not focus on CHD cases. During the subsequent two years, there were 12 cases. Of these, nine cases occurred in children <24 months of age and were haemodynamically significant in four.

We did not—as Feltes and Simoes apparently assume—use ICD codes for case catchment. As stated in the method section, 1 the ICD-9 codes (Q20–Q26) used in our study were included in the database. The large groups of haemodynamically insignificant VSD, ASD, and PDA are not included. All cases included in the registry were “CHD requiring medical therapy”. It follows that the definition of haemodynamically significant CHD used in our study to create the denominator is quite similar to the definition used by them. 1 Their claim that the true denominator of CHD in our population was children with 3 years of age and older, is incorrect in our opinion. Again, our main comparator study 1 used a less stringent definition of CHD (ICD-9 codes 743–747) which did not address the issue of haemodynamically significant, and was thus more likely to report estimates of low precision.
Feltes and Simoes also claim that we got it wrong with the “child-years” and thus over-estimated that denominator by a factor 2. Objection! We agree that RSV exposure only occurs during approximately half of the child-years, and that total child-years should be divided by factor 2 for calculation of incidence per child-year of RSV season. However, we compared our incidence rates with those of Boyce and colleagues, which were already corrected for this discrepancy (that is, our data in table 3 were compared to the column entitled “Hospitalisations per 1000 children” in table 1 of Boyce’s paper, p. 867, which were multiplied by factor 2). Had we truly committed the mistake claimed by Feltes and Simoes, we would have compared our data with the preceding column in the said table, which is entitled “Incidence” (meaning: hospitalisations per 1000 child-years of RSV season).

Reduction of our denominator by factor 2 was indeed necessary, when children <6 months of age only were investigated. This, however, we did for calculation of the figures in table 3 and we explicitly stated that we did so in the text on page 963. Thus, this allegation again is incorrect in our opinion.

It is true that we used the entire population of non-CHD patients as referent, because we did not have data of sufficient quality for analysis of other individual risk factors. This was clearly stated in the manuscript. However, to claim that such a comparison is “unfair” is difficult to understand, because (1) for comparison we used Boyce’s raw data to calculate non-CHD rates in their population, and (2) in Switzerland, palivizumab has been recommended for children with severe BPD only.

Thus, we believe that it does make sense to compare CHD patients to all others who do not receive palivizumab. The very small group of children with severe BPD makes no substantial difference here.

We agree with Feltes and Simoes that NNT should not play a major role when it comes to providing optimal care for children with CHD. The reason why the new 2004 Swiss recommendations for the administration of palivizumab include children <1 year of age with surgically uncorrected, haemodynamically significant CHD and cyanotic CHD or severe hypertension or diaphragmatic failure, as soon as the distributor of palivizumab successfully applies for mandatory coverage by the health insurance companies. If, however, resources are limited, and they increase, then in many European countries, cost-effectiveness analyses including NNT do play a role when authorities have to weigh different new interventions against each other.

In summary, we believe that Feltes and Simoes create a largely incorrect worst case scenario of what could have gone wrong with our study. As elaborated above, we believe that our data are correct and—with the limitations described in the paper—reflect the current epidemiology in the study area.

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References


The Royal College of Paediatrics and Child Health flagship meeting: is it value for money?

The most recent Newsletter from the Royal College of Paediatrics and Child Health (RCPCH) was accompanied by a call for abstracts for the 9th Spring Meeting. An article in a recent RCPCH trainee’s newsletter from the chairman of the trainees’ committee expressed disappointment at the level of attendance by trainees, and that those who did attend left almost immediately after giving their presentation. This is supported by official figures from the RCPCH which show the lowest number of SHO and SpR attendees at the 2004 meeting over the past six years (table 1). SpR attendances at the 2004 meeting accounted for less than one quarter of total attendees and SHO attendance for only 2%. Why is this happening?

I postulate that it is simply too expensive. To attend for the three full day sessions at the RCPCH meeting will cost in excess of £500. The total sum involved is in excess of most trainees’ annual study leave budget. Indeed, during inquiries many other factors were identified—European Working Time Directive, the introduction of shift systems at middle grade, shorter training attachments at Specialist Registrar level are some—which not only have the effect of reducing and availability for visits to the Spring Meeting, but mitigated against research activities by trainees, so reducing their chance of presenting at the Spring Meeting, and growth of sub-speciality training may also be attracting trainees to specialty groups in the UK and Europe instead of the RCPCH Spring Meeting.

The Academic Board Executive has written to RCPCH college tutors and the chairman and members of the National Association of Clinical Tutors to ensure that trainees are encouraged to attend and given study leave and funding to do so. Contrary to popular belief, the Spring Meeting does not make money for the College, even when profits from the trade exhibition are included (these latter are far smaller than abroad, because of rules about sponsorship). Indeed, the meeting runs within a very narrow margin of making a loss. The figures are published in the annual accounts. Concessions for any group would mean an increase in costs for another.

