with source traced only 13 arose from the lungs.

That isolations of *Pseudomonas aeruginosa* have become less frequent in certain hospitals in the USA does not necessarily imply the same to be true or even likely in hospitals elsewhere—this organism was the second commonest cause of Gram-negative bacteraemia in patients with neutropenia in Addenbrooke's Hospital in the last three years.

Further aspects of this article are open to similar criticism; we do not wish to labour the point, but simply to emphasise the importance for those who treat leukaemia of working in close collaboration with their own microbiological colleagues and establishing patterns of practice in conformity with their own local needs.

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¹ The EORTC International Antimicrobial Therapy Project Group. *J Infect Dis* 1978;137:14-29.

SIR,—The recent leading article (8 November, p 1235) on this topic is likely to create misunderstanding about the pattern of infections occurring during treatment of childhood leukaemia. It is implied that the use of methotrexate and the intensification of treatment regimens are recent innovations—as methotrexate has been in use for 30 years and combination chemotherapy with central nervous system prophylaxis for 10 years, neither can surely be classed as such.

The article misinterprets data about the incidence of pneumonia and the time when patients are at risk. The review from the Hospital for Sick Children (HSC)¹ concerning children diagnosed between 1973 and 1978 related only to infections occurring during remission induction and therefore is not comparable with the report from the Children's Cancer Study Group (CCSG),² which although it concerned patients treated during the same years calculated the incidence of pneumonia throughout the duration of treatment. The CCSG data clearly show that the peak incidence of pneumonia is not during induction but 40-80 days after diagnosis during continuing (maintenance) therapy. A similar survey of our own patients confirms that pneumonia is an important cause of morbidity and mortality.³

Unfortunately more effective antibacterial regimens are unlikely to be of benefit because bacterial pneumonia is not a major cause of death. Treatment of *Pneumocystis carinii* pneumonia with high dose co-trimoxazole has proved effective in our experience.^{4,5} The commonest cause of death in remission in patients treated at the HSC is measles pneumonia. Five of 14 deaths in the survey and two additional deaths this year were caused by this infection.

We are concerned at the omission of a strong recommendation for the prevention of measles by immunisation. Live vaccine is, of course, contraindicated in children receiving treatment for leukaemia, but with less than 50% uptake of measles vaccine in this country a high proportion of children who develop leukaemia have not been immunised. We now recommend that all siblings, and if possible other close contacts of our patients who have not had measles or measles vaccination,

should be immunised in an attempt to prevent exposure to infection.

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¹ Chessells JM, Leiper AD. *Arch Dis Child* 1980; 55:118-23.

² Siegel SE, Nesbit ME, Baehner R, Sather H, Hammond D. *Am J Dis Child* 1980;134:28-34.

³ Ninane J, Chessells JM. *Arch Dis Child*. In Press.

⁴ Lipson A, Marshall WC, Hayward AR. *Arch Dis Child* 1977;52:314-9.

⁵ Rapson NT, Cornbleet MA, Chessells JM, Bennett AJ, Hardisty RM. *Br J Haematol* 1980;45:41-52.

* * * The American source cited in the leading article associated the recent increase in the incidence of pneumonia in children with the recent use of intrathecal methotrexate and intensified chemotherapy—Ed, *BMJ*.

Granulocytopenia and infections

SIR,—The passion for supplying granulocytes (leading article, 25 October, p 1091) and for using newer antibiotic regimens (leading article, 8 November, p 1235) in patients who are susceptible to infection should be tempered by the realisation that inadequate defences can be bolstered by provision of specific antibody.

This has been done quite successfully by the use of pneumococcal vaccine and by the use of pseudomonas LPS vaccine. In the case of pseudomonas infections Pollack and Young¹ showed that antibodies to the exotoxin A and to lipid-A provide good protection even in patients who are granulocytopenic, and there is much supporting evidence.^{2,3} Protection against all Gram-negative infections (and in addition against meningococcus) would be so much more effective if we organised ourselves so as to provide antilipid A antibody⁴ or knew which vaccine would effectively do this.

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¹ Pollack M, Young LS. *J Clin Invest* 1979;63:276-86.

² Kazmierowski J, et al. *J Infect Dis* 1977;135:438-46.

³ Pennington JE, Kuchmy D. *J Infect Dis* 1980;142:191-8.

⁴ Wardle EN. *J Clin Path* 1980;33:888.

Perinatal and neonatal mortality

SIR,—Renee Short said of her recent report,¹ "GPs will not like it, but it's lives that count." She is only partly correct; many GPs will not like it because it's lives that count.

The hypothesis of the working party is that general practitioner obstetrics, other than in units physically attached to consultant units, is unsafe. For this hypothesis no evidence is produced; instead, incomplete evidence to support the opposite conclusion is reported. A number of studies in different parts of the country from GP maternity units, both peripheral and attached, consistently show a perinatal mortality of about one-third of that of consultant units. This is claimed in Mrs Short's report to be due solely to selection of low-risk cases. This is, however, only one more conjecture. To our knowledge, there has been no comparative evaluation of the welfare of a matched group in a consultant unit. In our own peripheral GP maternity unit there has been one only possibly avoidable perinatal death in the last six years, and 2851 deliveries—and these figures include those women

transferred to a consultant unit in labour. In our opinion, there is good reason to believe that selected patients fare better in GP units than in consultant maternity units; for them the latter may be dangerous.

