higher incidence of drug reactions than other patients. The different surveillance systems used (nurse monitors in Boston and Glasgow and a pharmacist in Florida) are likely to affect both the type and number of drug reactions detected. Although definitions of drug reactions are consistent between studies, the definition of what constitutes a drug is rarely given. Also, in determining total adverse drug reaction rates, possible reactions are sometimes included alongside definite and probable reactions.

In this study anticonvulsants were the group of drugs most likely to cause a detectable drug reaction. This is probably related to the narrow therapeutic range of anticonvulsants. It may also be partly explained by the bias towards patients with neurological disorders in the study. These children were more severely ill than other children and thus at greater risk from a drug reaction.

That 6 of the 15 adverse drug reactions were preventable suggests that doctors need to be more careful in the drugs they prescribe—asking themselves whether the drug is necessary or not, whether the dosage is correct, and whether any drug interaction is likely. The results suggest that if these simple measures were carried out, fewer iatrogenic problems would arise.

We thank Dr J Martin and Dr L Rosenbloom for permission to study their patients and the ward nursing staff for their assistance.

References

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Cleft palate and gonadotrophin deficiency

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SUMMARY A boy who had previously had a cleft lip and palate repaired and bilateral orchiopexies presented at 16 years of age with delayed puberty. Isolated gonadotrophin deficiency and testicular hyporesponsiveness to human chorionic gonadotrophin were found. The possibility of bilateral cryptorchidism due to gonadotrophin deficiency should be considered in boys with either cleft lip or palate, or both.

Case report

A 16 year old boy was investigated for delayed puberty and short stature. He was born in July 1967 with a cleft lip and palate which were repaired at the ages of 3 months and 15 months respectively. The only details of his previous growth available were a height of 131 cm (25th centile) at 9-8 years and 140 cm (25th centile) at 11-5 years. He developed moderately severe asthma at 8 years of age and because of acute exacerbations required brief admissions to hospital on three occasions. His only exposure to corticosteroids was a 10 day course of hydrocortisone and prednisone during each of the latter two admissions to hospital. Bilateral cryptorchidism was not diagnosed until 9 years of age; right and then left orchiopexies were performed at ages 10 and 12 years. A nasal septoplasty was necessary at 15 years of age. He has been asymptomatic apart from occasional rhinitis and wheezing for which he has continuously taken bronchodilators and sodium cromoglycate. There is no family history of short stature, delayed puberty, or atopy.

Physical examination showed a short prepubertal boy of normal habitus and intellect with both height (156.5 cm) and weight (45.4 kg) below the third centile. He had bilateral, partial nasal obstruction and some degree of hyposmia. He seemed neurologically intact; his optic fundi, visual fields, and colour vision were normal. There was no physical
Investigations

The skull radiograph was normal. His bone age (according to the method of Greulich and Pyle) was reported to be between 12 and 13 years. His karyotype was 46, XY. Routine haematological and serum biochemical analyses were normal as were his thyroid function tests. Anterior pituitary function was assessed using a combined insulin tolerance, thyrotrophin releasing hormone, and luteinising hormone releasing hormone test similar to the protocol described by Savage et al. The results of this test (Table 1) were normal except for the poor gonadotrophin responses. Presumptive hypogonadotropic hypogonadism was confirmed by a four hour luteinising hormone releasing hormone infusion (50 µg/hr). The peak plasma follicle stimulating hormone and luteinising hormone concentrations during this test were 2.7 U/l and 1.7 U/l respectively; luteinising hormone was not detected (less than 0.9 U/l) after the 120 minute sample. A five day human chorionic gonadotrophin stimulation test was conducted on two occasions. On the first occasion an injection of human chorionic gonadotrophin (1500 U) was given daily for four days. The second test was performed two months later when 5000 U was injected daily for four days. The plasma testosterone concentration was measured immediately before the first injection of human chorionic gonadotrophin, then again on days three and five of each test. These results are presented in

Table 1  Plasma concentrations of growth hormone, cortisol, thyroid stimulating hormone, prolactin, follicle stimulating hormone, and luteinising hormone before and after combined test*

<table>
<thead>
<tr>
<th></th>
<th>Before test</th>
<th>After test (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Growth hormone (mU/l)</td>
<td>3.6</td>
<td>&lt;1-1</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>274</td>
<td>232</td>
</tr>
<tr>
<td>Thyroid stimulating</td>
<td>2.4</td>
<td>25</td>
</tr>
<tr>
<td>hormone (mU/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin (mU/l)</td>
<td>&lt;40</td>
<td>404</td>
</tr>
<tr>
<td>Follicle stimulating</td>
<td>&lt;0.4</td>
<td>1.7</td>
</tr>
<tr>
<td>hormone (U/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luteinising hormone</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
</tr>
<tr>
<td>(U/l)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Intravenous insulin (5 U Actrapid); thyrotrophin releasing hormone (200 µg); luteinising hormone releasing hormone (100 µg).

