LETTERS TO THE EDITOR

Association between SIDS and Helicobacter pylori infection

EDITOR,—The article in the November issue of the Archives on the association between sudden infant death syndrome (SIDS) and Helicobacter pylori infection, Arch Dis Child 2000;83:429–34.

...the children have at least one

- The discovery that Helicobacter pylori is the prime cause of peptic ulcer disease, is one of the most important advancements in medicine in the 20th century. Subsequently, its importance in the causation of gastric cancer has been recognised. It is a rare cause of gastric lymphoma. Despite its significance as a pathogen, this organism colonises the gastric mucosa in up to 50 percent of the world’s population. Not surprisingly research interest is intense. There has been much speculation (though little proof) that it might have a role in various other gastrointestinal and non-gastrointestinal disorders, including failure-to-thrive in infancy, short stature, anaemia, and even cardiovascular disease. Now a link has been proposed between H pylori and sudden infant death syndrome (SIDS). Recently, Kerr et al examined gastric, tracheal, and pulmonary tissue, looking for evidence of H pylori in SIDS victims and controls. Based on polymerase chain reaction (PCR) techniques, they reported a highly significant association between SIDS and the presence of two H pylori genes (UreC, cagA) in these tissues. Not surprisingly, this reported association has evoked a lively correspondence.

I would value a response from Drs Fleming, Blair, and Berry who co-authored the CESDI study of SUDI.

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Ammonia—not the culprit

EDITOR,—We were interested to read the article by Kerr et al on the SIDS problem. With regard to the interesting results we would like to point out some related findings. As pointed out by Kerr et al, H pylori is abundant in less advantageous parts of society where smoking is often frequent, and sometimes where SIDS occurs. The fact that smoking is often inversely related to the ability of H pylori to colonise and to be transmitted from mother to child1 might indicate that it is sensitive to smoke itself, or products generated after smoke inhalation. It is interesting to note that endogenous products of smoke, like nitrate and nitrite, often inhibit bacterial growth.2

Furthermore, we have previously shown that total breakdown of all ingested urea takes place in all normal infants without causing problems of ammonia intoxication.3 This is in contrast to SIDS victims, most of whom have unmetabolised urea in their faeces.4 Due to these related circumstances it may seem a little adventurous to suggest that ammonia produced by H pylori could cause death in SIDS.

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Control your controls and conclusions

EDITOR,—In a retrospective study, Kerr and coworkers investigated formalin fixed, paraffin embedded tissues (stomach, trachea, and lung) of 32 infants who died of SIDS, and eight control cases, with nested polymerase chain reaction (PCR) and ELISA of the amplificates. A child was considered as infected with H pylori if the optical density of the ELISA was above the mean value plus 2 SD obtained in the tissue of control infants. The authors found that 28 of the 32 SIDS cases, but only one of the eight control cases fulfilled these criteria. They conclude from their results that H pylori infection may play a causative role in SIDS. We have serious doubts about their results and conclusions.

The control group was extremely small in size and we would expect most, if not all, of these eight infants to have received one or more antibiotics in high doses intravenously over several days before death, as the causes of death were bacterial meningitis, septicaemia, pneumonia, necrotising enterocolitis, ileal perforation, and prematurity. In contrast, few if any of the SIDS victims would have received intravenous antibiotics. Therefore, if control children had been colonised with H pylori, the bacteria may have been suppressed. These eight infants are certainly not appropriate controls for this kind of study.

Nestcd PCR is a very sensitive method with a high risk of false positive results caused by contamination. The applied ELISA is yet another amplifying method which also increases the risks of unspecific binding. Although the authors stated that they tried to minimise contamination, no precautions have been performed at the time of autopsy and preservation of the tissue due to the retrospective character of the study. Because of the low specificity of the methods used, it is mandatory to prove the identity of the PCR amplicons as H pylori specific by sequencing the products. Such verification was not reported in the paper. To show the specificity of their method, the authors could have also performed analyses on control tissues—for example, brain, which are unlikely to be H pylori infected even when other tissues were assessed as “positive”.

The fact that H pylori was not shown in the stomach, trachea, or lung by histology in any of the children must raise major concerns that the applied methods were not specific. Other methods for detection of H pylori infection like fluorescence in situ hybridisation (FISH) have not been applied. The authors do not report whether any of the children had histological signs of acute or chronic gastritis, which is found even in young children with H pylori infection.5 If the bacterial load was so small that neither the bacteria nor the associated inflammation could be detected by histology, it seems questionable that metabolitic products produced by H pylori—for example, ammonia, may play a causative role as a cause of SIDS as suggested by the authors.

Finally, the authors mention that both H pylori infection and SIDS are more common in poor socioeconomic populations but fail to provide any information on the ethnic and socioeconomic background of both the SIDS control infants. From many epidemiologic studies and our own experience, it seems extremely unlikely that 28 of 32 infants (87%) under 28 weeks of age are infected by H pylori in a country such as the UK, unless these children are from immigrant groups. We are, for example, following a cohort of German children from birth with regular testing for H pylori infection by two non-invasive tests: the detection of H pylori antigen in stool (HpSA, Meridian Diagnostics, Cincinnati, USA) and the ‘C-urea breath test corrected for estimated individual CO2 production rate. ’ Although a quarter of the children have at least one positive serology and/or a positive ‘C-urea breath test’ only 1.5% of the children have positive tests during the first three years of age.

On publication, this paper was widely reported by the media, a process actively assisted by the authors. This is likely to result in considerable anxiety among young parents and pregnant women, feelings of guilt in parents of SIDS children and unjustified H pylori...
eradication therapy in asymptomatic children. Since neither the selection of the control group nor the methodology used is fully robust, this study does not, however, permit valid conclusions on the association of *H pylori* infection with SIDS. We believe it is irresponsible to promote inconclusive results in the light of such inadequate data.

