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

Association between SIDS and H 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.

I would value a response from Drs Fleming, Blair, Bacon, 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 child 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. Furthermore, we have previously shown that total breakdown of all ingested urea takes place in all normal infants without causing problems of ammonia intoxication. This is in contrast to SIDS victims, most of whom have unmetabolised urea in their faeces. 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 sequencing 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. If the bacterial load was so small that neither the bacteria nor the associated inflammation could be detected by histology, it seems questionable that metabolic 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 examined 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 parent (positive serology and/or a positive ‘C-urea breath test) only 1.5% of the children have positive tests during the first year of life or 2 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 *H pylori* and colonisation or infection with *H pylori* and SIDS. However, the evidence is clearly suggestive of an association between *H pylori* and SIDS, although the findings do not necessarily prove causality. The authors should have provided evidence for the specific role of *H pylori* in SIDS, and the association between *H pylori* and SIDS should be considered in the context of other risk factors associated with SIDS.

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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, followed 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 immunohistochemistry 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 pneumonia?), etc.).

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 year whereas two babies not participating in the screening programme died out of 1130 home 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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**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.1 Close person to person contact and increased exposure to the infective agent is a likely 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, 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 Elifors *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 related to the increased dwelling crowding during this 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.5 Given the importance of SIDS and the growing body of evidence supporting *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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**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...
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 livers, particularly when no organisms were visible on histology.

This interesting report could well describe a proxy for the already widely known association between sudden infant death syndrome (SIDS) and *H pylori* infection. Regarding our controls, use of these cases, on which 14 were positive for the ureC gene), was quite appropriate and to illustrate this we include additional relevant data in table 1. Dr Vieth says our controls have had no normal livers, particularly when no organisms were visible on histology. 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 undigestated 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...

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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 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 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 (days)</th>
<th><em>H. pylori</em> ureC gene</th>
<th><em>H. pylori</em> cagA gene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;1 month</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>0.100</td>
<td>0.150</td>
</tr>
<tr>
<td>C2</td>
<td>4</td>
<td>prematurity</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>0.095</td>
<td>0.105</td>
</tr>
<tr>
<td>C3</td>
<td>7</td>
<td>ileal perforation</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>0.200</td>
<td>0.250</td>
</tr>
<tr>
<td>C4</td>
<td>7</td>
<td>Necrotising enterocolitis</td>
<td>AM</td>
<td>1 day only</td>
<td>+</td>
<td>0.170</td>
<td>0.175</td>
</tr>
<tr>
<td>C5</td>
<td>20</td>
<td><em>E. coli</em> septicaemia</td>
<td>AM</td>
<td>–</td>
<td>+</td>
<td>0.210</td>
<td>0.150</td>
</tr>
<tr>
<td>C6</td>
<td>24</td>
<td>suffocation</td>
<td>NT</td>
<td>–</td>
<td>–</td>
<td>0.100</td>
<td>0.140</td>
</tr>
<tr>
<td>C7</td>
<td>32</td>
<td>pneumonia</td>
<td>NT</td>
<td>–</td>
<td>+</td>
<td>0.100</td>
<td>0.140</td>
</tr>
<tr>
<td>C8</td>
<td>44</td>
<td>Pneumococcal septicaemia</td>
<td>PM</td>
<td>–</td>
<td>–</td>
<td>0.100</td>
<td>0.140</td>
</tr>
</tbody>
</table>

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 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 55°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. Regarding our controls, use of these cases, which is 100% specific. And in one of our PCR-ELISAs, there were five such interactions.

In response to Dr Vieth’s claim that our suggested role for interleukin-1β (IL-1β) in *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 histological recognition of the cagA 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 as compared with cagA strains is associated with increased production of IL-1β. 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, 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 undigestated 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...
lung to produce toxic amounts of ammonia in infants that presumably had normal lives.\(^4\) To reiterate, there are two parts to the hypothesis. First, interleukin-1β production in the \(H\) \textit{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 ammonia is 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-reading our papers and those of Patterson and colleagues\(^5\) in order to clarify the proposed role of \(H\) \textit{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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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 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 when triggered by other factors. To explain how these bacteria might contribute to the series of events that lead to SIDS.

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No association in a Chinese population

EDITOR—We read with great interest the paper by Kerr et al on the 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 the 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 for a 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 that 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 or trachea of eight patients (cagA 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 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

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).

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 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 explanation. Taken together, the significance of H pylori as a cause of SIDS is highly questionable.

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www.archdischild.com

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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 such 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 al13 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.14

Blackwell regards this as “as valuable as suggested, but not essential, as the PCR-ELISA utilised was specific, tests were performed in duplicate and positive and negative controls consistently gave expected results.”

