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.

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 transferred 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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4 Wiklund L, George M, Nord CE, et al. 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.

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eradication therapy in asymptomatic children. Since neither the selection of the control group nor the methodology used is fully robust, this study does not, however, permit valid conclusions on the association of H pylori infection with SIDS. We believe it is irresponsible to promote inconclusive results in the light of such inadequate data.

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Association is not the same as causation

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

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Death kisses for newborns?

EDITOR.—Kerr et al claim H pylori as a potential etiologic factor in SIDS. Fatal systemic ammonia intoxication through hydrolysis of urea by H pylori produced urease in the lungs and trachea, following aspiration of gastric juice, was proposed as a possible pathogenic pathway. In general we cannot agree with this hypothesis. The molecular procedure (nested PCR and ELISA based detection) used in this study could explain some incorrect data—for example, H pylori DNA detection in lungs or trachea but not in the stomach. Furthermore, it is debatable whether haematoxylin and eosin (H&E) routine staining is an efficient method to visualise Helicobacter like organisms. A Warthin-Starry silver stain, modified Giemsa or unimmunocytochemistry 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 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 fluid. 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 hypolasia 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 is particularly apparent when the head is turned aside. This hypoplasia especially in the prone sleeping position 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 3806 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 house born babies not participating in the screening programme died out of 1130 house born babies. The children’s hospital’s figures indicate that successful resuscitation can significantly decrease the risk of dying from SIDS. This hypothesis is supported by the results of 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 house born babies. The children’s hospital’s figures indicate that successful resuscitation can significantly decrease the risk of dying from SIDS. This hypothesis is supported by the results of 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 house born babies. The children’s hospital’s figures indicate that successful resuscitation can significantly decrease the risk of dying from SIDS. This hypothesis is supported by the results of 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.
which 14 were positive for the ureC gene). Amplified DNA was detected semiquantitatively using an ELISA, with a cut off value calculated from the mean of eight controls. The authors offered little explanation for the discordant detection of *H pylori* DNA between the two PCR assays used. It may be appropriate to compare the prevalence of *H pylori* in SIDS and controls, but inappropriately to make these two groups the basis for defining cutoffs for an *H pylori* assay.

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

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

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

**Table 1** Information on antibiotic exposure, environmental exposure, and PCR-ELISA testing for *H pylori* ureC and cagA gene 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 to the home environment</th>
<th>Exposure to &gt;1 month</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>Stomach</td>
<td>Trachea</td>
<td>Lung</td>
<td>Stomach</td>
</tr>
<tr>
<td>C1</td>
<td>3</td>
<td>prematurity</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.100</td>
</tr>
<tr>
<td>C2</td>
<td>4</td>
<td>prematurity</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.200</td>
</tr>
<tr>
<td>C3</td>
<td>7</td>
<td>ileal perforation</td>
<td>AM</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0.265</td>
</tr>
<tr>
<td>C4</td>
<td>7</td>
<td>Necrotising enterocolitis</td>
<td>AM</td>
<td>1 day only</td>
<td>+</td>
<td>–</td>
<td>0.200</td>
</tr>
<tr>
<td>C5</td>
<td>20</td>
<td>E. coli septicaemia</td>
<td>AM</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>0.170</td>
</tr>
<tr>
<td>C6</td>
<td>24</td>
<td>suffocation</td>
<td>PM</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>0.210</td>
</tr>
<tr>
<td>C7</td>
<td>32</td>
<td>pneumonia</td>
<td>PM</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>0.210</td>
</tr>
<tr>
<td>C8</td>
<td>44</td>
<td>Pneumococcal septicaemia</td>
<td>PM</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>0.100</td>
</tr>
</tbody>
</table>

Mean ±SD

- Stomach: 0.174 ± 0.065
- Trachea: 0.163 ± 0.063
- Lung: 0.181 ± 0.060

Dr Kerr, Barson, and Burnie respond

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

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

Dr Koletzko suggests that the two separate nested PCR-ELISAs utilised in our study may have doubtful specificity as we did not sequence the products. We agree that amplification sequencing is desirable not only to ensure specificity but in the present context would be optimal for microscopic visualisation of *H pylori*.

In response to Dr Vieth’s claim that our suggested role for interleukin-10 (IL-10) 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-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. IL-10 gene polymorphisms associated with increased IL-10 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- compared with cagA- strains is associated with increased transcription of IL-10. 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-10.