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**Association is not the same as causation**

**Editor,—**The paper by Kerr *et al* describes an association between SIDS and colonisation with *H pylori*. In the introduction, the authors state that both SIDS and colonisation with *H pylori* are known to be linked with poor socioeconomic status and overcrowding. This clearly suggests that some common factor (possibly smoking, possibly something else) may predispose to both conditions. Yet, in the discussion, the authors ignore this possibility and prefer to postulate on how *H pylori* might cause sudden unexpected death. Not only is this approach unscientific, it is also irresponsible. The proposed causation has been taken up by the media and I have already been asked to see a mother who is receiving eradication therapy for *H pylori*. She fears that her child may already be infected and will die from cot death.

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**Death kisses for newborns?**

**Editor,—**Kerr *et al* claim *H pylori* as a potential etiologic factor in SIDS. Fatal systemic ammonia intoxication through hydrolysis of urea by *H pylori* produced urease in the lungs and trachea, following aspiration of gastric juice, was proposed as a possible pathogenic pathway. In general we cannot agree with this hypothesis. The molecular procedure (nested PCR and ELISA based detection) used in this study could explain some incorrect data—for example, *H pylori* DNA detection in lungs or trachea but not in the stomach. Furthermore, it is debatable whether haematoxylin and eosin (H&E) routine staining is an efficient method to visualise Helicobacter

**H pylori DNA may not imply infection**

**Editor,—**Kerr *et al* report an association between SIDS and *H pylori* infection. In 32 SIDS cases aged up to 26 weeks old, the *H pylori* ureC gene was amplified from the stomachs of 15, from the trachea of 19, and from the lungs of 16. The *H pylori* cagA gene was amplified from the stomachs of 13 (of which seven were positive for the ureC gene), from the trachea of 20, and the lungs of 23 (of

**Dwelling crowding as a pertinent factor**

**Editor,—**Kerr *et al* report a highly significant association between *H pylori* infection and SIDS. This finding raises the possibility of (and a plausible mechanism for) a link between dwelling crowding and SIDS, as there are a number of studies that have documented a strong relation between dwelling crowding and *H pylori* infection.4 Close person to person contact and inhalation of any contamination to the infective agent is likely a cause of this relationship. Dwelling crowding has also been associated with increased passive exposure to tobacco smoke, and this, coupled with parental smoking being strongly associated with SIDS,5 provides yet another clear link between dwelling crowding and SIDS.

There are likely to be many causes of dwelling crowding. It has often been associated with low socioeconomic status, but the study by Elistrat *et al* suggests that there may be a direct link between crowding and *H pylori* infection, which is independent of socioeconomic status. SIDS has also been associated with lower environmental temperature and it is possible that the increase in SIDS rate during winter is in part relate to the increased dwelling crowding during such time.

Very few studies have examined the links between dwelling crowding and SIDS. One recently published study found only a non-significant increase in relative risk for SIDS associated with dwelling crowding.6 Given the importance of SIDS and the growing body of evidence suggesting *H pylori* as a cause of SIDS, it would be pertinent for future studies to consider dwelling crowding in more detail.

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which 14 were positive for the ureC gene. Amplified DNA was detected semiquantitatively using an ELISA, with a cut off value calculated from the mean of eight controls. The authors offered little explanation for the discordant detection of *H. pylori* DNA between the two PCR assays used. It may be appropriate to compare the prevalence of *H. pylori* in SIDS and controls, but inappropriately to make these two groups the basis for defining cutoffs for an *H. pylori* assay.

The presence of *H. pylori* DNA does not itself imply infection and no visible bacteria were observed in any tissue sections. *H. pylori* can be acquired early in life probably from other members of the family. Infection has only previously been detected in the microenvironment of the gastric mucosa and its presence is closely related to socioeconomic status, as is SIDS. No details of the socioeconomic status of the infants from whom tissues were obtained, nor details of familial contact were given. Four of the controls died under eight weeks of age from what could possibly be neonatal complications and no details of whether they had been discharged home were provided.

The authors propose that primary gastric infection and subsequent aspiration into the lungs led to lethal production of ammonia in infants as young as two weeks of age. It is difficult to imagine that an organism specifically adapted to the microaerophilic and acidic conditions of the gastric mucosa thriving well enough in the lungs to produce toxic amounts of ammonia in infants that presumably had normal lives, particularly when no organisms were visible on histology.

This interesting report could well describe a proxy for the already widely known association between *H. pylori* and poor socioeconomic status. Arguing that the discordant presence of *H. pylori* DNA in various organs of SIDS cases represents causation is premature, but warrants further investigation.

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Dr Kerr, Barson, and Burnie respond

Eviron—Following the publication of our paper, we would like to thank the above authors for their comments and respond in order to clarify our study methodology, interpretation of the data, the impact of the media, and concern on the directions of future work in this area.

The possibility of PCR contamination has been suggested by Franciosi and Koletzko and we agree that this is a potential problem in studies of this type. We guarded against this by utilisation of separate laboratory areas and pipettes for pre-PCR, PCR and post-PCR stages of the procedure, use of sterile bunged pipette tips, and inoculation of the positive control as a last step in the pre-PCR preparation. In each run, we used sterile distilled water and DNA extract from human ureter as negative controls, and examined samples in duplicate. Throughout our study, duplicated samples consistently gave concordant results, and negative controls were consistently negative.

Dr Koletzko suggests that the two separate nested PCR-ELISAs utilised in our study may have doubtful specificity as we did not sequence the products. We agree that amplification sequencing is desirable not only to ensure specificity but in the present context would also provide additional data on the molecular epidemiology of the *ureC* gene which was detected in these cases. We believe our assays to be specific. For example, the binding of oligonucleotides of 20 or more bases to template DNA at 1°C has been shown to be 100% specific. And in one of our PCR-ELISAs, there were five such interactions.

We agree with Dr Koletzko and other workers that it would be valuable to test other tissues from the same patients by the same method.

