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

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Association between SIDS and \textit{H pylori} infection

EDITOR,—The article in the November issue of the \textit{Archives} on the association between sudden infant death syndrome (SIDS) and \textit{Helicobacter pylori} infection (A \textit{Arch Dis Child} 2000;85:429–34.) 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. Nowadays a link has been proposed between \textit{H pylori} and sudden infant death syndrome (SIDS). Recently, Kerr et al examined gastric, tracheal, and pulmonary tissue, looking for evidence of \textit{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 \textit{H pylori} genes (UreC, cagA) in these tissues. Not surprisingly, this reported association has evoked a lively correspondence. Important questions have been raised regarding both methodology and interpretation.

M STEPHEN MURPHY
Associate Editor


Ammonia—not the culprit

EDITOR,—We were interested to read the article by Kerr et al on the SIDS problem. With regard to the interesting results we would like to point out some related findings. As pointed out by Kerr et al, \textit{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 \textit{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 nitrates and nitrites, 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 \textit{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 \textit{Helicobacter pylori} amplicons. A child was considered as infected if total breakdown of all ingested urea takes place in all normal infants without causing problems of ammonia intoxication. As pointed out by Kerr et al, \textit{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 \textit{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 nitrates and nitrites, often inhibit bacterial growth.

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

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

We also regret that no histopathological data were given which could have provided essential information about a possible infectious etiology. From our experience, we observed that an acute \textit{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 prematurity cases with apparently no normal environmental contact, one case with pneumonia (aspiration pneumonia?)

The discussion is totally speculative—for example, the role of interleukin 1 in \textit{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 \textit{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 \textit{H pylori} from tracheal or lung fluid.

Even if the presence of \textit{H pylori} cells in the respiratory system can be established, some kind of experimental model should be used to establish \textit{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 house born babies in the region of Bamberg (1.8%). For statistical significance 5000 births are necessary; a number that will be reached end of the year 2001. Further reports are pending.

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\textit{H pylori} DNA may not imply infection

EDITOR,—Kerr \textit{et al} report an association between SIDS and \textit{H pylori} infection. In 32 SIDS cases aged up to 28 weeks old, the \textit{H pylori} ureC gene was amplified from the stomachs of 15, from the trachea of 19, and from the lungs of 16. The \textit{H pylori} cagA gene was amplified from the stomachs of 13 (of which seven were positive for the ureC gene), from the trachea of 20, and the lungs of 23 (of


Dwelling crowding as a pertinent factor

EDITOR,—Kerr \textit{et al} report a highly significant association between \textit{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 \textit{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 Ellis et al suggests that there may be a direct link between crowding and \textit{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 such times.

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.2 Given the importance of SIDS and the growing body of evidence suggesting \textit{H pylori} as a cause of SIDS, it would be pertinent for future studies to consider dwelling crowding in more detail.

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

The presence of H pylori DNA does not itself imply infection and no visible bacteria were observed in any tissue sections. H pylori can be acquired early in life1 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,2 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.


Dr Kerr, Barson, and Burnie respond

Editor,—Following the publication of our paper,1 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 comments on the directions of future work in this area.

The possibility of PCR contamination has been suggested by Franciosi and Kolczetko 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 after 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.1

Dr Kolczetko 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 provide additional data on the molecular epidemiology of the ureC gene which was detected in these cases. We believe our assays to be specific. For example, the binding of oligonucleotides of 20 or more bases to template DNA at 1°C has been shown to be 100% specific. And in one of our PCR-ELISAs, there were five such interactions.1 We agree with Dr Kolczetko and other workers that it would be valuable to test other tissues from the same patients by the same method. Regarding our conclusions that some of these cases is quite appropriate and to illustrate this we include additional relevant data in table 1. Dr Vieth says our controls have had no normal environmental contact, however, five of these eight had spent time in the home environment since birth. Regarding antibiotic treatment, only one control had received antibiotics for more than one day prior to death, and this is the case in which H. pylori was detected.