Mrs Short is correct in her assertion that it is lives that count, but her conclusions are not based on evidence, and may therefore be wrong. Let us not arbitrarily close (peripheral) GP maternity units without proper evidence that this is a wise course of action.

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¹ Social Services Committee. *Perinatal and neonatal mortality*. Second report from the Social Services Committee 1979-80. London: HMSO, 1980.

Site of action of intrathecal morphine

SIR,—May I further comment on Dr J Selwyn Crawford's response (25 October, p 1144) to my previous letter (27 September, p 870)?

It has been demonstrated that opiate receptors exist in the spinal cord¹; that opiates introduced intrathecally bind to these receptors; and that, related to this event, analgesia free from the other systemic and cerebral effects of opiates is apparent. Furthermore this can be antagonised by intrathecal naloxone in a dose-dependent fashion.² I trust that this conforms with Dr Crawford's interpretation of "classical 'opiate' activity."

The use of intrathecal³ and extradural opiates⁴ in humans has been promising and emphasises the possible relevance of the spinal action of opiates. Furthermore, the observation that intravenous naloxone reverses respiratory depression but not analgesia associated with the administration of intrathecal morphine is another indication of the possible spinal analgesic action.⁵

It has indeed been demonstrated that the human placenta contains two β -endorphin-like peptides which differ in size from the classical pituitary-derived hormone.⁶ In the same paper⁶ (cited by Dr Crawford), it is mentioned that extracts of liver, lung, thymus, spleen, and kidney were shown to be devoid of β -endorphin activity. Naturally occurring substances with opiate activity are found mainly in the central nervous system (CNS) and gastrointestinal tract.⁷ Thus Dr Crawford's suggestion that specific receptors for narcotics may be scattered throughout the body appears unfounded in the light of the evidence available.^{8,9}

Naturally occurring opiates may serve as neurotransmitters or modulator substances.⁸ They are capable of producing analgesia. There appear to be multiple opiate receptors in the CNS and gastrointestinal tract with differing characteristics,⁹ and evidence has recently become available that opiate analgesia is mediated by a subpopulation of opiate receptors.¹⁰ Hence a pattern appears to be emerging with respect to receptor distribution and opiate function which is at variance with Dr Crawford's suggestion that "endorphins may be analogous to prostaglandins."

The laboratory evidence for a selective spinal

analgesic action for opiates is strong. The clinical results, while not absolutely conclusive, grow steadily more convincing as further information becomes available. The onus remains with us—that is, with clinicians and clinical investigators—to unravel the remaining uncertainties concerning these substances when used in human subjects.

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- ¹ Pert CB, Kuhar MJ, Snyder SH. *Proc Natl Acad Sci USA* 1976;73:3729-33.
- ² Yaksh TL, Rudy TA. *Science* 1976;192:1357-8.
- ³ Wang JK, Nauss LA, Thomas JE. *Anesthesiology* 1979;50:149-51.
- ⁴ Cousins MJ, Mather LE, Glynn CJ, Wilson PR, Graham JR. *Lancet* 1979;i:1141.
- ⁵ Jones RDM, Jones JG. *Br Med J* 1980;281:645-6.
- ⁶ Houck JC, Kimball C, Chang C, Pedigo NW, Yamamura NI. *Science* 1980;207:78-9.
- ⁷ Snyder SH. *Sci Am* 1977;236:44-56.
- ⁸ Chang K-J, Cuatrecasas P. *J Biol Chem* 1979;254:2610.
- ⁹ Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. *J Pharmacol Exp Ther* 1976;197:517.
- ¹⁰ Pasternak GW, Childers SR, Snyder SH. *Science* 1980;208:514-6.

Cimetidine and ranitidine in duodenal ulcer

SIR,—Dr Janet D Elashoff (8 November, p 1284) suggests that our conclusion that ranitidine and cimetidine give equivalent results in duodenal ulcer¹ is unjustified. She bases her claim on a statistical analysis of data carried out at a single fixed point, after four weeks' treatment, and by doing so she ignores the information accumulated during the rest of the trial. Ultimately all except one (95%) of the cimetidine-treated patients' ulcers healed and all except two (89%) of the ranitidine-treated patients', and these two failed to respond to cimetidine. Furthermore, we know that the only material difference between cimetidine and ranitidine is in potency rather than in method of action. Since in terms of ability to suppress acid secretion they were being given in roughly equipotent doses, it would have been surprising if equivalent results were not obtained.

Dr Elashoff refers in her letter to a recent article of hers which emphasises the very large size of patient groups needed if distinctions are to be made between drugs.² However, in that same article she and her co-author say: "This would require large multicentre trials that are difficult to administer. . . . The advisability of such a massive undertaking early on in the evaluation of a new drug is debatable."

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- ¹ Langman MJS, Henry DA, Bell GD, Burnham WR, Ogilvy A. *Br Med J* 1980;281:473-4.
- ² Peterson WL, Elashoff JD. *Gastroenterology* 1980;79:585-8.