In response to Dr Vieth’s claim that our suggested role for interleukin-1β (IL-1β) *H. pylori* infection is “totally speculative”, we would like to point out that these mechanisms have been demonstrated in an animal model. Also, proteins of *H. pylori* are known to activate macrophages leading to production of IL-1β which is known to inhibit acid secretion by parietal cells and may actually be the most potent inhibitor of acid secretion discovered to date. IL-1β gene polymorphisms associated with increased IL-1β production have recently been associated with an increased risk of gastric cancer. In addition, systemic and mucosal humoral recognition of the cag protein has been linked with peptic ulceration, duodenal ulcer patients may more frequently harbour cagA *H. pylori* strains, and it has been shown that infection with cagA strains as compared with cagA strains is associated with increased IL-1β expression. This is therefore interesting that 25 of 28 cases of *H. pylori* associated SIDS in our study had a detectable cagA gene in their tissues, which may provide further support for the proposed pathogenesis of *H. pylori* in SIDS and a contributory role for IL-1β.

Dr Paul Beggs from Macquarie University in Australia points out the link between dwelling crowding and *H. pylori* infection, which has been shown to be independent of socioeconomic status, and the need for research on the possible link between dwelling crowding and SIDS. We agree that “given the importance of SIDS and the growing body of evidence suggesting *H. pylori* as a cause of SIDS, it would be pertinent for future studies to consider dwelling crowding in more detail.”

We feel that Wiklund and colleagues, and MacKay and colleagues (in separate letters) have misunderstood the proposed hypothesis. Wiklund states that total breakdown of ingested urea occurs in all normal infants without ammonia intoxication and that SIDS victims have undigested urea in their faeces. MacKay states that “it is difficult to imagine that an organism specifically adapted to the microaerophilic and acidic conditions of the gastric mucosa thriving well enough in the

Table 1 Information on antibiotic exposure, environmental exposure, and PCR-ELISA testing for *H. pylori* ureC and cagA genes in the stomach, trachea, and lungs of control cases used in the study “An association between sudden infant death syndrome (SIDS) and Helicobacter pylori infection.” Results of PCR-ELISA testing is expressed as optical density. Those specimens with a cット off value greater than or equal to the mean plus two times the standard deviation of these controls (designated negative) are marked with an asterisk

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at death (lbs)</th>
<th>Cause of death</th>
<th>Time of diagnosis</th>
<th>Antibiotic exposure</th>
<th>Exposure to the home environment</th>
<th>&gt;1 month</th>
<th><em>H. pylori</em> ureC gene</th>
<th><em>H. pylori</em> cagA gene</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stomach</td>
<td>Trachea</td>
</tr>
<tr>
<td>C1</td>
<td>3</td>
<td>prematurity</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>0.00</td>
<td>0.100</td>
<td>0.150</td>
</tr>
<tr>
<td>C2</td>
<td>4</td>
<td>prematurity</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>0.00</td>
<td>0.200</td>
<td>0.090</td>
</tr>
<tr>
<td>C3</td>
<td>7</td>
<td>ileal perforation</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>0.00</td>
<td>0.090</td>
<td>0.150</td>
</tr>
<tr>
<td>C4</td>
<td>7</td>
<td>Necrotising enterocolitis</td>
<td>AM</td>
<td>day only +</td>
<td>0.00</td>
<td>0.200</td>
<td>0.150</td>
<td>0.180</td>
</tr>
<tr>
<td>C5</td>
<td>20</td>
<td>E. coli sepsicaemia</td>
<td>PM</td>
<td>–</td>
<td>+</td>
<td>0.00</td>
<td>0.150</td>
<td>0.180</td>
</tr>
<tr>
<td>C6</td>
<td>24</td>
<td>suffocation</td>
<td>PM</td>
<td>–</td>
<td>+</td>
<td>0.00</td>
<td>0.120</td>
<td>0.090</td>
</tr>
<tr>
<td>C7</td>
<td>32</td>
<td>pneumonia</td>
<td>PM</td>
<td>–</td>
<td>+</td>
<td>0.00</td>
<td>0.120</td>
<td>0.090</td>
</tr>
<tr>
<td>C8</td>
<td>44</td>
<td>Pneumonococcal septicaemia</td>
<td>PM</td>
<td>–</td>
<td>+</td>
<td>0.00</td>
<td>0.120</td>
<td>0.090</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean</th>
<th>±SD</th>
<th>±0.065</th>
<th>±0.063</th>
<th>±0.060</th>
<th>±0.16</th>
<th>±0.071</th>
<th>±0.080</th>
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<tbody>
<tr>
<td>0.174</td>
<td>0.163</td>
<td>0.181</td>
<td>0.179</td>
<td>0.150</td>
<td>0.166</td>
<td>0.116</td>
<td>0.071</td>
</tr>
</tbody>
</table>

C1, control case number 1; AM, ante-mortem; PM, post-mortem; NT, not tested.

lungs to produce toxic amounts of ammonia in infants that presumably had normal livers.\textsuperscript{9} To reiterate, there are two parts to the hypothesis. First, interleukin-1 production in the Helicobacter pylori infected stomach, and second, supply of ammonia to the systemic circulation (and not the hepatic circulation as MacKay implies). Therefore, faecal urea content is irrelevant and so is ammonia produced in the stomach as this will be detoxified by the liver. Regarding comments in the media, these are clearly not under our control and we have always stated that our findings are preliminary and require confirmation.

In conclusion, we would encourage recent studies and those of Pattison and colleagues\textsuperscript{15} in order to clarify the proposed role of Helicobacter pylori in SIDS. In the meantime, we re-emphasise accepted measures to reduce mortality from SIDS and suggest the following additional precautions, all of which constitute good personal hygiene and are therefore advisable even in the absence of such a link. First, to prevent the transfer of saliva from the mouths of carers to babies. Second, prompt disposal of vomitus, decontamination of soiled surfaces, and washing of soiled clothes/bedclothes, followed by hand washing, in order to minimise transmission to the baby via the gastro-oral route. Third, good general hand and personal hygiene. In addition, parents should be reassured that they do not need to do anything more than the above at present.