Finally, the venue of the Spring Meeting is regularly reviewed, but there are few alternative venues, when the requirements for simultaneous sessions, technical support, accommodation, and provender are taken into account. Currently, York University offers good value and a fine setting where paediatricians, senior and junior, from the UK and abroad can meet, make and renew

Table 1 Attendance figures for RCPCH Spring Meeting 1997–2004

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<th>Staff grade</th>
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Competing interests: none declared


Reply by the RCPCH

I am pleased to have the opportunity to respond on behalf of the Academic Board. The trainee representatives on the Academic Board have taken soundings from their peers and formal approaches have been made to regional advisers, to inform our extensive discussions of these same data.

The data above show a fall in attendance, but do not provide any evidence that the reducing attendance is because the meeting is too expensive. Indeed, during inquiries many other factors were identified—European Working Time Directive, the introduction of shift systems at middle grade, shorter training attachments at Specialist Registrar level are some—which not only have the effect of reducing and availability for visits to the Spring Meeting, but mitigated against research activities by trainees, so reducing their chance of presenting at the Spring Meeting. The growth of sub-speciality training may also be attracting trainees to specialty groups in the UK and Europe instead of the RCPCH Spring Meeting.

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Finally, the venue of the Spring Meeting is regularly reviewed, but there are few alternative venues, when the requirements for simultaneous sessions, technical support, accommodation, and provender are taken into account. Currently, York University offers good value and a fine setting where paediatricians, senior and junior, from the UK and abroad can meet, make and renew
Meningitis is a common cause of convulsive status epilepticus. With the benefit of hindsight from this study, which refuted the perception that convulsive status epilepticus is atypical of acute bacterial meningitis (ABM) and cerebrospinal fluid (CSF) sampling might have been more readily undertaken, and perhaps more blood cultures done, given the fact that the latter modality sometimes tests positive even when CSF is sterile.

The crux of the matter is how the index of suspicion for meningitis is “packaged”, and the bottom line is that, given the fact that both ABM and tuberculous meningitis (TBM) are eminently amenable to treatment, and without treatment death is an almost invariable outcome for both, common ground must be found in the “packaging” in order to optimise diagnostic potential. A package which acknowledges the true prevalence of disease manifestations risks relegating those stigma to oblivion, the latter being the fate of the blanching maculopapular rash which, notwithstanding its prevalence of 13% in meningococcaemia,11 nevertheless totally escaped mention in the section on ABM in a leading textbook.12 With a prevalence of 5.6–9.7% in ABM, the CSF which is characterised by normal cellularity and biochemistry13 is another parameter that deserves greater recognition than is usually the case, especially because this is a feature which may characterise TBM as well.14 One view is that, in the latter context coexisting HIV/AIDS is the operative factor for this manifestation of TBM,15 What is also evident from the HIV/AIDS epidemic, is that tuberculous patients who have acquired HIV virus are more likely to have extrapulmonary tuberculosis than their counterparts who do not have HIV/AIDS.16 The paradigm shift dictated by the HIV/AIDS era is that the index of suspicion for miliary tuberculosis, hence, TBM, should be correspondingly higher, and that parallels between ABM and TBM should be more readily recognised. For example, like the four patients reported with ABM in the absence of meningococcal signs,17 the 8 month old HIV/AIDS patient with TBM reported by Janner et al.18 The armamentaria for the heightened index of suspicion for TBM include a more overt acknowledgment of the significance of the blanching maculopapular rash in ABM, routine fundoscopy to detect choroidal tubercles, a greater willingness of CSF sampling and blood cultures in convulsive status epilepticus, and a recognition that a CSF which is normal for cell count and for biochemistry may be a feature of either ABM or TBM, and so may be the total absence of signs of meningeal irritation.

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Competing interests: none declared

References

BOOK REVIEWS


And it’s only £18, including postage! But how does one review a book like this, a collection of twelve dozen editorials spanning four decades? I thought of the late Ronnie Mac Keith (“I am not your boss, I am your colleague!”) whose evocative personal memory by Martin rounds off this book, and looked for a bottle of Madeira to accompany my morning coffee and sweet biscuit. All I could find was port, and at once I was then watching Ronnie standing on the college dining room table between the silver giving flounce to an after-dinner speech, while Martin, already an editor since 1961, sat beaming below. But before I continue, I should explain about the editor date. The year 1961 is when Martin first became co-editor (with Ronnie Mac Keith) of Developmental Medicine and Child Neurology. Martin had already been editor of MacKeith, the literary and artistic magazine with poetry and visual arts side by side http://www.3ammagazine.com/litarchives/2002/jun/interview_mac Keith.html since 1959. That may give a clue as to why the present collections of editorials show such a fascinating synthesis, and not just to paediatric neurologists or students of developmental medicine. These editorials are well written (as befits a literary man), wide ranging, and a delight to dip into, delightful enough to find a place on the bedside table or even—and this is a compliment—in the loo.