Cleft palate and gonadotrophin deficiency

Table 2  Plasma concentrations of testosterone before and after stimulation with human chorionic gonadotrophin (HCG)

<table>
<thead>
<tr>
<th></th>
<th>Test 1 (1500 U HCG/day)</th>
<th>Test 2 (5000 U HCG/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1-1</td>
<td>1-3</td>
</tr>
<tr>
<td>Day 3</td>
<td>0-8</td>
<td>4-2</td>
</tr>
<tr>
<td>Day 5</td>
<td>0-6</td>
<td>6-1</td>
</tr>
</tbody>
</table>

*Normal adult range: 13-0 to 40.0 nmol/l.

Table 2. The high dose human chorionic gonadotrophin test alone showed some Leydig cell function.

Discussion

This case report is the first to our knowledge describing cleft lip and palate and isolated gonadotrophin deficiency, although the association of cleft lip or palate, or both with either panhypopituitarism or isolated growth hormone deficiency has been reported previously. The well recognised association of bilateral cryptorchidism and delayed puberty with gonadotrophin deficiency prompted investigation of pituitary function while the close embryologic relation between the lip, palate, and adrenohypophysis as well as the above previous reports, supports the opinion that the gonadotrophin deficiency and cleft palate are associated. The testicular hyporesponsiveness to human chorionic gonadotrophin indicated testicular dysfunction and though this is recognised in hypogonadotropic hypogonadism, the mechanism is unclear. Awareness of the described association between cleft lip or palate, or both and gonadotrophin deficiency has relevance. Boys with cleft lip or palate, or both should be examined at infancy for bilateral cryptorchidism as gonadotrophin treatment may circumvent the need for orchiopexies. This treatment might also prime the Leydig cells. Subsequent surveillance of statural growth and pubertal development is essential even after correction of the bilateral cryptorchidism as further treatment may be necessary.

References

Trimethoprim sulphonamethoxazole in neonatal *Flavobacterium meningosepticum* infection

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**SUMMARY** During an outbreak of *Flavobacterium meningosepticum* septicaemia in a neonatal intensive care unit 9 infants were treated with intravenous trimethoprim sulphonamethoxazole. Bacteriological cure was achieved in 8 patients; one infant died of massive intraventricular haemorrhage on the first day of treatment. Apart from prolonged persistence of pre-existing thrombocytopenia there was no evidence of side effects. Trimethoprim sulphonamethoxazole should be considered in the treatment of neonatal *F meningosepticum* sepsis in view of its activity against this organism, good penetration of the blood brain barrier, and the absence of serious side effects.

*Flavobacterium meningosepticum*, an opportunistic Gram negative bacillus, has been implicated in several outbreaks of epidemic meningitis and septicaemia in newborn nurseries causing appreciable morbidity and mortality.\(^3\) It is characteristically resistant to conventional first line treatment for neonatal sepsis including penicillin, ampicillin, chloramphenicol, kanamycin, and gentamicin. It is generally susceptible to erythromycin, vancomycin, rifampycin, clindamycin, and trimethoprim sulphonamethoxazole. The use of this combination antibiotic in neonatal *F meningosepticum* sepsis has not been described previously.

**Patients and methods**

**Patients.** In January 1982 *F meningosepticum* was isolated from blood cultures of 9 newborn infants within a 6 day period in the neonatal intensive care unit at the Hadassah University Hospital. Clinical data on the patients are presented in the Table.

**Bacteriological procedures.** Cultures and identification were performed according to Rubin *et al.*\(^3\) Susceptibility testing was performed as described by Barry and Thornsberry.\(^4\)

**Laboratory monitoring.** Haemoglobin, white cell count, platelets, acidbase, electrolytes, bilirubin, urea, and urinalysis were checked at least daily. Urine microscopy was performed on alternate days. Blood cultures were drawn before and two to three days after starting treatment with trimethoprim sulphonamethoxazole. Lumbar puncture was performed on five of the 9 patients before treatment.

**Results**

**Clinical manifestations.** Signs of neonatal sepsis included lethargy, bradycardia, apnoea, acidosis, and bleeding tendency. Abdominal distension was an early indicator of sepsis in all 9 infants. In three patients considerable intra-abdominal pathology, necrotizing enterocolitis, ileal perforation, and postoperative duodenal atresia preceded the onset of the septicaemia. All infants were receiving hyperalimentation at the time of their illness and none had received enteral nutrition.

**Bacteriological studies.** The antibiotic susceptibility pattern of *F meningosepticum* isolated from all 9 infants was identical: the organism was sensitive to tetracycline, fuxitin, and trimethoprim sulphonamethoxazole; was resistant to ampicillin, cephalorin, amikacin, and gentamicin; and had an intermediate sensitivity to chloramphenicol and erythromycin. Blood cultures taken from the surviving patients two to three days after starting treatment were sterile. Cerebrospinal fluid samples obtained from five patients before treatment were sterile.
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