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\textsuperscript{1} Kerr JR, Al-Khatafi A, Barson AJ, et al. An association between sudden infant death syndrome (SIDS) and Helicobacter pylori infection. \textit{Arch Dis Child} 2000;83:429–34.


The need for further evidence for the proposed role of Helicobacter pylori in SIDS

Editor—We read with interest the article by Kerr et al.\textsuperscript{1} While the proportion of samples positive for Helicobacter pylori was significantly higher in the SIDS group compared with the control group, the findings need to be interpreted with caution. PCR is a useful tool for detection of DNA. It is, however, evidence that the DNA of the organism is present, not evidence that the organisms were alive or caused disease. Culture, microscopy, serological evidence or histological evidence of inflammatory or immune responses are needed to support the hypothesis that the bacteria were involved with pathological processes, not just transient contamination of the infant with DNA from non-viable bacteria. There are several points that detract from the paper:

1. In relation to the findings reported: 1. Only the PCR assays provided positive evidence. In contrast to other studies reported as abstracts, microscopic examination of the stained sections did not find any evidence of Helicobacter pylori and no discrepant findings and no data from histological examinations to provide evidence that the bacteria were causing infection or that inflammatory responses had been elicited.

2. The proportion of PCR positive samples among SIDS infants (88%) was significantly larger than that among controls (2.5%), and no correlation was found between age and Helicobacter pylori infection. There was no demonstration by molecular methods that the DNA detected was from different strains. Helicobacter pylori strains show great genetic variability, and previous studies demonstrated that most individuals carry unique strains. Isolates from different individuals that appear to be genetically identical are those obtained from close contacts, usually within a family. The interpretation of the epidemiological data for Helicobacter pylori and socioeconomic factors was not related to infection in incidence of SIDS among different ethnic groups. In Britain, white families in lower socioeconomic groups have more evidence of Helicobacter pylori infections and more SIDS. If the data for incidence of infections with Helicobacter pylori is assessed for ethnic groups and SIDS, this parallel breaks down. The incidence of seropositivity for Helicobacter pylori among Bangladeshi women in the UK ranges from 66% among women born abroad to 81% among women born in the UK; however, the incidence of SIDS in Bangladeshi families was the lowest in Britain (0.3%). A similar trend was observed in the United States; seropositivity for Helicobacter pylori in 61% among Hispanics and 26.2% among non-Hispanic whites.\textsuperscript{2}

This evidence questions the assumptions made by the authors.

While there is increasing evidence for other hypotheses that SIDS might be triggered by inflammatory responses to infection,\textsuperscript{3} there is no physiological or histological evidence to support the hypothesis that urease in the lung of the infants is causing increased levels of ammonia in the blood (see detailed assessment of pathology of SIDS and the hypothesis below). Animal models\textsuperscript{3,4} do not reflect the combination of genetic, environmental, and developmental factors associated with SIDS, and results from animal studies must be interpreted with extreme caution when extrapolated to the human infant. Helicobacter pylori infection does not fit the common bacterial hypothesis, a mathematical model which accurately predicted the age range for SIDS.\textsuperscript{5} According to the model, 50% of infants should acquire the bacteria during the first 50 days of life. While 19% of Gambian children were positive for the C13 urea breath test by 3 months of age,\textsuperscript{6} in industrialised countries the evidence is that Helicobacter pylori infection in infants under 1 year of age is much lower. Among 67 children born to seropositive mothers, only 1 (1.5%) had a positive breath test by the age of 12–15 months.\textsuperscript{7} Among Finnish children 10.6% had IgG to Helicobacter pylori at birth, but the antibodies decrease to less than 1% by the age of 7 months and there were no seroconversions in these children. The Finnish study concluded that maternal seropositivity is not a straightforward risk factor for acquiring Helicobacter pylori infection.\textsuperscript{8}

The oral/oral route of transmission is suggested to be the route by which infants acquire Helicobacter pylori, mainly by vomit.\textsuperscript{9} Helicobacter pylori has been cultured from one of four vomit samples from children and detected by PCR in two of four culture negative samples. There is much stronger direct (culture) evidence for transmission from mother to child of other bacterial species implicated in SIDS.\textsuperscript{10} The pathogenic mechanism proposed for the role of ammonia cannot be substantiated by the available evidence:

1. There are no acute changes in the upper respiratory tree or lungs consistent with inflammatory responses to H. pylori.

2. The presence of ammonia in the lower respiratory tree would initiate a broncho- spasmod which should produce clinical features such as wheezing which has not been reported by parents of SIDS infants.
This type of reaction should be demonstrable histologically by muscular, glandular and secretory changes identified by microscopy.

3. If ammonia is present in excess, it has been acutely affected by an influx of ammonia, there should be changes.

4. The liver in SIDS cases shows no abnormality and has been completely counted in blood samples and vitreous fluid, and there is no evidence for this.

5. Ammonia in excess leads to cerebral petechiae in the lungs due to local tissue changes of an acute type and none have been demonstrated.

6. If the ammonia is postulated as a cause of petechiae in the lungs due to local damage, this does not account for the presence of petechiae in the thymus and pericardium.

There is evidence to explain how risk factors could contribute to susceptibility of infants to infective agents by triggering the series of events leading to SIDS; however, that presented for *H pylori* needs to be substantiated by more than one method and testable hypotheses proposed to explain how these bacteria might contribute to the series of events that lead to SIDS.