Martin’s first editorial was on animal behaviour, summarising the work of Harry Harlow on infant Macaque monkeys and the contrasting effects of cloth and wire “imimate surrogates mothers” on the child’s behaviour and affection. He was then fresh from Guy’s, having previously been up at New College, Oxford. In a later editorial, he tells us that at his first paediatric unit two elderly paediatricians took him aside and advised him not to continue in that specialty, which they saw as declining and coming to an end, what with the eradication of tuberculous meningitis and other infectious diseases of childhood. But, he writes (p. 141) “There were two straws blowing in the wind: one was the developing interest in neonatology, the second was that people were beginning to wonder about the fate of the many children treated with congenital disabilities who at that time, were often fated to be placed in institutions and to spend the rest of their lives there.” As Martin’s mentor (if not boss) Ronnie Mac Keith predicted, paediatrics did not disappear, and by 1984 (p. 96) Martin is making “a plea for not too many more paediatric specialties. A paediatrician is a doctor who looks after the child, intending both to promote health and development and to care for the child who becomes ill. This is a species that should not be endangered by too much fragmentation.”

Nonetheless, in this travel through the academic life of Martin Bax, I sometimes sense a whiff of conflict between neurologists whole, in one piece, and dividing up even into subsections of paediatric neurology, so that rare disorders may be properly dealt with, so that doctors know more than the internet learned parents. Another conflict is between the role of paediatric neurologists in centres for handicapped children (p. 56) and the Aicardi view that the prime task or skill of paediatric neurologists is to make precise diagnoses, whereas “The glory of language is its flexibility and its failure to obey the rules.” Regarding meetings and conferences, he favours the view of Mac Keith that the “greatest benefit results when small groups of 10 to 30 are together for three or four days” with “the intelligent use of guests from far-away parts of the world” (p. 61). The final Editorial in 2003 (p. 252) includes the immortal lines “Indeed it was Hippocrates who denied that epilepsy was due to the erotic behaviour of the gods, but to some disorder which could be rationally investigated.” Much better than erratic.

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www.archdischild.com

PostScript
A PAR is a different trajectory of development that the fetus takes as a result of its intrauterine (or perhaps early postnatal) environment, with the aim of maximising chances of survival to reproductive maturity, in a particular *expected* postnatal environment. For example, in the pregnant snowshoe hare, stress (due to predation, cold, or starvation, for example) may lead to increased maternal cortisol levels. Cortisol may cross the placenta, and the fetus may detect, via signalling from the mother and placenta, that the external environment is a harsh one. The cortisol levels may enhance maturation of fetal organs, such as the lungs, and prepare the fetus for the rigours of postnatal life. However, it appears that exposure to such high cortisol levels in utero may alter the sensitivity of the hypothalamo-pituitary-adrenal axis, making it hyper-responsive after birth. So the offspring of hares that have been stressed during pregnancy, may be hyper-alert—a predictive adaptive response to the expected postnatal environment. One wonders what the effects of an analogous human PAR might be.

Gluckman and Hanson propose that while we have reached a stage in the 150,000 year history of *Homo sapiens* where Darwinian evolution is no longer active or has slowed dramatically, the predictive adaptive responses we have evolved now threaten our post-reproductive health, in terms of obesity, type 2 diabetes, atherosclerosis, and hypertension. These responses could be initiated soon after conception, mediated by DNA methylation. What is unclear is the extent to which PARs may play a role in human disease outside the context of birth weight (or rather suboptimal fetal growth) and the metabolic “syndrome X”. Gluckman and Hanson make a case for other diseases such as osteoporosis, cognitive decline, psychosis, and polycystic ovarian syndrome, with varying degrees of persuasiveness.

The message from the book appears to be twofold: that the evidence for PARs playing a role in human disease is a persuasive one, which should not be overlooked in favour of “sexy” genome research; and secondly, that if these hypotheses are correct then this has significant implications for society, and how we try to reduce the burden of disease in later life. Unfortunately, there appear to be few recommendations we can make for optimising the intrauterine, and postnatal, environment to minimise the potentially harmful effects of inappropriate PARs.

The idea that the intrauterine environment has an effect on disease later in life is not new. The “Barker hypothesis” has been around for over 10 years. For those unfamiliar with the hypothesis at its simplest level, it suggests that a low birth weight reflects an adverse intrauterine environment that the fetus has adapted to, in order to survive. This “thrifty phenotype” is the result of altered development in utero to cope with poor supply of nutrients and oxygen from the mother. The consequence of this phenotype, however, is a doubling in the risk of death from heart disease in individuals born with low birth weights (less than 2.5 kg).

Gluckman and Hanson develop these ideas, and draw on evidence from zoology and fetal physiology, and suggest that many diseases may, at least in part, result from “predictive adaptive responses”.

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**Reference**


**The fetal matrix: evolution, development and disease**


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**CORRECTION**

The author of the book review *Minor trauma in children, a pocket guide* (*Arch Dis Child* 2005;90:656) was misspelt and should be S Fountain-Polley. We apologise for the error.