controlling platinum associated vomiting it is no better than chlorpromazine for chemotherapeutic regimens not including cisplatin. We question whether it is reasonable on the evidence to conclude that high dose metoclopramide is not more effective in the second category of patients. Our own experience (unpublished) has been that the antiemetic activity of high dose metoclopramide is dose and schedule dependent in patients on cisplatin chemotherapy and that a minimum serum concentration of 850 ng/ml has to be maintained during at least the first six hours after the cisplatin infusion. In the series of Dr Cunningham and his colleagues a small loading dose of 50 g was used with a continuous infusion of about 0.4 mg/kg/hour thereafter, which would not be expected to achieve the desired plasma concentration. More importantly, in their study the participation of several centres implies that the assessment of subjective end points, especially nausea and "patient preference," would have been rather variable. How many observers were there in all, and was a single standard questionnaire used by these observers?

We strongly endorse the efforts of the authors in attempting to improve the quality of patients' experiences in facing the rigours of cytotoxic chemotherapy and would encourage other research in this area. For patients on cisplatin chemotherapy major advances have already been made in the control of these side effects. It would be a pity, however, if potentially effective remedies were to be discarded for the wrong reasons.

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*Dr Cunningham and Dr Soukop reply below.—Ed, *BMJ*.

SIR,—The issue of plasma metoclopramide concentrations and antiemetic control is important and deserves comment. Meyer *et al* were the first to focus attention on the need to obtain a plasma metoclopramide concentration of at least 850 ng/ml six hours after cisplatin administration to optimise control of emesis.¹ It is probable that our loading dose and continuous intravenous infusion (total dose 5.5 mg/kg) did not allow such a plasma concentration to be reached at six hours and that a loading dose of 2–3 mg/kg would be required to achieve this. However, other workers using a similar dose of metoclopramide (6 mg/kg) have shown adequate control of emesis with an acceptable level of side effects.^{2,3} Moreover, for cytotoxic regimens without cisplatin the current evidence would suggest that there is no clear relation between plasma concentration and control of emesis⁴; indeed, a recent clinical study showed no apparent advantage of increasing the dose of metoclopramide beyond 20 mg (stat) intravenously every two hours for six doses.⁵

A likely explanation for these findings is that there is a lower plasma threshold for optimum control of emesis induced by cytotoxic drugs other than cisplatin because with these drugs metoclopramide exerts its antiemetic effect by a central, rather than peripheral, pathway. In practical terms this means that escalating the dose of metoclopramide to improve emesis

control for cytotoxic regimens without cisplatin is unlikely to be fruitful. Furthermore, although it may be acceptable to give an antiemetic as an intravenous infusion in circumstances where a prolonged intravenous infusion is necessary for the safe delivery of the cytotoxic agent (such as cisplatin) it hardly seems sensible that such a method should be used where a regimen is given by an intravenous bolus or short intravenous infusion. In this context, we have recently shown using the combination of an oral synthetic cannabinoid (nabilone) and prochlorperazine that emesis control is possible in over 80% of patients receiving cytotoxic regimens without cisplatin,⁶ which enables the chemotherapy to be administered on an outpatient basis.

Regarding the methods, ours was a prospective multicentre study so the same questionnaire was used by all participating centres, and there was a total of five observers, which is not unreasonable given the size of the study. The comment with respect to subjective assessment is not relevant since each patient acted as his own control. Therefore we feel that our conclusions were valid and that high dose metoclopramide is not an appropriate first line antiemetic for cytotoxic regimens without cisplatin.

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Unithiol in Wilson's disease

SIR,—We found it difficult to understand why Dr J M Walshe had decided to try the chelating agent unithiol, an agent with unproved merit, for the treatment of Wilson's disease in a boy who had developed intolerance towards two other chelating agents (penicillamine and triethylene tetramine) (2 March, p 673).

Until recently patients with Wilson's disease had no choice. Chelating therapy was the only treatment available, and when untreated the disease is invariably fatal. Penicillamine became regarded as the best of the chelating compounds. It may be given orally and was found to be less toxic than dimercaprol. However, treatment with penicillamine was not completely satisfactory: in some patients neurological signs increased during the first weeks of treatment and a few patients developed severe intolerance to penicillamine.¹ Because of its potential toxicity penicillamine had to be given in minimal doses during long term therapy, with the risk of a reaccumulation of copper.

There is sufficient evidence to show that Wilson's disease can also be treated effectively with oral zinc and that patients who do not

tolerate chelating therapy may profit greatly from the change to zinc.² Zinc is easily tolerated by most patients.

It should be emphasised that chelating therapy and oral zinc therapy differ completely in their way of action: the former induces the excretion of copper via the urine, the latter via the stools. Zinc can be given as zinc sulphate or in the form of other salts of low toxicity. A dose of 600–900 mg zinc sulphate a day is usually sufficient to obtain a good result.

In view of the side effects in two of his three patients we were astonished to read that Dr Walshe concludes that unithiol might become a fall back treatment for patients who do not tolerate penicillamine. When chelating agents were the only possibility for patients with Wilson's disease, many patients profited from Dr Walshe's discovery that penicillamine could be taken by mouth and induce cupriuresis.³ Now oral zinc therapy is available—an effective treatment of low toxicity. After such severe complications caused by two chelating agents it would have been a more rational therapeutic decision to have started zinc therapy.

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*Dr Walshe replies below.—Ed, *BMJ*.

SIR,—I am impressed by the enthusiasm of Drs Hoogenraad and Van Hattum for the use of zinc sulphate in the treatment of Wilson's disease. If they cannot understand why I did not use this drug in the patient referred to in my short report of 2 March I can only refer them to my letter, also in the *British Medical Journal*, of 1 September 1984.¹ From the difference in our two experiences of zinc sulphate I can only conclude that the gastric mucosae of his patients are more resistant to irritants than those of my patients. As to his assertion that unithiol is untried in the treatment of Wilson's disease I must again refer him to published reports; the drug has been in use at least since the late 1950s.²

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Cleft lip and palate

SIR,—It was of great interest to read the recent article in your series "Plastic and Reconstructive Surgery" (23 February, p 625). However, we were disappointed to find no mention of the importance of preventive dental care for children with cleft lips and palates. Poor dental health can make successful orthodontic treatment extremely difficult and will jeopardise the final result achieved in these