the preoperative management of hypertension varies in our hospital, the variation being at least partially explained by the number of anaesthetic opinions represented.

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High dose cisplatin compared with high dose cyclophosphamide in the management of advanced epithelial ovarian cancer

SIR,—In their randomised prospective study of 86 patients with epithelial ovarian cancer Dr Hannah E Lambert and Professor Roger Berry (23 March, p 889) concluded that cisplatin (120 mg given intravenously monthly for six months then 30 g intravenously monthly for a further six months) was superior to cyclophosphamide (2 g intravenously monthly for six months followed by 1 g intravenously monthly for six months). This superiority was seen with respect to both survival and time to relapse after complete clinical response.

When one looks at the patient characteristics in the two treatment groups age and stage are comparable, but analysis of tumour type shows a bias toward the cisplatin treated groups for mucinous tumours (18% v 5%) and toward the cyclophosphamide treated group for undifferentiated tumours (27% v 12%). With respect to grade generally 22.5% of the cisplatin treated patients had grade I tumours compared with 3% of the cyclophosphamide group; 54% of the cyclophosphamide group had grade III tumours compared with 35% of the cisplatin group. Thus any effect of the increase in grade I tumours in the cisplatin group was maximised by a comparable increase in grade III tumours in the cyclophosphamide group. There was also a preponderance of patients who had had optimal surgery in the cisplatin treated group (53% v 43%).

After standardisation for the differences in surgical debulking between the two groups the statistical significance of the survival difference between the two arms decreased and that of duration of complete response disappeared. At three years the curves depicting duration of complete response had come together whether considered with respect to chemotherapy received or to adequacy of initial debulking surgery.

The question which this paper seems not to answer is this: Do these results reflect any difference in effect of chemotherapeutic regimen or simply a difference in biological behaviour of different ovarian tumours? When stage of tumour is standardised grade of tumour remains prognostically important.¹ This importance has previously been shown to be independent of treatment protocol.² Other aspects of ovarian cancer biology may be implicated—for example, there appears to be a relationship between DNA ploidy and grade, borderline tumours being almost exclusively diploid whereas undifferentiated tumours are mainly aneuploid.^{3,4} Analysis of another prognostically important variable—adequacy of tumour debulking—with respect to tumour biology also suggests that well differentiated and diploid tumours are more often surgically removable.⁴

The preponderance of biologically favourable

characteristics in the cisplatin arm of this study raises the possibility that the difference in survival may be due to inherent prognostic differences between the two groups of patients.

The recommendation that "cisplatin is a more effective chemotherapeutic agent than cyclophosphamide for advanced ovarian cancer and should be the agent of choice in future trials" cannot be made on the basis of these data. The question of cisplatin versus other less toxic cytotoxic drugs either as single agents or as part of combination chemotherapy requires prospective randomised trials large enough to standardise for the many prognostically important variables. We appreciate the difficulty in conducting such a study.

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SIR,—Drs Hannah E Lambert and Roger J Berry conclude from their study comparing cisplatin with cyclophosphamide that cisplatin "should be the agent of choice in future trials comparing combination chemotherapy with a single agent." Examination of the study, however, reveals major imbalances that make such a conclusion difficult to substantiate. Because randomisation was performed immediately after surgery 21% of those randomised had to be withdrawn after histological review. This left a major imbalance in patient numbers (cisplatin 49 v cyclophosphamide 37). When these patients were further examined according to the known major prognostic factors there was a much higher proportion of patients with favourable factors in the cisplatin arm.

The findings of this study contradict those of four major studies comparing a single alkylating agent with a cisplatin based combination (Vogl SE, *et al*, 13th International Congress in Chemotherapy 1983 and refs¹⁻³). Each of these studies showed a significantly higher surgically documented response rate for the cisplatin based combination, though in none was there any difference in overall survival. An additional, unpublished, Australian study of 369 patients has shown similar results (Tattersall M, unpublished data). This study of 86 evaluable patients from 51 participating clinicians has major methodological flaws and its conclusion must remain unproved.

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- 1 Sturgeon JF, Fine S, Gospodarowicz MK, *et al*. A randomised trial of melphalan alone versus combination chemotherapy in advanced ovarian carcinoma. *Proceedings of the American Society of Clinical Oncology* 1982;1:108.
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* * *The authors reply below.—Ed, *BMJ*.