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

In response to Dr Vieth’s claim that our suggested role for interleukin-1β (IL-1β) H pylori infection is "totally speculative", we would like to point out that these mechanisms have been demonstrated in an animal model.2 Also, proteins of H pylori are known to activate macrophages leading to production of IL-1β3 which is known to inhibit acid secretion by parietal cells and may actually be the most potent inhibitor of acid secretion discovered to date.4 IL-1β gene polymorphisms associated with increased IL-1β production have recently been associated with an increased risk of gastric cancer.5 In addition, systemic and mucosal humoral recognition of the cag protein has been linked with peptic ulceration;6,7 duodenal ulcer patients may more frequently harbour cagA+ H. pylori strains,8,9 and it has been shown that infection with cagA strains as compared with cagA− strains is associated with increased transcription of IL-1β.10 It is therefore interesting that 25 of 28 cases of H pylori associated SIDS in our study had a detectable cagA gene in their tissues,1 which may provide further support for the proposed pathogenesis of H pylori in SIDS and a contributory role for IL-1β.11

Dr Paul Beggs from Macquarie University in Australia points out the link between dwelling crowding and H pylori infection,12 which has been shown to be independent of socioeconomic status,13 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”.1

We feel that Wilek and colleagues, and MacKay and colleagues (in separate letters) have misunderstood the proposed hypothesis. Wilek 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 stomach to be optimal for microscopic visualisation of H pylori.”
lung to produce toxic amounts of ammonia in infants that presumably had normal lives.\(^9\) To reiterate, there are two parts to the hypothesis. First, interleukin-1\(_\beta\) production in the \(H\) pylori infected stomach, and second, supply of ammonia to the systemic circulation.\(^{10}\) (And the hepatic circulation as MacKay implies). Therefore, faecal urea content is irrelevant and so is ammonia produced in the stomach as this will be detoxified by the liver.

Regarding comments in the media, these are clearly not under our control and we have always stated that our findings are preliminary and require confirmation. In conclusion, we would encourage re-reading our papers and those of Patterson and colleagues\(^{11}\) in order to clarify the proposed role of \(H\) pylori in SIDS. In the meantime, we re-emphasise accepted measures to reduce mortality from SIDS and suggest the following additional precautions, all of which constitute good personal hygiene and are therefore advisable even in the absence of such a link. First, to prevent the transfer of saliva from the mouths of carers to babies. Second, prompt disposal of vomitus, decontamination of soiled surfaces, and washed 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 per-sonal 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 demonstrated in blood samples and vitreous fluid, and there is no evidence for this.

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

5. Ammonia in excess leads to cerebral 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 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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References


10 Patterson 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

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 ureC gene1 and the cagA gene2 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 asymptomatic gastrointestinal colonization into the lung and result in bronchopneumonia. However, the failure to detect the organism in the stomach, the 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 epidemiological observations. Taken together, the significance of H pylori as a cause of SIDS is highly questionable.

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Table 1 Characteristics of SIDS cases and controls

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

Cases

1 M 3 months SIDS
2 M 3 months SIDS
3 M 3 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


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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 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 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 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 histochemistry in particular, 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.2

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. We must state here clearly that we consider that they do argue against it. Epidemiological data for *H pylori* and socioeconomic factors in various ethnic groups are not clear cut and are incomplete. Such factors as prevalence of bottle feeding, parental smoking, family size, adherence to supine sleep position, etc., may explain differences of SIDS incidence in various ethnic groups. Blackwell gives data regarding bottle feeding 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 Houston, Texas.3

Blackwell reminds us of the accepted fact that animal work is not directly applicable to humans. Other studies have shown inflammation of the upper respiratory tract is a feature of *H pylori* infection in infants.9 “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 return after sequential 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 include intraepithelial peptechiae, patchy pulmonary oedema, emphysema, and increased muscle mass in pulmonary arteries, and although these are not invariably findings.

“Any 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 urease activity.5 Increased production of IL-1β could not be clearly defined.6

“The liver should be affected by hyperammonaemia and it is not in SIDS”. Blackwell has misunderstood our hypothesis. First, interleukin-1β production in the *H pylori*-infected stomach, and second, aspiration of urease into the lung and supply of ammonia to the systemic circulation (and not the hepatic circulation as Blackwell implies).7 “The brain should be affected by hyperammonaemia and not in SIDS”. If our hypothesis is correct, then the terminal event, involving hyperammonaemia in the systemic circulation is an acute and rapidly fatal occurrence, which may not result in brain pathology.8

We do not understand this point. Marshall’s views on controls used in the original paper do not take account of further information provided at the request of other authors9 which show that of eight controls used, five had an exposure to the home environment of more than one month.