Palpable spleen and bleeding oesophageal varices

SIR,—Following the report last year by Dr J Bull and others (24 November 1979, p 1328) on upper gastrointestinal haemorrhage in patients with known oesophageal varices, a retrospective study was carried out to test the author's conclusion that the absence of a palpable spleen makes it unlikely that the bleeding is from varices.

Endoscopy was performed on 16 patients presenting to the University Hospital of Wales with known oesophageal varices and upper gastrointestinal haemorrhage. Fourteen had cirrhosis (nine alcoholic, three primary biliary, and two cryptogenic) and two had portal vein obstruction. Out of the 16, 12 had bled from their varices and only seven of these had palpable spleens. The other four patients had bled from another source (two from peptic ulceration and two from erosions) and two of these had palpable spleens. There was no significant difference in age, results of liver function tests, or clotting screens between the two groups.

This study shows that reliance on the presence or absence of a palpable spleen to determine the source of haemorrhage would have resulted in erroneous management in seven out of the 16 cases—that is, greater than 40%. This unfortunately means that all patients with oesophageal varices who are bleeding should have a definitive investigation in the form of endoscopy or barium studies so that the source of haemorrhage can be accurately identified and correct therapy therefore established.

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Neurological Examination in Clinical Practice

SIR,—In your 15 November issue (p 1342), you published an excellent review by Dr E M Critchley of our book by Dr Edwin Bickerstaff, *Neurological Examination in Clinical Practice* (4th ed). It contains one misleading comment, in that he compares the £18.00 price of the fourth edition with the £2.50 price of the "paperback third edition." The only paperback version was that which we produced for the Government-subsidised ELBS scheme for sale in various Third World countries. The only version of the third edition generally available was the hardback, which rose in price from £6.00 on publication in 1972 to £9.50 with the last reprint in 1978.

Since such an apparently enormous leap in the price is bound to have an adverse effect on sales, I should be most grateful if you could either publish this letter or some suitable correction.

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Statistics in medical research

SIR,—The least enjoyable part of a research project is often the struggle to calculate a *t* value in order to state with confidence the difference between two sets of figures whose means are clearly miles apart, $p < 0.05$, or to try to fit recalcitrant numbers into some analysis which will confirm what one knows in one's bones to be true. Insult is added to injury when in the *BMJ* of 8 November, which incidentally is carrying an instalment of the series "Statistics and Ethics in Medical Research," the first paper (p 1237), after using χ^2 statistics, contains the statement "Neonatal mortality was higher (though not significantly so) in infants born at King's Mill Hospital than in those born at University College Hospital, London." The second paper (p 1241) uses the Kolmogorov Smirnov test, analysis

of variance, F tests, and Spearman's test for coefficient of correlation (non-parametric). After all that, it concludes, "Chlorthalidone produced a decrease in blood pressure that was not statistically significant" and "Plasma renin activity rose with chlorthalidone and decreased with atenolol though this was not statistically significant." The third paper (p 1243) breaks the pattern, perhaps because it comes from an epidemiology unit.

If we are to be allowed to ignore statistics after we have gone through the laborious task of calculating them, could we not skip them altogether?

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Occupational hazards of anaesthesia

SIR,—The recent review by Professor M P Vessey and Dr J F Nunn of occupational hazards of anaesthesia (13 September, p 696) provides a thoughtful and balanced analysis.

We would like to elaborate, however, on certain methodological objections raised by the reviewers relevant to the referenced dental study to which they refer.¹ To our mind, availability of a group of non-anaesthetic users among dentists and dental assistants using anaesthetics provided a unique study opportunity for comparing groups exposed with groups unexposed to such agents. Although certain age differences were subsequently noted between groups, the age distributions were completely overlapping, and several statistical approaches were used to adjust for the differences found. Furthermore, other possible differences in the exposed and unexposed groups were studied concerning geographic distribution, mercury use, smoking habit, overall response rates, response to individual mailings, and so forth. Statistical analyses were carried out to ensure that these variables could not be responsible for the apparent differences between the two groups. Although there may be a hidden explanatory factor other than exposure, no such indication is known to us or suggested by the data.

On another point, we agree with the reviewers that a response rate less than 100% is "disappointing"; however, return rates of 74-78% in large-scale surveys are realistic and as high as can be achieved without exorbitant cost. Bias is, of course, always a serious concern in terms of experimental design and in responder response. We took great pains to distinguish early responders from late and to attempt to measure the differential changes in endpoint rates among the subgroups. Our analyses suggested differential trends but in the direction of minimising rather than exaggerating the differences seen. It remains possible that non-responder bias entered our study despite strong efforts to minimise it, but we can find no evidence for such in our data. It is of interest that the original postcard survey represented participation in a routine effort by the American Dental Association to update its membership file and had no health assessment objectives. A single question asked whether or not the dentist used inhalation anaesthetics in his practice.

Finally, we concur with Professor Vessey and Dr Nunn in their conclusions that sufficient evidence exists to warrant continued efforts to reduce anaesthetic contamination in