Correspondence

The most striking omission is the lack of any controls. It is well recognised that psychosocial factors can exert extreme effects on the growth of children, even at this relatively late age, and the increased attention plus a placebo effect could well have contributed substantially to the observed increase in growth. In particular, I note that all the children in this study were suffering from psychological disturbances of one type or another and I wonder how much active psychotherapy was provided at the same time as the endocrine treatment. This could only be interpreted if there were comparable control patients who were not given oxandrolone but whose management otherwise remained the same.

The second anxiety relates to the pubertal status. While I accept that one would not expect a substantial growth spurt due to puberty in boys with an average testicular volume of 9-3 ml, which was achieved at the end of their treatment period, one might certainly expect it in those boys near the extreme upper limit of their range (15 ml). I would suggest that in at least some boys all that was observed was the normal events of advancing puberty, and there is no evidence that oxandrolone influenced this.

Thirdly, only a mean and SEM are quoted for the change in growth velocity from pretreatment to treatment period (4·4 (0·37)) and unlike the other variables no range is given. As this implies a standard deviation of 1-8 cm/year there is an implication that in some boys the acceleration was extremely small unless the distribution was skewed. I think it would be helpful to know the minimum and maximum acceleration observed.

The observations that they make have important potential but, unfortunately, I think they are not really sustained by the present study. I would be interested to see further elaboration of their data to take in some of these points.

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Drs Stanhope, Noone, and Brook comment:
We are grateful to Dr Preece for giving us the opportunity to clarify some points about our paper.1 He has raised three separate issues.

Adolescent boys who are small and delayed in puberty are anxious and unhappy and our treatment is aimed at alleviating this situation. Our Department of Child Psychiatry is actively involved in all the activities of our clinic and some of the boys in this study had diagnostic interviews; none entered a psychotherapeutic programme.

Although controls might be desirable, we are doubtful that a placebo treatment would now be justified in this clinical situation, since it has been known for at least 20 years that the growth inducing effects of anabolic steroids are not dose dependent.2 We have recently published the results of another earlier study of a similar group of boys treated with low doses of the anabolic steroid fluoxymesterone (which is no longer available) with almost identical results,3 and we have now been able to confirm our hypothesis that oxandrolone acted by increasing growth hormone secretion using 24 hour profiles of growth hormone concentrations.4

While this might have been secondary to psychological mechanisms, our profiles also showed a minor suppression of pulsatile luteinising hormone secretion and alterations in the concentrations of thyroxine binding globulin which one would expect after administering an anabolic steroid. These are not the hallmarks of a placebo effect.

The second point concerns growth velocity data and the raw data from our study are shown in the Figure. The changes between pretreatment and treatment growth velocities are obvious without statistical analysis. We have added growth velocity data from a further 17 boys with constitutional delay of growth and puberty treated with only 1-25 mg oxandrolone for three months. The results using either dose regimen are similar and we have still not defined the lowest effective dose.

With regard to pubertal status, mean testicular volume at the end of the treatment period using oxandrolone 2·5 mg daily was 9·3 ml with an upper range of 15 ml. Only two boys had testicular volumes greater than 12 ml and we accept that their growth acceleration may have been spontaneous. On the other hand the mean testicular volume at the end of treatment in the 17 boys shown in the Figure treated with oxandrolone in a dose of 1·25 mg daily was 6-9 ml and none was greater than 10 ml. It is certainly possible that as testicular volume increased during the post treatment periods a secondary effect on growth velocity became indistinguishable from spontaneous growth acceleration but this was after all the object of the exercise. Oxandrolone used for this indication was effective in

Figure Growth velocities of 24 boys treated with oxandrolone 2·5 mg daily (solid circles) and 17 boys treated with oxandrolone 1·25 mg daily (open circles). Before treatment, treatment, and after treatment periods were consecutive in each series.
advancing the onset of the pubertal growth spurt and had no adverse effect on adult height prediction.

References

Ceftazidime in neonatal infections

Sir, Ceftazidime has been shown to be effective against both Gram negative and Gram positive organisms commonly causing neonatal infections. It is now being used as a first line antibiotic for the treatment of neonatal infections for the reasons given by Low et al.2 Their analysis suggested that ceftazidime may not be effective against Gram positive organisms. I was surprised that case 12 was included. Would it not be too optimistic to expect sterilisation of the cerebrospinal fluid 6-75 hours after a single dose when using any antibiotic? Why (case 11) was penicillin only given 15 hours before death (day 11) when ceftazidime had been begun at 16 hours, the infant's condition was deteriorating, and the organism was not sensitive? The persistence of Staphylococcus aureus (case 9), despite an adequate serum concentration, suggests that the child may have had an infected venous catheter or a collection of pus.

On the basis of this report I feel it is premature to abandon the use of ceftazidime as a first line drug for the treatment of neonatal infections.

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Drs Low and Bissenden comment:
Dr Blumenthal's comments arise partly because our study was based on 14 cases of proved sepsis, each of which would have merited further discussion, and the need to restrict clinical data to the absolute minimum within the constraints of the Table. Nevertheless, there is obvious confusion over case 12. This was group B streptococcal meningitis, diagnosed early, treated promptly, and where sterilisation of the cerebrospinal fluid was achieved after 54 hours of treatment (not 6-75 hours—that was when the cerebrospinal fluid ceftazidime concentration was measured). It seemed a reasonable case to report, and we see no reason to exclude it. What is difficult to explain in that particular case, and in the case of staphylococcal septicaemia (case 9), is that despite these organisms, on the basis of their minimum inhibitory concentrations being sensitive to ceftazidime, and bacteriocidal concentrations of ceftazidime achieved in cerebrospinal fluid and blood, organisms could still be cultured after 54 and 36 hours respectively. Maybe there was a focus of infection seeding the blood in case 9, but fluoroxyacin addition coincided with bacteriological eradication and clinical improvement. Finally, case 11 (also group B streptococcal septicaemia) was diagnosed late on the second day of life, as her symptoms had been ascribed to hyaline membrane disease. She continued to deteriorate throughout the next 15 hours of ceftazidime treatment (two doses), and penicillin was then added, which resulted/coincided in eventual bacterial eradication. Bilateral intraventricular haemorrhages had already occurred, however, and intensive care was stopped on day 11.

de Louvois's article,1 quoted by Dr Blumenthal, no more shows ceftazidime to be effective against Gram positive organisms than our paper shows it to be ineffective; it merely reviewed theoretical advantages of ceftazidime, with which we would not argue. By no means should ceftazidime be abandoned for use in neonates on the basis of three cases of Gram positive sepsis which fared badly. Much more experience is necessary, but we can only say from our data that it was inappropriate as a single first line antibiotic.

References

Campylobacter enteritis and bloody stools in the neonate

Sir, Surely a throw away remark as in the Discussion of the paper by Youngs et al1 should be either retested or edited out. I refer to 'in our experience anal fissures are not infrequently associated with necrotising enterocolitis and other forms of colitis in the newborn': this in a paper on campylobacter not necrotising enterocolitis or anal fissures. If mentioned it must surely be substantiated—what is their evidence?

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Dr Youngs and co-workers comment:
The statement quoted by Dr McIntosh is based upon observations during an epidemic of necrotising enterocolitis in 1981 and 1982. The presence of inflammation of the distal large bowel in necrotising enterocolitis was shown by