Table 1: Characteristics of SIDS cases and controls

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
</tr>
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<tbody>
<tr>
<td>F</td>
<td>4 months</td>
<td>Congenital heart disease</td>
</tr>
<tr>
<td>F</td>
<td>2 months</td>
<td>Morphone toxicity</td>
</tr>
<tr>
<td>M</td>
<td>13 hours</td>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td>M</td>
<td>1 hour</td>
<td>Amniotic fluid aspiration</td>
</tr>
<tr>
<td>M</td>
<td>6 months</td>
<td>Premature, septicaemia</td>
</tr>
<tr>
<td>M</td>
<td>3 months</td>
<td>Congenital brain tumour</td>
</tr>
<tr>
<td>M</td>
<td>6 months</td>
<td>Glutaric aciduria type I</td>
</tr>
<tr>
<td>M</td>
<td>2 months</td>
<td>Extreme prematurity</td>
</tr>
</tbody>
</table>

Cases

| M   | 3 months | SIDS |
| M   | 3 months | SIDS |
| M   | 13 months | SIDS |
| M   | 7 days | SIDS |
| M   | 5 days | SIDS |
| F   | 8 months | SIDS |
| F   | 2 months | SIDS |
| F   | 2.5 months | SIDS |
| M   | 2 months | SIDS |

No association in a Chinese population

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The formalin-fixed and paraffin-embedded stomach, trachea, and lung specimens obtained during post-mortem examination were retrieved. Initial histological examination was performed by an experienced pathologist to look for any evidence of *H pylori* colonisation in these specimens. In addition, we used three different PCR assays that amplify two regions of the ureB gene and the cagA gene to detect the presence of *H pylori* DNA in these samples.

Histological examination failed to show any *Helicobacter* like organism in these samples. Moreover, despite using three different sensitive PCR assays, we failed to show the presence of *H pylori* DNA in the stomach, lung, or trachea of the SIDS and control patients.

Viable *H pylori* has recently been recovered from the vomitus of infected children and adults. Conceivably, it could lead to silent aspiration of gastric contents into the lung and result in bronchopneumonia. However, the failure to detect the organism in the stomach, trachea, and lung specimens, together with the absence of features to suggest aspiration pneumonia as the cause of death in these infants, argue against the validity of this speculation. With the high prevalence of *H pylori* infection in Chinese, one would expect a parallel high incidence of SIDS in our ethnic group, which does not fit into any epidemiological observations. Taken together, the significance of *H pylori* as a cause of SIDS is highly questionable.

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Editor,—We read with great interest the paper by Kerr et al on the association between *H pylori* infection and SIDS. However, we cannot agree with the speculation the authors made.

Recently, we performed a similar retrospective analysis of nine cases of SIDS and eight controls collected in our hospital over the past two years. Controls were selected from infants with known cause of death, including congenital malformation, infection, metabolic disease, and drug intoxication (see table).


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EYTON—The paper by Kerr et al reported an association between *H pylori* and sudden infant death syndrome (SIDS). We have reviewed their data and believe that the methods used may have led to incorrect conclusions.

Kerr et al examined retrospective material from 32 cases of SIDS infants and 8 non-SIDS controls. They used nested PCR followed by an ELISA detection step which would have made their method exquisitely sensitive. Consistent with this, no other method was able to confirm that *H pylori* was actually present. Instead, Kerr et al used a relative increase of “*H pylori* signal” above that of the mean + 2SD control group, as an indicator of *H pylori* presence.

This prompted us to more carefully consider the appropriateness of their control and patient groups.

Since ethnicity and socioeconomic details of the SIDS infants were not given, we could not confirm that these matched the control infants. We also noted important clinical details of the controls which could make them inappropriate. It appears that most of the controls would have had very little bacterial contamination of the PCR specimens because they died in hospital while on antibiotic therapy for sepsis, or were deceased very soon after premature birth. In addition, they might have been transferred to refrigeration very soon after death. SIDS infants however, probably died at home, many hours before being refrigerated.

Finally, as *H pylori* is a gastric organism, it was surprising to find the bacterium in lung aspirates in eight patients (ureC gene) or six patients (cagA gene) in whom gastric samples were negative. Therefore, it would have made their method exquisitely sensitive. Consistent with this, no other method was able to confirm that *H pylori* was actually present. Instead, Kerr et al used a relative increase of “*H pylori* signal” above that of the mean + 2SD control group, as an indicator of *H pylori* presence. This prompted us to more carefully consider the appropriateness of their control and patient groups.

Since Kerr’s paper was widely reported in the media, we believe that it needs to be stated that the case for *H pylori* as a cause of SIDS is certainly unproven and is in quite considerable doubt.

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No association in a Chinese population

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More on SIDS and H pylori—Authors’ response

EDITOR.—At present, we do not understand the pathogenesis of sudden infant death syndrome (SIDS), however, it is accepted to be a multifactorial disease for which certain risk factors have been identified. Various theories have been developed to explain the existence of these risk factors.

Blackwell reminds us of the accepted fact that PCR detects DNA from both live and dead organisms, but her phrase “transient contamination of the infant with DNA from non-viable bacteria” seems inappropriate. The detection of H pylori DNA in the trachea and lungs of some babies is a finding of particular importance both for our understanding of the pathogenesis and epidemiology of H pylori infection in infants.

The study by Kerr et al showed H pylori DNA in the stomach, trachea, and lung tissues of SIDS cases, but did not visualise bacteria at these sites. As stated in the paper and by several other authors, the study used haematoxylin and eosin staining, a suboptimal methodology for visualisation of gastric bacteria. Other studies have shown inflammatory changes in both antrum and trachea of H pylori-PCR positive SIDS cases.13

(a) “There is no inflammation in the lungs of SIDS cases”.
(b) “Ammonia in the lower respiratory tract would cause bronchospasm and wheezing which has not been reported by SIDS parents”. In animal studies (not yet published as a full paper), bronchospasm was suggested by progressively less bronchoalveolar lavage (BAL) fluid detection on continual doses of intratracheal urease.6 Since parents are invariably absent at the time of death, it would be unlikely that wheezing would be detected.
(c) “If ammonia accounts for death, this should be demonstrable in blood and vitreous”. Our hypothesis is supported by intratracheal urease administration to rats which caused increased ammonia in BAL fluid although this was not accompanied by significantly increased serum ammonia. The physiological effects of pre-treatment with IL-1β could not be clearly defined.
(d) “The liver should be affected by hyperammonaemia and it is not in SIDS”. Blackwell has misunderstood our hypothesis. First, interleukin-1 production in the H pylori-infected stomach, and second, aspiration of urease into the lung and supply of ammonia to the systemic circulation (and not the hepatic circulation as Blackwell implies).
(e) “The brain should be affected by hyperammonaemia after infection in SIDS”. If our hypothesis is correct, then the terminal event, involving hyperammonaemia in the systemic circulation is an acute and rapidly fatal occurrence, which may not result in brain pathology.

