LETTERS TO THE EDITOR

The discovery that Helicobacter pylori is the prime cause of peptic ulcer disease, is one of the most important advances 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. Important questions have been raised regarding both methodology and interpretation.

M STEPHEN MURPHY
Associate Editor


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.1

Furthermore, we have previously shown that total breakdown of all ingested urea takes place in all normal infants without causing problems of ammonia intoxication.2 This is in contrast to SIDS victims, most of whom have unmetabolised urea in their faeces.3 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 had died of SIDS, and eight control cases, with nested polymerase chain reaction (PCR) and ELISA of the amplicons. 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.

Nested 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 data were 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 histo logical signs of acute or chronic gastritis, which is found even in young children with H pylori infection. If the bacterial load was so small that neither the bacteria nor the associated inflammation could be detected by histology, it seems questionable that metabolite 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 the 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 two weeks of life.

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

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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 inconsistent 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 like organisms. A Warthin-Starry silver stain, modified Giemsa or immunocytochemistry would have been more advisable.

We also regret that no histopathological data were given which could have provided essential information about a possible infectious etiology. From our experience, we observed that an acute H pylori infection always causes marked inflammatory changes of the gastric mucosa.

We also find that the negative control group was not a good reference, as this group did not comprise enough cases and was too heterogeneous (including two premature cases with apparently no normal environmental contact, one case with pneumonia (aspiration pneumonitis?)).

The discussion is totally speculative—for example, the role of interleukin 1 in H pylori infection: the main cytokines involved are (decreased production of) transforming growth factor, (local production of) tumour necrosis factor (TNF), interleukin 2 and interleukin 8. From the data presented, only the presence of H pylori DNA in the respiratory system (some cases without infection of the gastric mucosa) can be claimed. All other conclusions are not substantiated and should be considered as speculative until further evidence is provided—for example, culturing of H pylori from tracheal or lung fluids. Even if the presence of H pylori cells in the respiratory system can be established, some kind of experimental model should be used to establish H pylori as a causative agent in SIDS.

Recent findings established by the Children’s Hospital of Bamberg, Germany, suggest a hypoplasia of the basilar artery as a more plausible explanation for SIDS. It has been shown that this anatomical defect can cause blockage of the cerebral blood circulation especially in the prone sleeping position when the head is turned aside. This hypoplasia can be detected by ultrasound. Data of this study performed by the same hospital, seem to confirm this hypothesis. Among 3506 births over the last two years, 31 newborns (0.88%) could be identified with marked hypoplasia of the basilar artery, six of these newborns were considered as high risk cases (1.7%). The babies were given a monitor and the parents were instructed in resuscitation. None of the children born and screened in the Children’s Hospital of Bamberg died from SIDS in the last years, whereas two babies not participating in the screening programme died out of 1130 house born babies in the region of Bamberg (1.8%). For statistical significance 5000 births are necessary; a number that will be reached end of the year 2001. Further reports are pending.

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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


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which 14 were positive for the ureC gene. Amplified DNA was detected semiquantita-
vatively 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 prevalences of H pylori in SIDS and controls, but inappropri-
ate 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 microen-
vironment of the gastric mucosa and its pres-
cence 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 con-
trols died under eight weeks of age from what could possibly be neonatal complications and no details of whether they had been dis-
charged 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 dif-
cult to imagine that an organism specifically associated with H pylori infection and subsequent aspiration into the lungs led to lethal production of ammonia in all normal infants. Particularly when no organisms could possibly be neonatal complications and no details of familial contact were given. Four of the con-
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charged home were provided.

