Comment

In this study children were more commonly exposed to pertussis by a sibling (22/26) than a parent, and 25 of the 26 children and adults responsible for transmitting the infection had typical disease. Atypical disease occurred in older children and parents but was almost exclusively associated with secondary rather than primary infection. Furthermore, isolation of *B pertussis* (which may reflect a person's infectiousness) was more common in those with typical pertussis (16 of 46 who had swabs taken) than in those who were asymptomatic or had atypical pertussis (one of 25 who had swabs taken). These results could not have been influenced by erythromycin treatment as the only family members treated in this way were children with typical pertussis (17/43).

We suggest that pertussis is most commonly transmitted by subjects with typical disease and that atypical disease and asymptomatic infection are not an important source of pertussis in this community. Thus a greater uptake of pertussis vaccination would probably affect transmission of the disease sufficiently to reduce its incidence.

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Near fatal drug interactions with methotrexate given for psoriasis

Methotrexate and trimethoprim are folate antagonists which, given together, may produce a synergistic effect on folate metabolism. Non-steroidal anti-inflammatory drugs may also interact with methotrexate.[1] We describe a patient who developed necrotic skin ulceration and pancytopenia after concurrent administration of methotrexate, trimethoprim, and naproxen.

Case report

An 80 year old woman with a 24 year history of psoriasis was started on intramuscular methotrexate in June 1986 because her psoriasis had deteriorated. Treatment with oral methotrexate in 1967-8 had been discontinued because of a slight increase in serum transaminase activities; since then she had been managed with topical steroids and tar.

From June to September 1986 she received three 15 mg injections of methotrexate. Two more (25 mg each) were given in October and November. The sixth injection (25 mg methotrexate) was given in January 1987, seven weeks after the fifth. Concurrent therapy was naproxen, 250 mg twice daily, which she had started in August 1986, before the second methotrexate injection.

Renal function was unremarkable in June 1986 (urea 8·6 mmol/l, creatinine 99 μmol/l). Before the sixth injection the blood count was normal (haemoglobin 120 g/l, white cell count $9·4\times10^9$/l, and platelet count 219×10^9/l); five days later, however, she presented with painful, ulcerated areas and contact bleeding over the thighs, buttocks, back, and upper chest (figure). Five days before the sixth injection she had started taking trimethoprim 200 mg twice daily for a urinary tract infection.

Investigation showed severe neutropenia (white cell count $0·9\times10^9$/l, neutrophils $0·3\times10^9$/l, haemoglobin 114 g/l, and platelet count 200×10^9/l), slightly raised urea concentration (13·3 mmol/l), and a red cell folate concentration of 504 μg/l (normal 125-600 μg/l). We considered that the methotrexate and trimethoprim had interacted, producing skin ulceration and leucopenia.

Folinic acid 60 mg daily was started. The white cell count rose to $3·5\times10^9$/l by day 7; the platelet count fell to 36×10^9/l but recovered and was normal from day 9. The urea concentration rose by day 3 owing to dehydration (urea 20·2 mmol/l, creatinine 99 μmol/l), and folinic acid was continued to cover delayed excretion of methotrexate. The skin healed and contact bleeding had stopped by day 7. The urea concentration was normal on day 8 (5·3 mmol/l).

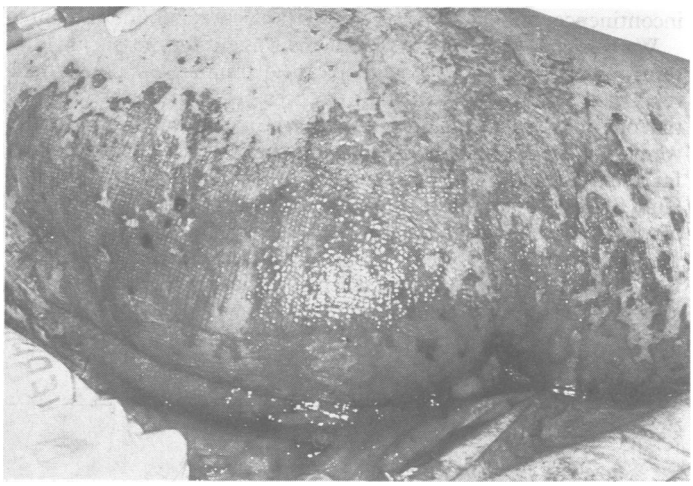
On day 8, when still neutropenic (neutrophils $1·7\times10^9$/l), she developed pneumonia. She received gentamicin, piperacillin, and metronidazole and dobutamine for cardiogenic shock. She was comatose for about 24 hours, but by day 10 she was conscious and well perfused. The white cell count was then $15·3\times10^9$/l. Folinic acid, metronidazole, and dobutamine were stopped, and she continued taking oral antibiotics.

Her recovery was complicated by temporary renal impairment and an acute confusional state lasting about 10 days. She was discharged one month later.

Comment

The recommended intramuscular dose of methotrexate in psoriasis is 7·5-50 mg weekly.[2] In this case a full blood count was normal before each methotrexate injection.

Methotrexate is excreted unchanged, principally through the kidneys by glomerular filtration and active secretion,[2] and impaired renal function may necessitate a reduced dosage. Our patient gave no suggestion of impaired renal function before the sixth injection of methotrexate, although she had had a urinary tract infection.



Skin ulceration over buttocks.