We do not understand this point. Marshall’s views on controls used in the original paper7 do not take account of further information provided at the request of other authors8 which show that of eight controls used, five had an exposure to the home environment of more than one month.

Marshall states that H pylori is a gastric organism and that it is surprising to find evidence of infection in lung and trachea. However, H pylori has been detected at other sites, for example, the respiratory tract of intubated adults,9 and in the liver of patients with primary sclerosing cholangitis and primary biliary cirrhosis.10

The pathogenesis of SIDS is accepted to be multifactorial, and therefore, small studies with a negative association between H pylori and SIDS such as that of Leung and colleagues, are to be expected.

Emotion aside, the fact remains that three groups have found H pylori in some cases of SIDS, and all three groups have detected the organism in the lung.11

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www.archdischild.com
Growth hormone in Turner syndrome

EDITOR,—The recent interesting and valuable article by Johnston and colleagues describing the outcome of a trial of recombinant growth hormone (GH) and low dose oestrogen in girls with Turner syndrome (TS) concluded that low dose oestrogen before planned induction of puberty was not beneficial for adult height. However, they extend their conclusions by the cautious word that although the majority of girls might benefit from GH treatment, a “realistic appraisal” suggests “modest” benefit. Although evidence to the contrary is fully discussed in their paper, this generalisation might lead the reader to doubt the effect of GH in TS.

The best known of the trials of GH in TS is that of Rosenfeld and colleagues who followed their patients until the age of 17–18 years (near final height). Although they started this trial with a randomised untreated control arm who grew at a rate of 3.8 cm per year in contrast to girls in the treatment arms who grew more rapidly, the former were placed in a treatment arm of the study. Therefore, historical controls were needed for comparison of near final height. The historical controls achieved an adult height of 142.2 (6.0) cm, comparable with their original projected adult of 142.2 (6.1) cm. The group treated with GH alone gained 8.4 (4.5) cm height and the group treated with GH and oxandrolone gained 10.3 (4.7) cm over their projected heights. The benefit from GH treatment seemed to be more than modest, so why the discrepancy between the US results and those of Johnston et al? There could be a number of reasons but a striking contrast is in the use of oestrogen, Rosenfeld and colleagues did not induce puberty until a minimum age of 14 years and at least three years of GH treatment. Johnston et al induced puberty at 12 years and many of the girls had already had low dose oestrogen for some years, the very purpose and design of the study. Chernauskas and colleagues have thrown light on the timing of the use of oestrogen in girls who received GH treatment. They found that the number of years of GH treatment prior to introduction of oestrogen was a strong predictor of height gained (the equation was given simply: height gain in cm = 2.1 x years on GH before oestrogen; p < 0.0001; r 41%). There is no doubt that the lack of a prospec	
tive randomised control study with an untreated arm until adult height has raised important doubts about the accuracy of GH for improved adult height. These doubts have been reinforced by the lack of clinicians’ experiences of treating individual girls subsequently to the licensing of GH for TS. The availability of GH treatment for TS girls led to the treatment of a much older population compared to the UK trial, and GH dosages were often introduced close to the onset of GH treatment. The results were “modest” or of no benefit.

To overcome the problem of being the lowest dose group they projected heights were 146.2 (7.5) cm and their achieved last heights were 158.8 (7.1) cm. The group receiving 8 IU/m/day had significantly greater gains over projected heights and greater latest heights. This seems to be good evidence that there is a GH effect and that the gains are clinically useful.

What then should be our “best” practice in 2001? Based on the evidence of the thorough trials discussed above, we feel that is justified to make efforts to diagnose girls with TS early so that they can receive at least four years of oestrogen free GH treatment with a standard dose. The issues involved in the timing of pubertal induction are complex and not just related to height as an outcome, but one should be aware of Chernauskas’s analysis of the relationship of oestrogen free years and height gained.

However, rough cohorts of TS girls may incur significant benefit in adult height, there remains considerable variability in response, both in the short and long term, between individuals. A reasonable approach would be for the child and the interpreter to be given an estimate of the expected response in the first and subsequent years, and should there be a serious shortfall in achieved response, then issues of treatment adherence, tissue resistance, and other concomitant diseases need investigation. Ranke and colleagues have shown that a major predictor of growth response in the second, third, and fourth years of GH is the first year response, and therefore the end of the first year of GH treatment is an appropriate time for reassessment of likely long term benefit. If the factors inhibiting first year response cannot be satisfactorily addressed, then the probability that there will be more than a modest effect on adult height, and then the patient, parents, and doctor may agree on cessation of treatment.

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Bronchodilator responsiveness testing in young children

EDITOR,—There is some concern that asthma may be misdiagnosed when reported symptoms only are considered.1 In Britain, asthma is usually diagnosed without any lung function testing whereas in the USA, measurement of bronchodilator responsiveness (BDR) is recommended.2 Perhaps routine spirometry is perceived as impractical. If lung function testing is to be recommended for the diagnosis of asthma, the method used must be easy.

Measurement of BDR using spirometry in children over 7 years has been reported feasible in children.3 We have shown that in 55% (49/89) of 5–7 year olds and 30% (14/47) of 7–10 year olds, BDR could not be measured because a satisfactory FEV$_1$ could not be obtained. These were children with respiratory symptoms who were attending the laboratory for the first time and so had no previous practice. Of the 6% of children with a variable spirometry, in 48 the effort for forced expiration was submaximal or they did not breathe in to total lung capacity (TLC) before the expiration, nine coughed, and three did not blow for one second. Three refused the test. Modern spirometers have expiratory incentive devices, but inspiratory incentive displays are still needed to encourage children to reach TLC before a forced expiration.