SIR,—Drs Ward and Slevin and Dr Williams and Professor Whitehouse raise the possibility that the superiority of cisplatin over cyclophosphamide found in our study may have been due to an imbalance of prognostic factors between the two treatment groups, perhaps as a result of the different numbers in the two groups. As far as grade and histology are concerned, we can reassure them that these factors in no way explain the observed superiority. Since 10 of the 12 grade I tumours were debulked, grade provided little extra discrimination after allowance for debulking, and the histological subtypes did not appear to be correlated with survival at all. These results were confirmed using a stepwise linear regression based on Cox's proportional hazards model,¹ which allows for the imbalance in numbers.

Responses longer than three years remain in the minority in late stage ovarian cancer, our trial being no exception, but this does not invalidate the benefits seen for the majority of responders receiving cisplatin in our study.

We understand the writers' concern, however, since ovarian cancer is a disease where many factors affect the outcome, and such factors may always confound observed effects. DNA ploidy might indeed be influencing our results in such a fashion. However, the greater the p value observed for the difference the more unlikely this possibility becomes. With the smallish numbers in our study and significance levels of the order of 0.05 the observed superiority may, of course, have been a chance finding. Indeed we allowed for this possibility by suggesting rather than recommending cisplatin as the agent of choice in future trials. The results from the trials using combinations containing cisplatin quoted by Dr Williams and Professor Whitehouse confirm our improved response with cisplatin. However, published reports now show a diversity of results as far as survival is concerned.²

A final point is that the present management of advanced carcinoma of the ovary requires a multidisciplinary approach. This is reflected by the fact that the North Thames Cooperative Group includes, as well as the 10 radiotherapists who administered the chemotherapy, gynaecologists, pathologists, and medical statisticians.

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Management of delayed puberty

SIR,—Dr Charles G D Brook's leading article (2 March, p 657) was correct to highlight the paramount importance of early treatment of

delayed puberty. I disagree, however, with the treatment he suggests for boys.

For several years I have used human chorionic gonadotrophin 1000-2000 units intramuscularly twice weekly, for three to six months only, and have not encountered any "emotional" problems in these patients as a result of this treatment. Indeed, the only emotional problems for these patients stem from their physical and sexual immaturity. These doses quickly cause early changes of puberty, with improvement of the patient's emotional state and without excessive skeletal maturation compared to height increase. Thereafter puberty generally continues smoothly over the next two to three years, unless, of course, the patient has hypogonadotrophic hypogonadism.

Follow up to their mid to late 20s of these successfully treated patients with constitutional delayed growth and development shows normal sexual orientation, social intercourse, and fertility.

The very low doses of human chorionic gonadotrophin suggested by Dr Brook are unlikely to result in early pubertal changes and I believe that the teenagers I see would not tolerate this treatment for very long in the absence of clearly visible improvement of their physical and sexual development.

In addition, pulsatile use of gonadotrophin releasing hormone as a treatment for teenage boys with delayed puberty is cumbersome, expensive, and unproved. Since there is a danger of down regulation of the gonadotroph, numerous blood samples are required to ensure that this treatment is not counterproductive. I believe that this, again, would not be tolerated by many teenagers.

At present teenage boys, not concerned with fertility but only with overt physical and sexual development, should still be treated with human chorionic gonadotrophin, as described. Later, if puberty has not occurred—for example, in the occasional patient with congenital isolated hypogonadotrophic hypogonadism—androgen treatment should be given until fertility is desired. At this stage pulsatile gonadotrophin releasing hormone may be tried as an alternative to conventional human chorionic gonadotrophin and follicle stimulating hormone therapy. Properly conducted trials are required to assess these two forms of treatment for infertility in men due to hypogonadotrophic hypogonadism.

Finally, your leading article failed to emphasise that growth hormone deficiency should always be excluded, with growth measurements and pituitary function tests, before starting treatment to induce puberty, to ensure that bone fusion does not occur in the absence of height increase.

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*. *Dr Brook replies below.—ED, *BMJ*.

SIR,—The treatment which Dr Cohen uses for boys with delayed puberty will induce adult concentrations of plasma testosterone within two weeks. Of course, these doses will quickly cause changes of puberty but at a quite unphysiological rate. I accept that many boys will be able to cope with such a rapid advance but I can assure Dr Cohen that some will not be able to. The point is that there would be no need to go at this rate if he saw patients at an earlier age. In clinical practice

there is a substantial difference between the rate of progress that one might seek in a 13 year old from that in an 18 year old—both are teenagers.