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

We feel that Wiklund and colleagues, and MacKay and colleagues (in separate letters) have misunderstood the proposed hypothesis. Wiklund states that total breakdown of ingested urea occurs in all normal infants without ammonia intoxication and that SIDS victims have undigested urea in their faeces. MacKay states that “it is difficult to imagine that an organism specifically adapted to the microaerophilic and acidic conditions of the gastric mucosa thriving well enough in the...
lungs to produce toxic amounts of ammonia in infants that presumably had normal lives.\textsuperscript{1} To reiterate, there are two parts to the hypothesis. First, interleukin-1\textbeta production in the \textit{H pylori} infected stomach, and second, supply of ammonia to the systemic circulation,\textsuperscript{1} (and not the hepatic circulation as MacKay implies). Therefore, faecal urea content is irrelevant and so is ammonia produced in the stomach as this will be detoxified by the liver.\textsuperscript{1}

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 researchers to repeat our studies and those of Pattison and colleagues\textsuperscript{1} in order to clarify the proposed role of \textit{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. We also encourage 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 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 has 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 by triggering the series of events leading to SIDS; however, that presented that for H pylori needs to be substantiated by more than one method and testable hypotheses proposed to explain how these bacteria might contribute to the series of events that lead to SIDS.

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10 Pattison CP, Scott LW, Herndon B, et al. Proposed link between Helicobacter pylori and SIDS: possible pathogenic mechanisms in an animal model. II. Effects of intratracheal urease after pretreatment with intravenous IL-1b. Ibid.


Controls not matched

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

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

Finally, as H pylori is a gastric organism, it was surprising to find the bacterium in lung 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, argues 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 epidemio
omological investigations. Taken together, the significance of H pylori as a cause of SIDS is highly questionable.

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1 Leung WK, Sung JY, Ling TK, et al. Does the use of chopsticks for eating transmit Helico-


Table I 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>Amniotic fluid aspiration</td>
</tr>
<tr>
<td>M</td>
<td>6 months</td>
<td>Premature, septicaemia</td>
</tr>
<tr>
<td>M</td>
<td>3 months</td>
<td>Congenital brain tumour</td>
</tr>
<tr>
<td>M</td>
<td>6 months</td>
<td>Glutaric aciduria type I</td>
</tr>
<tr>
<td>M</td>
<td>2 months</td>
<td>Extreme premature</td>
</tr>
</tbody>
</table>

Cases

1 M 3 months SIDS
2 M 3 months SIDS
3 M 13 months SIDS
4 M 7 days SIDS
5 M 5 days SIDS
6 F 8 months SIDS
7 F 2 months SIDS
8 F 2.5 months SIDS
9 M 2 months SIDS

No association in a Chinese population

EDITORS,—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 retro-
spective 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 1 and the cagA gene 2 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.
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 process 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 certain babies is a finding of particular importance both for our understanding of the pathology and epidemiology of H pylori infection in infants. The study by Kerr et al showed H pylori DNA in the stomach, trachea, and lung tissues of SIDS cases, but did not visualise bacteria at these sites. As stated in the paper and by several other authors, the study used haematoxylin and eosin staining, a suboptimal methodology for visualisation of gastric bacteria. Other studies have shown inflammatory changes in both antrum and trachea of H pylori-PCR positive SIDS cases.14

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 socio-economic factors in various ethnic groups are not clear cut and are incomplete. Such accounts for a proportion of cases of SIDS. While other bacteria may be readily transmissible, population prevalence 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 3

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References

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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/yr 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 gain (the equation was given simply: height gain = 2.1 × years on GH before oestrogen; p < 0.0001; r = 41%). There is no doubt that the lack of a prospective 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 exacerbated 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, and the GH boosters 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 9.3 (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 it 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 intervention 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 interrupter 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 co-existing diseases need investigation. Ranke and colleagues have shown that a major predictor of growth response in the second, third, and fourth years of GH is the first year response, and therefore the end of the first year of GH treatment is an appropriate time for reassessment of likely long term benefit. If the factors inhibiting first year response cannot be satisfactorily addressed then 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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B Bronchodilator responsiveness testing in young children

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

Measurement of BDR using spirometry in children over 7 years has been reported feasible in children.3 We have shown that in 55% (49/89) of 5–7 year olds and 30% (14/47) of 7–11 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 so had no previous practice. Of the 67 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 spiroimeters have expiratory incentive devices, but inspiratory incentive displays are still needed to encourage children to reach TLC before a forced expiration.