The possibility of PCR contamination has been suggested by Francosi 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 dis-
tilled water and DNA extract from human urer as negative controls, and we examined samples in duplicate. Throughout our study, duplicated samples consistently gave con-
cordant 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 ampli-
con sequencing is desirable not only to ensure specificity but in the present context would also provide additional data on the molecular epidemiology of the cagA 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 a GC content 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. Regarding our controls, use of these cases is quite appropriate and to illustrate this we include additional relevant data in table 1. Dr Vieth says our controls have had no normal environmental contact, however, five of these eight had spent time in the home environ-
ment since birth. Regarding antibiotic treat-
ment, only one control had received antibiot-
ics for more than one day prior to death, and this is the case in which H pylori was detected.

Dr Koletzko states that the “fact that H pylori was not demonstrated in the stomach, trachea or lung by histology in any of the children must raise major concerns that the applied methods were not specific”. How-
ever, as pointed out by Dr Vieth, haematoxy-
lin and eosin staining, although a routinely used stain in histopathology practice, may not be optimal for microscopic visualisation of H pylori.

In response to Dr Vieth’s claim that our suggested role for interleukin-10 (IL-10) and H pylori infection is “totally speculative”, we would like to point out that these mech-

++isms have been demonstrated in an animal model.12 Also, proteins of H pylori are known to activate macrophages leading to produc-
tion of IL-10 which is known to inhibit acid secretion by parietal cells and may actually be the most potent inhibitor of acid secretion discovered to date.13 IL-10 gene polymor-
phisms associated with increased IL-10 production have recently been associated with an increased risk of gastric cancer.14 In addition, systemic and mucosal humoral rec-
ognition of the cag protein has been linked with peptic ulceration.15 Duodenal ulcer patients may more frequently harbour cagA/ H pylori strains,16 and it has been shown that infection with cagA+ as compared with cagA strains is associated with increased production of IL-10.17 It is therefore interesting that 25 of 28 cases of H pylori associated SIDS in our study had a detectable cagA gene in their tissues,1 which may provide further support for the proposed pathogenesis of H pylori in SIDS and a contributory role for IL-10.18

Dr Paul Beggs from Macquarie University in Australia points out the link between dwelling crowding and H pylori infection,19 which has been shown to be independent of socioeconomic status,18 and the need for research on the possible link between dwell-
ing 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. Wildlund 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 lung of control cases used in the studies “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 cut 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 (wks)</th>
<th>Cause of death</th>
<th>Time of diagnosis</th>
<th>Antibiotic exposure</th>
<th>Exposure to the home environment</th>
<th>H. pylori ureC gene</th>
<th>H. pylori cagA gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 3</td>
<td>prematurity</td>
<td>AM – –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.100 ± 0.150</td>
<td>0.100 ± 0.130</td>
</tr>
<tr>
<td>C2 4</td>
<td>prematurity</td>
<td>AM – –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.200 ± 0.200</td>
<td>0.200 ± 0.120</td>
</tr>
<tr>
<td>C3 7</td>
<td>ileal perforation</td>
<td>AM – +</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.100 ± 0.140</td>
<td>0.120 ± 0.150</td>
</tr>
<tr>
<td>C4 7</td>
<td>Necrotising enterocolitis</td>
<td>AM 1 day only</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.100 ± 0.100</td>
<td>0.100 ± 0.100</td>
</tr>
<tr>
<td>C5 20</td>
<td>E. coli septicaemia</td>
<td>PM + –</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.100 ± 0.100</td>
<td>0.100 ± 0.100</td>
</tr>
<tr>
<td>C6 24</td>
<td>pneumonia</td>
<td>PM + +</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.100 ± 0.100</td>
<td>0.100 ± 0.100</td>
</tr>
<tr>
<td>C7 32</td>
<td>Pneumococcal septicaemia</td>
<td>PM – +</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.100 ± 0.100</td>
<td>0.100 ± 0.100</td>
</tr>
<tr>
<td>C8 44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.100 ± 0.100</td>
<td>0.100 ± 0.100</td>
</tr>
</tbody>
</table>