Methotrexate inhibits dihydrofolate reductase, and the erythrocyte concentration of folate is significantly decreased in psoriatic patients treated with long term methotrexate.[3] Changes in mean corpuscular volume and haemoglobin concentration do not occur until folate deficiency is pronounced, however,[3] and frank megaloblastic anaemia is rare.[4] Our patient had a normal red cell folate value, but a single estimation is inadequate for a firm diagnosis of folate deficiency without a pretreatment reference level.[3]

Trimethoprim competitively inhibits bacterial dihydrofolate reductase at a different site from methotrexate. It has low affinity for human dihydrofolate reductase but may produce haematological side effects in patients with folate or vitamin B_{12} deficiency.

Non-steroidal anti-inflammatory drugs may interact with methotrexate.[1] Naproxen is highly protein bound, and administering methotrexate and naproxen together may therefore increase the unbound level of both drugs owing to their displacement from plasma protein. Because methotrexate and naproxen are both excreted by active tubular secretion, an interaction may also occur at this site, reducing the renal clearance of methotrexate. Our patient had taken naproxen for six months before admission, however, and had received four doses of methotrexate uneventfully.

Acute ulceration of the skin is a rare complication of methotrexate therapy which may occur when the dose is within the therapeutic range.[5] Among seven psoriatic patients with such ulceration six were also taking a non-steroidal anti-inflammatory drug.[5]

In this case, although deteriorating psoriasis, non-steroidal anti-inflammatory drug therapy, and an undetected deterioration in renal function may have been cofactors, methotrexate toxicity was probably precipitated by concurrent treatment with trimethoprim. This case emphasises the need for care when prescribing for patients receiving methotrexate.

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Undescended testes in low birthweight infants

Cryptorchidism is a known risk factor for infertility and testicular malignancy. The reported incidence is rising and is now over 2%,[1] bilateral abnormality occurring in 10-25% of cases. Undescended testes are more common in low birthweight infants,[2] but there is little detailed information on this subgroup. We collected extensive data on preterm infants, enabling us to determine the incidence of cryptorchidism and its associations.

Patients, methods, and results

Altogether 355 male infants with birth weights under 1850 g who had been admitted to Cambridge, Norwich, Ipswich, or Kings Lynn in 1982 or 1983 and all units in East Anglia in 1984, were examined by one of us (RM) at 18 months after term. An undescended testis was defined as one that could not be brought down to the bottom of the scrotum by manipulation (alternatively, a previous operative diagnosis was taken).

The overall incidence of undescended testes was 35/355 (9·9%). Cryptorchidism was strongly related to birth weight (table). In infants below and above 1500 g the incidence was 29/186 (16%) and 6/169 (3·6%), respectively (p=0·001). Bilateral abnormality occurred in 15 of the 35 cases (43%). Of the 260 infants born at up to 32 weeks' gestation, 33 (13%) had undescended testes compared with two of the 95 (2%) born after 32 weeks (p<0·01). A birth weight of under 1850 g was the criterion for entry to this study; thus larger infants born after 31 weeks were excluded. Undescended testes were, however, unrelated to being small for gestational age.

Extensive data on antenatal, perinatal, and postnatal factors, collected in a subgroup of 287 infants enrolled in a preterm feeding trial,[3] showed significant associations between undescended testes and both necrotising enterocolitis (p=0·025) and eczema at 18 months (p=0·001; table) (enterocolitis and eczema were evenly distributed across the range of birth weight). Cryptorchidism tended to be more common in infants whose mothers had been given steroids (8/44 (18%) compared with 21/243 (8·6%); p=0·053). No significant associations were found with maternal age or parity, conception while the mother was taking oestrogens, breech delivery, phototherapy (which affects plasma luteinising hormone concentration[4]), severity of neonatal respiratory disease, or any other factor analysed.

Incidence of undescended testes by birth weight and presence of necrotising enterocolitis and eczema 18 months after term

	No with normally descended testes	No (%) with undescended testes	Significance*
Birth weight (g):			
≤999	29	7 (19)	p<0·001
1000-1199	34	7 (17)	
1200-1399	59	9 (13)	
1400-1599	75	7 (9)	
1600-1849	123	5 (4)	
Necrotising enterocolitis†:			
None	250	25 (9)	p=0·025
Present	8	4 (33)	
Eczema at 18 month examination†:			
None	224	20 (8)	p=0·001
Mild or moderate	31	7 (18)	
Severe	1	2 (67)	

*χ^2 Test, one degree of freedom for trend.
†Infants enrolled in preterm feeding trial.

Comment

Cryptorchidism emerges as one of the commonest abnormalities in surviving male infants of very low birth weight, occurring in 19% of those weighing below 1000 g. Testicular descent, normally a late fetal event, may be interrupted by preterm birth; interestingly, in infants born after 32 weeks' gestation the incidence of cryptorchidism was similar to that reported in infants born at term.

We failed to find an association between undescended testes and factors described previously.[1] The association between undescended testes and necrotising enterocolitis may be a chance finding, given that multiple factors were analysed, but intra-abdominal disease might interfere with testicular descent. The association with eczema is probably not a chance finding. Given the trend towards a higher incidence of cryptorchidism in the small group whose mothers received steroids, we speculate that cutaneous absorption of corticosteroid creams for infantile eczema may interfere with the descent of testes.

We calculate that an increase in the survival of infants weighing under 1500 g from 50% to 80% (as occurred in Cambridge during 1952-82) would increase the incidence of undescended testes in the population by only 0·04%, which does not account for the reported secular rise from around 1% to 2%.

The risk of testicular malignancy is reportedly up to 50 times higher in cryptorchid men.[5] Bilateral abnormality, which may increase the risk of malignancy, was common in low birthweight infants (43%), further raising their theoretical risk of later testicular cancer. The benefits of early orchidopexy in improving fertility and preventing malignancy remain uncertain. We suggest, however, that cryptorchidism should be sought at routine follow up of preterm infants and that long term epidemiological surveillance of cryptorchid infants born before term is required

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