Using the interpreter test (R$_n$), all but three could successfully undertake BDR testing. This test is no more difficult from a technical viewpoint and takes no more time than spirometry. We have shown that R$_n$ can detect BDR in preschool children with previous wheeze but not wheezy at the time of test, with 80% specificity and 76% sensitivity.4 If the specificity and sensitivity profile for BDR is acceptable in older children using R$_n$, we suggest that this method is preferred to spirometry.

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BOOK REVIEWS

Improving newborn infant health development in developing countries. Edited by Costello AJ and Manandhar D. Imperial College Press. (Pp 570, hardback; ISBN 099.00) UK: Imperial College Press. ISBN 186094 097 8

Improving neonatal care, as with improving any service in any part of the world, would require two main components; (a) good quality information and (b) co-operation to deliver this service to the client. The information required would have to be specific to that region’s demographic, geographic, cultural, economic, characteristics, as well as encompass evidence based appropriate technical and scientific information.

Costello and Manandhar's book on improving newborn care in developing countries arose from a workshop held in Kathmandu, Nepal in 1997. As with all books produced this way there are specific strengths and weaknesses with a bias towards areas of specific interest. This book's bias appears to be towards the provision of good quality information. The contributors, most of whom have worked in developing countries, come from a variety of professional backgrounds and include epidemiologists, health planners, scientists, paediatricians, obstetricians, and anthropologists.

They have made a serious effort at putting together all the available information on neonatal care, and the problems encountered with its delivery in the developing world. Three of the five sections deal with the current state of maternal and neonatal care and the relatively low technology-high efficacy interventions that would improve it. Of note are the chapters addressing birth asphyxia, effective neonatal resuscitation, and neonatal hypothermia. As birth asphyxia accounts for over 40% of all child deaths and hypothermia for neonatal deaths, I felt the studies were well reported. It is depressing that hierarchical monocentric systems—that is, government led health care systems, do not work effectively in most developing countries. In addition, it seems that health education delivered on a one to one basis also does not seem to work. So is there a third way? It is this exploration that I found lacking. The co-ordination of health care and the lines of communication necessary to deliver health care, or indeed newborn care, in developing countries are notably weak. Studies akin to home based neonatal care as described by Bang et al are not yet widespread.

The book does fill the large gap in compiled information on current trends in perinatal care in the developing world. It would probably be invaluable to health professionals working there and should make interesting reading to those paediatric specialist registrars planning to join the VSO scheme of working in the third world.

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Unexplained crying in young babies is a common and puzzling phenomenon. Stimulated by this, the last few years have brought paediatricians and developmental psychologists together, with the result that many traditional assumptions have begun to be questioned or overturned. This book is the first to draw this developmental perspective together, so that it is a welcome addition to the literature.

The book's enigmatic title refers to the distinction between crying behaviour as a "signal" of an underlying "disease" (which the editors define as a more subjective report or complaint by a patient), and a "signal" which has communicative purposes. Their introductory chapter proposes that crying can serve all three functions, but distinguishing between them helps to uncover the different starting assumptions which parents, clinicians and researchers may bring to bear.

As well as the editors' introduction and summary, the book contains 10 chapters which examine crying across a broad range of contexts. Three (Poole and Magliner's review of hospital emergency department practice towards crying complaints; Lehtonen, Gormally, and Barr's model of the aetiology and outcome of "early increased" crying, and Blackman's summary of crying in children with disability) are of obvious clinical relevance. Other chapters will be of most interest to researchers. These include Hopkins' analysis of the development of infant crying behaviours, which discusses continuity with fetal behaviour and highlights the question of how crying begins and change in their function with age. Craig, Gilbert-MacLeod, and Liley review the findings on infant crying as a sign of pain, pointing both to the advances in understanding and the conceptual and methodological difficulties which remain. Poteval moves the focus to temper tantrums in toddlers, presenting a model of autonomic reactivity which parallels ideas elsewhere in the book about the aetiology of crying. Bard asks whether the crying "peak" found in western infants at around 6 weeks of age—now widely considered part of normal development—is also found in our evolutionary relatives, chimpanzees. The answer is a partial yes. A peak in maternal soothing of infant chimpanzees was found at a comparable age. However, Bard observed none of the prolonged, unsoothable crying which characterises the situation in human newborns.

The chapters are of a uniformly high standard, but two seem likely to have an especially lasting impact. One is Gustafson, Wood, and Green's review, titled "Crying: the aetiology of crying?" They take issue with the conclusion, widely reproduced in textbooks, that young babies produce qualitatively distinct cry types—for example, "hunger", "anger," and "pain" cries, which a sensitive parent can interpret to identify the causes of the crying. The unfortunate corollary is that a parent who cannot work out the cause and resolve the crying is inadequate. As Gustafson et al carefully point out, the evidence does not support this "cry type" view. Instead, the cries of young babies are "graded signals" which convey the degree to which a baby is upset, but not the specific cause of the crying. This is an important message, which needs a more general audience. An equally important message for researchers is carried by Barr and Gunnar's "transient responsibility" chapter. Prolonged unsoothable crying (or "colic") has often been attributed to an infant's "difficult temperament". Barr and Gunnar argue that the evidence does not support this, but is consistent with the notion of acute individual differences in infant's "regulation" of responsiveness as a cause of prolonged

As more and more rare syndromes are described and the clinical features of the common syndromes are enlarged upon, there have been calls for studies on long term follow up, to assess complications and prognosis. For the rare syndromes this has been slow in coming. Patients diagnosed by geneticists are rarely followed up, or seen again by them. They are mostly sent back to the referring paediatrician. This, in part, has arisen because geneticists in the UK had to wait, in the 1960s and 70s, to persuade paediatricians and physicians to refer their patients for diagnosis.