Using the interrupter to measure BDR testing. This test is no more difficult from a technical viewpoint and takes no more time than spirometry. We have shown that R25 can detect BDR in preschool children with previous wheeze but not wheezy at the time of test, with 80% specificity and 76% sensitivity.4 If the specificity and sensitivity profile for BDR is acceptable in older children using R25, 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 1 86094 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 all the available information on neonatal care, and the problems encountered with its delivery in the developing world. Three of the five sections deal with the current state of maternal and neonatal care and the relatively low technology-high efficacy interventions that would improve it. Of note are the chapters addressing birth asphyxia, effective neonatal resuscitation, and neonatal hypothermia. As birth asphyxia accounts for one in four of the 40 million annual 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. The compilation was 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 is terms that health education delivered on a one to one basis also does not seem to work. So is there a third way? It is this exploration that I found lacking. The co-ordination of health care between 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 are not called upon to do so for this vulnerable group of children. The book does fill the large gap in compiled information on current trends in perinatal care in the developing world. It would probably be invaluable to health professionals working there and should make interesting reading to those paediatric specialist registrars planning to join the VSO scheme of working in the third world.

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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 and as medics, 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, who care for infants. 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.

This 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 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”. A suggestion of 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 medical advisers. They are intended to provide a framework for group discussion. We thought these very helpful for higher specialist trainees as well.

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 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 five 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” underlying disease (“cdot”) (which the editors define as a more subjective report or complaint by a patient), and a “signal” which has communicative purposes. Their introductory chapter proposes that crying can serve all three functions, but distinguishing between them helps to uncover the different starting assumptions which parents, clinicians and researchers may bring to bear.

As well as the editors’ introduction and summary, the book contains 10 chapters which examine crying across a broad range of contexts. Three (Poole and Maglifier’s review of hospital emergency department practice towards crying complaints; Leighton; Gormally, and Barr’s model of the aetiology and outcome of “early increased” crying, and Blackman’s summary of crying in children with disability) are of obvious clinical relevance. Other chapters will probably provide interested patients with a diagnostically useful aid.

Other chapters will be of most immediate 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 change and 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. Petchov 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. Barr 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 characterizes 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 the general audience. An equally important message for researchers is carried by Barr and Gunnar’s “transient responsibility” chapter. Prolonged 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’ “readiness” or “maturity” 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.

There was, at that time, a small set of geneticists who had developed an expertise in dysmorphism 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 medicö-löгical cases changed all of that, but part of the unspoken bargain that was entered into in the 1960s and 70s to persuade paediatricians and physicians to refer their patients for diagnosis.

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To achieve this, the authors have drawn up checklists of what needs to be assessed at every age. There are for instance three tables for cerebral palsy, one from 0–1 years, one for 1–6 years, and finally a checklist for those after 6 years. There are tables for tuberous sclerosis, neurofibromatosis, Noonan syndrome, Ehlers-Danlos, and some 130 other conditions. They list patient groups and summarise clinical and laboratory diagnoses and key management issues. They have not gone back to original references, but refer frequently to Gorlin's textbook " Syndromes of the Head and Neck" for a fuller understanding of some of the differential diagnoses mentioned in this book, but that is of course for the clinician as well as the reader.

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

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Many doctors have difficulty with medical writing. There is a crying need for concise, clear text whether it be for papers, grant applications, books, or 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 long, rambling and lack a clear message, and are too long (even if this is not recognised by the writers!). Sadly most of us have had no teaching on how to write during our medical training and virtually none as part of our continuing medical education.

Tim Albert's book has been created to help with these problems. Paradoxically, electronic publishing is leading to an expansion in the need for written information and —outside of informal email communications—this needs to be of high quality. A large number of topics of relevance to medical writers has been chosen by the author and arranged in alphabetical order, so that the aim is for the reader to be able to dip into various sections as needed. There is good cross referencing between sections and book lists interspersed every few pages but there is no formal index. Although there are other books on medical writing for journals, the advantage of this modestly priced paperback is that it covers a wide breadth of writing and publishing. For example, how to write an editorial, systematic review, or writing for a medical magazine. This book does not 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 writing for patients and it would want to know whether surgery has anything to add to the treatment of spinal tuberculosis; what are the reasons for using lorcaserin 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?

Both workers in tropical countries are divided into two groups: those who are practicing in city hospitals with improving facilities, delivering services to a slowly growing affluent population, who are demanding more 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, 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.

NICK MANN
Consultant Paediatrician


This is a handsome book, with hand, 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, specifically chapter on practical procedures, such as insertion of chest drains, abdominal paracentesis, or subdural taps, yet there is a chapter on laboratory procedures.

The book lacks references. Are these are not considered necessary now that we all have access to electronic journals? Try getting on to Medline from Chad. If this is to be a comprehensive textbook, the reader needs need guidance on writing for patients and it would want to know whether surgery has anything to add to the treatment of spinal tuberculosis; what are the reasons for using lorcaserin 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?

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Death kisses for newborns?

M VIETH, M STOLTE, D DE GROOTE, K H DEEG and G SEITZ

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doi: 10.1136/adc.84.6.525e

Updated information and services can be found at:
http://adc.bmj.com/content/84/6/525.12

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