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 she does not state how exactly she considers that they do argue against it. Epidemiological data for H pylori and socioeconomic factors in various ethnic groups are not clear and are incomplete. Such factors as prevalence of bottle feeding, parental smoking, family size, adherence to supine sleep position, etc can explain differences of SIDS incidence in various ethnic groups. Blackwell asks for data regarding bronchitis testing in children aged 12-15 months is in contrast to the finding of 44% H pylori positivity by 13C-urea breath testing of 2 year olds in childcare centres serving low socioeconomic groups in Texas.15

Blackwell reminds us of the accepted fact that animal work is not directly applicable to humans, but her phrase “transient organism in the lung. 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 states that the proposed pathogenesis of SIDS 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.

(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 at progressively higher doses of intratracheal urease. 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”. Findings of relevance in SIDS would be, for example, alveolar necrosis, patchy pulmonary oedema, emphysema, and increased muscle mass in pulmonary arteries, 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 plasma 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-1α 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 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.

(f) We do not understand this point. Marshall’s views on controls used in the original paper1 do not take account of further information provided at the request of other authors16 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 and laryngeal pathogen 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,17 and in the liver of patients with primary sclerosing cholangitis and primary biliary cirrhosis.18

The pathogenesis of SIDS is accepted to be multifactorial, and therefore, small studies with a negative association between H pylori infection 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.1,15

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www.archdischild.com

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 gained benefit from GH treatment, this “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.

Cheruhas 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 gain (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 compounded 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 UK trial, and the older oestrogen-treated girls 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, oxandrolone 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 and 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 feel that this 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 Cheruhas’s analysis of the relationship of oestrogen free years and height gained.

However, though 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 medical conditions 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 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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1 Johnston DJ, Betts P, Dunger D, et al. A multicentre trial of recombinant growth hormone and low dose oestrogen in Turner syndrome: effect and that the


Bromchodilator 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 FEV1 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 measurable spirograms, 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 interrupter technique (Rc), 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 Rc could 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 Rc, 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; £99.00) UK: Imperial College Press. ISBN 186049 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-ordination 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.

www.archdischild.com
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 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 perinatal deaths, I felt the studies were well reported that introduced face mask to mouth resuscitation delivered by trained traditional birth attendants and room air versus 100% oxygen for infants whose resuscitation 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 find lacking. The co-ordination of health care delivery 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 notably under-reported. In addition, the experience of some regions of developing countries that have managed to establish an effective referral system within their geographic area is not called upon to help those paediatric specialist registrars planning to join the VSO mission to help a third world country.

This 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.

Shobha Cherian


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 book gives a review of the wide ranging issues. For doctors acting as mediators, the information will not be new. However, it provides a valuable resource in one volume to those community paediatricians, in permanent posts and in higher specialist training, when they are in infant care. They have to spend much time accumulating the same information from a variety of sources. It should be essential reading for those embarking on the medical adviser role for the first time.

The book deals with the history of medical advisers, issues relating to adult health and primary care, the diverse health needs of this vulnerable group of children together with chapters on young people’s own views and on medical records and of confidentiality. For the medical managers amongst us, there are invaluable service specifications and practice standards including model job descriptions for advisers in adoption and “looked after children”. Advice on whether the sessional requirement needed to do justice to these roles would have been a useful addition.

The back of the book contains several teaching exercises for trainee doctors. 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 SHOs, “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.

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 continuing professional development programme.

The “starfish story” of the late David Baum is an apposite reminder of the plight of children looked after in public care. He presented a starfish to BACC, 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.

Surekha Prabhu

Crying as a sign, a symptom, and a signal.

Elliott, Barr, Hopkins, et al. “Developing infant crying behaviours, which discusses continuity with fetal behaviour and highlights the question of how cry behaviors 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, 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 “Can we hear the causes 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 to reach a general audience. An equally important message for researchers is carried by Barr and Gunnar’s “transient responsibility” 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 infancy “reactivity” or “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 battle, 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 was that the family’s return, after diagnosis (or the attempt thereof) back to the referring physician.

Geneticists, have learned what becomes of some patients with 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.

Dr Wilson and Cooley have written a unique book that fills a gap in the market. They have chosen some of the more common malformations, syndromes, or rare conditions by reading the literature. This is an important book. 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 recognised clinical patterns, such as gastroenteritis, malaria, malnutrition, and HIV.

The chapter on paediatric emergencies is superb, and relative to the text. 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 a page on laboratory 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 who would 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?

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, 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 £30, much cheaper than some alternatives, it deserves better.
Association between SIDS and *H pylori* infection

RALPH A FRANCIOSI

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