*Mean ±SD

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 lives. To reiterate, there are two parts to the hypothesis. First, interleukin-1β production in the H pylori infected stomach, and second, supply of ammonia to the systemic circulation (and 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 re-statement of our studies and those of Pattison and colleagues11 in order to clarify the proposed role of H 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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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. While the proportion of samples positive for urease from the SIDS group 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 bacteria. There is a discrepancy needs to be explained. There were no serological data to support the PCR 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 (12.5%). It is possible that the contamination was not addressed for SIDS or the positive control case. There was no demonstration by molecular methods that the DNA detected was from different strains. H 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 H pylori and socioeconomic factors was not assessed in relation to incidence of SIDS among different ethnic groups. In Britain, white families in lower socioeconomic groups have more evidence of H pylori infections and more SIDS. If the diverse incidence of infections with H pylori is assessed for ethnic groups and SIDS, this parallel breaks down. The incidence of seropositivity for H 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 H pylori is 61% among Hispanics and 26.2% among non-Hispanic whites.15 The paper quoted in the manuscript, the incidence of seropositivity was similar for Hispanic and black groups and both were significantly higher than that of non-Hispanic whites.4,12 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,12 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 in the hypothesis below). Animal models16 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. H pylori infection does not fit the common bacterial hypothesis, a mathematical model which accurately predicted the age range for SIDS.4 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,17 in industrialised countries the evidence is that H pylori infection in infants under 1 year of age is much lower. Among 67 Gambian children born to seropositive mothers, only 1 (1.5%) had a positive breath test by the age of 12–15 months.17 Among Finnish children 10.6% had IgG to H pylori at birth, but the antibodies disappeared completely in all but one of the children 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 H pylori infection.17

The oral/oral route of transmission is suggested to be the route by which infants acquire H pylori, mainly by vomit.18 H 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.19

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 bronchoospasm which should produce clinical features such as wheezing which has not been reported by parents of SIDS infants.

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This type of reaction should be demonstrable histologically by muscular, glandular and secretory changes identified by microscopy.

3. If ammonia is present in excess in the blood as a proximate cause of death, this should be demonstrable in blood samples and vitreous fluid, and there is no evidence for this.

4. The liver in SIDS cases shows no abnormality and had it been acutely affected by an influx of ammonia, there should be changes.

5. Ammonia in excess leads to cerebral 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 infectious agents to triggering the series of events leading to SIDS; however, that presented for \( \text{H pylori} \) 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.

### Controls not matched

**EDITOR**—The paper by Kerr et al reported an association between \( \text{H pylori} \) 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 the method exquisitely sensitive. Consistent with this, no other method was able to confirm that \( \text{H pylori} \) was actually present. Instead, Kerr et al used a relative increase of "\( \text{H pylori} \) signal" above that of the mean +2SD of the control group, as an indicator of \( \text{H pylori} \) 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 were transferred home, many hours before being refrigerated.

Finally, as \( \text{H pylori} \) is a gastric organism, it was surprising to find the bacterium in lung or trachea of eight patients (ureC gene) or six patients (cagA gene) in whom gastric specimens were negative.

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

### No association in a Chinese population

**EDITOR**—We read with great interest the paper by Kerr et al on the association between \( \text{H pylori} \) 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).

The formalin-fixed and paraffin-embedded stomach, trachea, and lung specimens obtained during postmortem examination were retrieved. Initial histological examination was performed by an experienced pathologist to look for any evidence of \( \text{H pylori} \) 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 \( \text{H pylori} \) DNA in these samples.

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

Viable \( \text{H pylori} \) 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, argues against the validity of this speculation. With the high prevalence of \( \text{H pylori} \) 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 \( \text{H pylori} \) as a cause of SIDS is highly questionable.