There was, at that time, a small set of geneticists who had developed an expertise in dysmorphology and syndrome identification, but their colleagues were frightened that, if they used them, they would lose their patients; or they took the view that there was no need for a diagnosis if there was no treatment and so patients were not referred. Education, a few brilliant diagnoses and not a few medico-legal cases changed all of that, but part of the unspoken bargain that was entered into involved the family’s return, after diagnosis (or the attempt thereof) back to the referring physician.

Geneticists, have learned what becomes of some patients whose rare conditions by reading the literature. This information is important. Faced with a risk of recurrence, most sensible parents will want to know what has happened to other children with their child’s condition, what else is in store for them, and who will keep an eye open for the complications.

Drs Wilson and Cooley have written a unique book that fills a gap in the market. They have chosen some of the more common congenital anomalies or syndromes and written about preventative management. “Common” in their terms means those conditions with a frequency of more than 1 in 25 000 births, and by preventative management they mean knowing about and acting upon, complications. To achieve this, the authors have drawn up checklists of what needs to be assessed at every age. There are for instance three tables for cerebral palsy, one from 0–1 years, one for 1–6 years, and finally a checklist for those after 6 years. There are tables for tuberous sclerosis, neurofibromatosis, Noonan syndrome, Ehlers-Danlos, and some 130 other conditions. They list patient groups and summarise clinical and laboratory diagnoses and key management issues. They have not gone back to original references, but refer frequently to Gorlin’s textbook “ Syndromes of the Head and Neck” for a fuller understanding of some of the differential diagnoses mentioned in this book, but the authors have not added any new tables.

This is an excellent book. One for the shelf of every genetics department and also for easy reach of those following the patient. It comes with a CD-ROM and contains clinical genetics, instead of writing long letters to the GP, listing what needs to be checked, and simply printing the table from the CD.

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Many doctors have difficulty with medical writing. There is a crying need for concise, clear text whether it be for papers, grant applications, book chapters, or CVs. Furthermore, hospital doctors generate more than 40 million letters per year about their outpatients, as part of communication with the primary care team. Unfortunately many of us produce offerings that are too long, and lack a clear message, and are too long (even if this is not recognised by the writers!). Sadly most of us have had no teaching on how to write during our medical training and virtually none as part of our continuing medical education.

Tim Albert’s book has been created to help with these problems. Paradoxically, electronic publishing is leading to an expansion in the need for written information and—outside of informal email communications—this needs to be of high quality. A large number of topics of relevance to medical writers has been chosen by the author and arranged in alphabetical order, so that the aim is for the reader to be able to dip into various sections as needed. There is good cross referencing between sections and book lists interspersed every few pages but there is no formal index. Although there are other books on medical writing for journals, the advantage of this modestly priced paperback is that it covers a wide breadth of writing and publishing. For example, how to write an editorial, systematic review, or writing for a medical journal because of pressed efficacy. Many will have experienced “writer’s block” and some useful tips are given on how to circumvent this malenevolent condition. It is suggested that the condition is not a sign of failure but rather that we are taking the trouble to produce something worthwhile.

Overall, this book is helpful for potential medical writers. Inevitably some subjects are not covered in depth because of insufficient space. However, the text is easy to read with the book designed to dip into, rather than read from cover to cover. It should be useful to both trainees and senior doctors. Often there is a need to write an obituary or grant application at short notice and the practical advice will assist the writer in his task. The alternative is to seek advice from a wise old friend who has been there before.

Nick Mann
Consultant Paediatrician


This is a handsomely book, with hard, thick covers, quality printing, and superb illustrations. It will look just grand on a bookshelf, but how often will it come down from that bookshelf? This manual is a comprehensive textbook of child health. In 480 pages, it covers general paediatrics, as well as infective and nutritional disorders confined to developing countries. The quality of the illustrations is superb, and relative to the text. The x rays have particular enhance the teaching message. However, the microbiology illustrations seem designed to relieve the tedium of grey text, rather than adding useful information. The chapter on rashes would benefit from more illustrations but perhaps the cost implications were too high.

The chapter on paediatric emergencies is informative but not easy to access and the readability of the text would be improved by more tables and diagrams. There is, specific chapter on practical procedures, such as insertion of chest drains, abdominal paracentesis, or subdural taps, yet there is a chapter on laboratory procedures. The book lacks references. Are these are not considered necessary now that we all have access to electronic journals? Try getting on to Medline from Chad. If this is to be a comprehensive textbook, the reader needs need guidance on what not to want to know whether surgery has anything to do with the treatment of spinal tuberculosis; what are the reasons for using lorazepam rather than diazepam in the management of status epilepticus; and what advice would you give to a girl with rheumatic mitral valve disease who is about to get married?

Paediatricians in tropical countries are dividing into two groups: those who are practising in city hospitals with improving facilities, delivering services to a slowly growing affluent population, who are demanding neonatal intensive care, renal dialysis, etc, and the remainder who still deal with poor populations, poor medical resources, coping with recyclable diseases, such as gastroenteritis, malaria, malnutrition, and HIV.

The majority of children in developing countries are treated by health workers who do not have medical degrees. To them, the physiology in this book is largely irrelevant. Most would make diagnoses based on recognition of clinical patterns, as exemplified in the Integrated Management of Childhood Illnesses. They require a portable, cheap book with advice on practical procedures, drug doses, and management of acute conditions. Many will combine curative medicine with primary health. They will see many children with chronic intractable disease, where the disease impinges upon the whole family, such as cerebral palsy, or AIDS. These problems require a whole chapter to themselves, and will vary depending on cultural practices in individual societies. This is not easy to cover in a textbook written for the whole tropics.

I appear to have said little that is positive about this manual, which is written for two audiences with disparate needs. It is neither the authoritative textbook of child health with a tropical flavour, nor the pragmatic, functional pocket book. I suspect it will continue to look handsome sitting on the bookshelf. At £50, much cheaper than some alternatives, it deserves better.
Controls not matched

BARRY J MARSHALL and GRACE Y HO

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