Marshall states that *H pylori* is a gastric organism and that it is surprising to find evidence of infection in lung and trachea. However, *H pylori* has been detected at other sites, for example, the respiratory tract of intubated adults,10 and in the liver of patients with primary sclerosing cholangitis and primary biliary cirrhosis.11

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

Emotion aside, the fact remains that three groups have found *H pylori* in some cases of SIDS, and all three groups have detected the organism in the lung.12–14

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14 Kerr JR, Barson AJ, Burnie JP. Further information on an association between sudden infant death syndrome (SIDS) and Helicobacter pylori infection. *Arch Dis Child* 2001 (in press).

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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 effectiveness 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, historically, controls were needed for comparison of near final height. The historical controls achieved an adult height of 142.2 (6.0) cm, comparable with their original projected adult of 142.2 (6.1) cm. The group treated with GH alone gained 8.4 (4.5) cm height and the group treated with GH and oxandrolone gained 10.3 (4.7) cm over their projected heights. The benefit from GH treatment seemed to be more than modest, so why the discrepancy between the US results and the others to diagnose girls with TS early so that they can receive at least four years of oestrogen free GH treatment with a good chance of achieving an adult height of 150 cm. Is sudden osuspicion of a new predictor of height gained (the equation was 2.2 x years of oestrogen free GH treatment with a good chance of achieving an adult height of 150 cm. Is sudden

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 pulmonary function testing are complex and not just related to height as an outcome, but one should be aware of Chernauske’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 medical and psychosocial needs disease need investigation. Ranke and colleagues have shown that a major predictor of growth response in the second, third, and fourth years of GH treatment 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 the probability that there will be more than a modest effect on adult height, and then the patient, parents, and doctor may agree on cessation of treatment.

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Bromocliodinator responsiveness testing in young children

Editor,—There is some concern that asthma may be misdiagnosed when reported symptomes only are considered.1 In Britain, asthma is usually diagnosed without any lung function testing whereas in the USA, measurement of bromochlorinator 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 68 who were capable of achieving a reproducible 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 technique (Rint), 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 Rint 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 Rint, we suggest that this method is preferred to spirometry.

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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 problems encountered with its delivery in the developing world. The authors' key role in highlighting the plight of this forgotten group of children. The book gives a review of the wide ranging issues. For doctors working as medical advisers, 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 have an interest in 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.

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 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”. At the end of each chapter is a sessional requirement needed to do justice to these roles would have been a useful addition.

The book contains several teaching exercises for medical advisers. They are intended to provide a framework for group discussion. We thought these very helpful for higher specialist trainees as well. Simpler exercises aimed at SHOs, “core registrars” and GP, which could be used. 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 at the end of each chapter.

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.

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

As well as the editors’ introduction and summary, the book contains 10 chapters which examine crying across a broad range of contexts. Three (Poole and Magliner’s review of hospital emergency department practice towards crying complaints; 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 provide this diate interest to researchers. These include Hopkins’ analysis of the development of infant crying behaviours, which discusses continuity with fetal behaviour and highlights the question of how crying behaviours differ in the very young infant 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 the conceptual and methodological difficulties which remain. Poteagal moves the focus to temper tantrums in toddlers, presenting a model of autonomic reactivity which parallels ideas elsewhere in the book about the aetiology of crying. Bard asks whether the crying “peak” found in western infants at around 6 weeks of age—now widely considered part of normal development—is also found in our evolutionary relatives, chimpanzees. The answer is a partial yes. A peak in maternal soothing of infant chimpanzees was found at a comparable age. However, Bard observed none of the prolonged, unsustained crying which characterises the situation in human newborns.

The chapters are of a uniformly high standard, but two seem likely to have an especially lasting impact. One is Gustafson, Wood, and Green’s review, titled “Can infants cry?” 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 be communicated to a large 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 infant’s “degree 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 had 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 involved the family's return, after diagnosis (or the attempt thereof) back to the referring physician.

Geneticists, have learned what becomes of some children 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.

Drs Wilson and Cooley have written a unique book that fills a gap in the market. They have chosen some of the more common conditions with a frequency of more than 1 in 25 000 births, and by preventative management issues. To achieve this, the authors have drawn up checklists of what needs to be done at various ages and stages. To make this an achievable task, they have 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 neonatal intensive care, renal dialysis, etc, and the remainder who still deal with poor populations, poor medical resources, coping with recyclable diseases, such as gastroenteritis, malaria, malnutrition, and HIV.

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

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

H pylori

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Arch Dis Child 2001 84: 525
doi: 10.1136/adc.84.6.525g

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