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**Table 1** Characteristics of SIDS cases and controls

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
</tr>
</thead>
<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>Anmiotic fluid aspiration</td>
</tr>
<tr>
<td>M</td>
<td>6 months</td>
<td>Premature, sepsisemia</td>
</tr>
<tr>
<td>M</td>
<td>3 months</td>
<td>Congential brain tumor</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 premature</td>
</tr>
</tbody>
</table>

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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 lung tissues of SIDS babies is a finding of particular importance both for our understanding of the pathogenesis of SIDS and 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 histological analysis of 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.1,2 If *H pylori DNA was not demonstrable at the sites that were demonstrated by PCR in the study by Kerr et al, the authors’ hypothesis was not supported.

Our hypothesis is that *H pylori infection accounts for a proportion of cases of SIDS. Blackwell cites several epidemiological papers, stating that they argue against this hypothesis, but such papers do not state how exactly they consider that they do argue against it. Epidemiological data for *H pylori and socioeconomic factors in various ethnic groups are not clear cut and are incomplete. Such factors as prevalence of bottle feeding, parental smoking, family size, adherence to supine sleep position, etc, may explain differences of SIDS incidence in various ethnic groups. Blackwell states that her positive finding in children aged 12–15 months is in contrast to the finding of 44% of SIDS cases in children aged 12–15 months is in congruence with supply of ammonia to the systemic circulation may be lethal. Increased production of IL-1β alone as a result of gastric *H pylori infection may predispose to the development of SIDS due to other factors.10

Blackwell states that the proposed pathogenesis cannot be substantiated due to the following:

(a) “There is no inflammation in the lungs of SIDS cases”. This is not true; mild inflammation of the upper respiratory tract is a recurrent, although not invariable, finding in SIDS.13-15

(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 with increasing dosages of intratracheal urease.1-5 Since parents are invariably absent at the time of death, it would be unlikely that wheezing would be detected. “If bronchospasm occurs, this should be demonstrable histologically”.1-5 Findings of relevance in SIDS include intrathoracic peptic ulceration, patchy pulmonary oedema, emphysema, and increased muscle mass in pulmonary arteries,1-5 although these are not invariable findings.

(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 arterial ammonia.1-5 The physiological effects of pre-treatment with IL-1β could not be clearly defined.1-5

(d) “The liver should be affected by hyperammonaemia and it is not in SIDS”.1-5 Blackwell has misunderstood our hypothesis. First, interleukin-1β 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).1-5

(e) “The brain should be affected by hyperammonaemia and it is not 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.1-5 We do not understand this point.

Marshall’s views on controls used in the original paper2 do not take account of further information provided at the request of other authors21 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 organon 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,22 and in the liver of patients with primary sclerosing cholangitis and primary biliary cirrhosis.23

The pathogenesis of SIDS is accepted to be multifactorial, and therefore, small studies with a negative association between *H pylori DNA 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.1,9-11

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Letters, Book reviews
**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 height 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.

Chernausek 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 × 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 efficacy of GH for improved adult height. These doubts have been heightened because of clinicians’ experience of treating individual girls subsequent 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 US trial, among whom oestrogens were often introduced close to the onset of GH treatment. The results were “modest” or of no benefit. To overcome the problem of being unable now to run a study with an untreated arm, Sas and colleagues cleverly devised a randomised dose response study. The lowest dose of GH was 4 IU/m²/day in a group of girls who started GH at 7.9 (0.9) years, oestrogen at 12.7 (0.6) years, and completed 93.3 (8.5) months of GH treatment. For this standard dose group their projected heights were 146.2 (7.5) cm, their achieved last heights were 158.8 (7.1) cm. The group receiving 8 IU/m²/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 suggest 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 Chernausek’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 interruptor 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 medical conditions need investigation.

Rankle 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 it is likely 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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**Bromchodilator responsiveness testing in young children**

**EDITOR,—**There is some concern that asthma may be misdiagnosed when reported symp- toms 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.1 We have shown that in 55% (49/89) of 5–7 year olds and 30% (14/47) of 7–11 year olds, BDR could not be measured because a satisfactory FEV₁ could not be obtained. These were children with respiratory symptoms who were attending the laboratory for the first time and had no previous practice. Of the 65 evaluable 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 interruptor test (Rₑₙ), all three but 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 Rₑₙ can detect BDR in preschool children with previ- ous wheeze but not wheezy at the time of test, with 80% specificity and 76% sensitivity.3 If the specificity and sensitivity profile for BDR is acceptable in older children using Rₑₙ, we suggest that this method is preferred to spirometry.