Treatment with gonadotrophin releasing hormone therapy is clearly a research procedure at present. What we do not know is whether the long term prospects for fertility are the same for boys treated with testosterone or human chorionic gonadotrophin as they are for those treated with gonadotrophin releasing hormone. The danger of desensitisation of the pituitary is small if a low dose regimen of gonadotrophin releasing hormone is used. I accept, however, that this is unlikely to be a routine method of treatment and in most instances human chorionic gonadotrophin or testosterone will be used. I still think that it is better to mimic the physiology of puberty with these agents.

It ought to be possible to exclude growth hormone deficiency on auxological grounds. The problem with embarking on pituitary function tests in a boy going late into puberty is the well recognised transient deficiency of growth hormone which occurs in boys growing very slowly at this age.¹ If a dynamic test of growth hormone secretion is performed it needs to be performed after priming with sex steroids. In an unprimed test a rise of growth hormone to a provocative stimulus will exclude growth hormone deficiency, but a negative response means nothing.

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Neonatal meningitis

SIR,—We read with interest the PHLS report on neonatal meningitis in Britain 1975-83 (9 March, p 778) as we have recently completed a descriptive study of meningitis in this American community (population 393 000).¹

For all age groups we documented that only 16% (61/391) of hospital cases were reported to the county health department. Clear and contrasting seasonal trends for bacterial and non-bacterial cases were apparent with bacterial cases having a higher incidence in the winter months.

Consistent with the British report, neonates contributed 7% of bacterial cases. Although our study was much smaller than that reported by PHLS, we were struck by the absence of cases caused by *Escherichia coli* (see table). If this is not an effect of small numbers, it might represent a local variation or a continuation of the trend noted by PHLS of the emerging importance of group B streptococcus in neonatal meningitis.

There was no evidence of a superimposed epidemic of meningitis during the four years studied and we believe we have described "normal background activity in a typical American metropolitan area"¹ for meningitis. The number of patients, morbidity, cost, and mortality (although small) lead us to conclude that meningitis remains a community health burden.

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Alternatives to digitalis glycosides for heart failure

SIR,—The management of patients with chronic ischaemic heart failure is difficult, and Dr G D Johnston's leading article (16 March, p 803) takes a timely look at alternatives to digitalis glycosides. However, the investigation of oral inotropic agents is hampered by a lack of suitable animal models and the difficulty of assessing contractility in man. Pirbuterol exerts a more selective action on β_2 than β_1 adrenergic receptors and its haemodynamic and clinical effects may, like those of salbutamol, be due to vasodilatation rather than enhanced inotropism.¹ Controlled trials to determine the clinical role of these drugs are required but they may not elucidate their mode of action.

Although Dr Johnston suggested that no data have been published on long term oral treatment with prenalterol there have been three controlled trials of long term treatment in heart failure with this drug. Those of Lambertz *et al*² and Currie *et al*³ showed little benefit, but our own study in patients with stage III heart failure (New York Heart Association) did show moderate clinical improvement in the prenalterol group.⁴ Bicycle exercise capacity improved over six months in both placebo and prenalterol groups but reached statistical significance only in the patients treated with prenalterol. Maximum exercise heart rate was significantly reduced in the prenalterol group. The difference in outcome of the three trials is probably explained by the difference between the patients studied, the length of the trials, and the dose of prenalterol.⁴ The reduction in maximum exercise heart rate in those on prenalterol suggested that β_1 antagonistic activity might limit myocardial oxygen consumption of its agonist action and might have been the main way in which benefit was produced. Stimulation of the depressed myocardium may be difficult in ischaemic cardiomyopathy and need not necessarily be of benefit. Certainly the challenge is to produce a drug

Causative organism by age group

Age	<i>Haemophilus influenzae</i>	<i>Streptococcus pneumoniae</i>	Group B streptococcus	<i>Neisseria meningitidis</i>	<i>Staphylococcus</i>	Other	Total
≤28 days	2	1	7	0	0	0	10
1 month-5 yr	63	11	5	10	2	0	91
6 yr-	2	1	1	2	1	0	7
16 yr-	0	2	2	1	1	1*	7
31 yr-	0	1	1	2	1	1†	6
51 yr-	0	1	1	1	0	1‡	4
>65 yr	1	2	0	1	0	1§	5
Total cases	68	19	17	17	5	4	130

**Bacteroides fragilis*. †*Listeria monocytogenes*. ‡*Klebsiella pneumoniae*. §*Listeria monocytogenes*.