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REFERENCES

BOOK REVIEWS

Improving newborn infant health development in developing countries. Edited by Costello AJ and Manandhar D. Imperial College Press. (Pp 570, hardback; £99.00) UK. Imperial College Press. ISBN 1 86049 079 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-ordination to deliver this service to the client. The informa- tion required would have to be specific to that region’s demographic, geographic, cul- tural, economic, characteristics, as well as encompass evidence based appropriate tech- nical and scientific information.

This is the first book in recent times to deal with the health services needed for children looked after in public care. We are all aware of the authors’ key role in highlighting the plight of this forgotten group of children. The outcome in terms of their current health is a severe indictment of the lack of care they receive. Their risk of mental illness is four times that of their peers. One in six girls that leave care has already been pregnant or become pregnant within a year. Social outcomes are no better. Only one in six go on to higher education, compared with two thirds of their peers. Over a third of young prisoners have been in care.

The back of the book contains several teaching exercises for medical advisers. They are intended to provide a framework for group discussion. We thought these very helpful for higher specialist trainees as well. Simpler exercises aimed at SHO, “core registrars” and GP principals could usefully be added. Model answers might be helpful for non-specialist trainees although the resources needed (mostly British Association of Adoption and Fostering guidance and practice notes) are listed in the book.

With the advent of the “quality protects initiative” to improve the care of children in public care, this book is a timely reminder of what we as paediatricians can do to advocate for this vulnerable group of children. Our SpR will be offered the book as he starts his adoption and fostering module later in the year. We are also likely to use some of the training exercises in our own continuous professional development programme.

The “starfish story” of the late David Baum is an appropriate reminder of the plight of children looked after in public care. He presented a starfish to BACCH, as the chairman’s badge of office, as a constant reminder of the importance of the individual child in community child health services. The authors have used the story as their frontispiece. Read it when you buy the book.

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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 “sign” of an underlying disease process (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 then distinguishing between them helps to uncover the different starting assumptions which parents, clinicians and researchers may bring to bearing.

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 Magliren’s review of hospital emergency department practice towards crying complaints; Leeton, Gronnally, 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 hold particular 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 cry behaviours originate and change in their function with age. Craig, Gilbert-MacLeod, and Lilley review the findings on infant crying as a sign of pain, pointing both to the advances in understanding and to the conceptual and methodological difficulties which remain. Potegal 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, unsustained 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 Greenren’s review, titled “Can crying be a sign of abnormal 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 reaching a general audience. An equally important message for researchers is carried by Barr and Gunnar’s “transient responsivity” chapter. Prolonged early infant 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 infants’ “transient expression” of responsiveness as a cause of prolonged

Many doctors have difficulty with medical writing. There is a crying need for concise, clear text whether it be for papers, grant applications, books, 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 simply not good enough. They lack a clear message, and are too long (even if this is not recognised by the writers!). Sadly most of us have 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 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 in a way that is discussed effectively.

Many will have experienced “writer’s block” and some useful tips are given on how to circumvent this malvolent 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 wily old friend who has been there before.

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Manual of tropical pediatrics. Edited by Sear, MD, (Paperback), £50.00

This is a handsome 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, in particular, enhance the 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, to a 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 guidance on where to look. I would want to know whether surgery has anything to add to the treatment of spinal tuberculosis; what are the reasons for using lormetamor 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?

Physiotherapists in tropical countries are dividing into two groups: those who are practicing 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.

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www.archdischild.com
Bronchodilator responsiveness testing in young children

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Updated information and services can be found at:
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