matters to the professional competence of caring and concerned doctors.

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1 Dyer C. Rheumatologist convicted of attempted murder. *BMJ* 1992;305:731. (26 September.)

EDITOR,—It would be impossible to produce a satisfactory law allowing euthanasia: experience of the abortion law should have convinced most objective people that this is the case. Abortion law is suffering wholesale abuse, despite the safeguards written in that depend on the integrity of doctors and the supervisory responsibility thought to reside in the General Medical Council, BMA, and law enforcement agencies. Though aware of the situation, parliament—the author of the act—has not allowed amendments to be made that would correct matters.

This taken together with information coming from the Netherlands shows that we dare not permit legislation on euthanasia. Unfortunately, powerful pressure groups have perfected techniques to take our society into things that as a whole it does not approve of.

Richard Smith's editorial is a standard gambit.¹ I think it was David Owen who, in a moment of candour, admitted that royal commissions can be set up to produce the result wanted by those who set them up. This would be followed by a private member's bill (with government help, probably) with specious promises of proper safeguards, which would be passed, implemented, and put into practice with benign "Nelsonian" supervisory neglect, tranquillity being marred only when some troubled person protested about a specific case that could not be hushed up.

In view of Smith's revelations that a group that met at Leeds Castle was determined to circumvent "moral" opponents,² we should not be deluded into thinking that any debate that takes place in journals like the *BMJ* is free of management. This aspect of so called press freedom—complete freedom of action for editors—is perhaps more worrying than the antics of the editors of the tabloid press persecuting erring public figures.

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1 Smith R. Euthanasia: time for a royal commission. *BMJ* 1992;305:728-9. (26 September.)

2 Smith R. Promoting sexual health. *BMJ* 1992;305:70-1. (11 July.)

EDITOR,—The case of Dr Nigel Cox is a sad indication of the failure of transmission of accurate information on pain relief. Apparently the patient was considered no longer able to "absorb the amounts of diamorphine that Dr Cox was giving her"—up to 50 mg an hour.¹ That amazed me. I was working in a hospice 12 years ago, and I remember that, even then, a young woman with an inoperable carcinoma was stabilised on 500 mg diamorphine orally ever three hours, and on that dose she was able to go home and care for her baby. She was completely pain free and had a reasonable quality of life for several months.

Nowadays we tend to use oral morphine instead of oral diamorphine, and the equivalent dose would be 750 mg every three hours. Any amount of diamorphine can be used in a syringe pump as diamorphine is extremely soluble in a tiny volume of fluid. Patients should receive the amount needed to control their pain, and there is no ceiling. This simply is not appreciated by most medical and nursing staff. If patients' pain is properly treated the dose received will not impair their respiration and certainly will not kill them. This patient was receiving a totally inadequate amount, in my view.

Another misapprehension is that treating pain effectively always shortens life. Paradoxically, if pain is adequately relieved the quality of life is so much better than patients often live longer. Many doctors do not seem to realise that morphine can be used just as effectively for symptoms of chronic degenerative conditions and for the intractable dyspnoea of terminal heart failure or chronic respiratory disease as for cancer.

Why should patients in hospices be the only ones to have their symptoms relieved effectively? In the case of frail elderly people, tiny doses such as 1-2 mg every four hours may be adequate.

I think it would be a tragedy if euthanasia was legalised, and a total abrogation of our responsibility to care for patients with chronic sickness and terminal disease. Elderly people and those with chronic sickness already feel threatened by the reversion of responsibility for their care from health authorities to local authorities next year, which is a complete reversal of the National Health Service Act of 1948. They would feel even more threatened if they thought that doctors had the power legally to terminate their existence at any time that they wished. Our duty is to care to the end and not to duck out of the challenge of chronic suffering and pain. It will be expensive in terms of time, money, and compassion, but ultimately it is the only truly compassionate way.

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Propofol infusion in children

EDITOR,—I wish to correct inaccuracies in T J Parke and colleagues' paper and to comment on their conclusions.¹

Two of the cases—cases 4 and 5—were treated in the intensive care unit in which I work. The patient in case 4 received propofol for a total of 64 hours and died almost three days after the infusion was stopped, a fact not emphasised in the report. In case 5, at the time of his acute deterioration the patient had all the features of septicaemia with a core temperature up to 41°C and a core-periphery deficit of 14°C. He showed considerable vasoconstriction, had rigors, and was developing early renal failure with oliguria, granular cast formation, and rising blood urea concentrations. His acute deterioration occurred in relation to the intravenous injection of the first dose of ceftazidime.

These deaths were reported to the Committee on Safety of Medicines, and we decided to look formally at the metabolic effects of propofol infusion in children. This was organised jointly by the intensive therapy unit and the university department of paediatrics under Professor Aynsley-Green. Ethical committee approval was given for such a study. We have now looked at several children and can find no evidence of a direct effect of propofol or its vehicle on any aspect of metabolism in these patients. Details of the study are being prepared for publication.

Since Parke and colleagues' paper was published our hospital's solicitor has advised us that we cannot continue to use propofol in this way without fully documented informed consent, which will now be difficult to obtain. We do not know whether propofol played a part in the reported deaths, but it will now be almost impossible to establish. The inaccuracies in the reports of two of the cases lead me to wonder if there are similar inaccuracies in the other cases. If propofol was implicated, all of the studies in adults and our studies in children suggest that this is a rare idiosyncratic reaction. It is a sad day when our use and assessment of drugs (both their value and their adverse effects, if any) is

governed by events such as these. This report has brought forward the time when we must practise medicine in a transatlantic manner, with use of agents being controlled by fear of litigation and not by scientific investigation.

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1 Parke TJ, Stevens JE, Rice ASC, Greenaway CL, Bray RJ, Smith PJ, *et al.* Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992;305: 613-6. (12 September.)

EDITOR,—T J Parke and colleagues' paper and the ensuing coverage in the lay media have led to confusion regarding the use of propofol in children.¹ In the United Kingdom propofol is licensed for anaesthesia in adults and in children aged over 3 and has been used extensively in such cases. It is also licensed for the sedation of ventilated adult patients requiring intensive care, for up to three days. This indication was approved in the United Kingdom in 1991 as our clinical programme with propofol continued and the range of indications was extended. Experience in these licensed indications has not raised similar concerns to those that Parke and colleagues report.

Propofol is not licensed for sedation of children receiving intensive care, and the cases reported by Parke and colleagues are clearly of concern. Though no causative association between the adverse events and propofol was established, we wish to draw attention to our earlier communications to the medical profession.^{2,3} We agree with Parke and colleagues' conclusion that "until further data delineating the appropriate dose range are available, propofol should not be used in paediatric intensive care."

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EDITOR,—T J Parke and colleagues suggest that the new intravenous anaesthetic agent propofol should not be used for sedation in paediatric intensive care.¹ This drug is licensed for induction and maintenance of anaesthesia in adults and children over the age of 3 and for sedation of ventilated adults receiving intensive care. It is not clear from their paper whether or not Parke and colleagues were using the drug with a clinical trial exemption certificate. The manufacturers have repeatedly informed the medical profession of the age limitation.

The authors report that lipaemic serum was observed after three or more days of propofol infusion in all five children who died. Our recent work and that of others has shown that even induction doses of propofol (2.5 mg/kg) are associated with appreciable adrenocortical depression.^{2,3} This cortisol suppression is likely to be more important when infusions of propofol are used for sedation in intensive care as the provoking stimulus of surgical trauma is absent. We speculate that cortisol depression induced by propofol may be a mechanism for the development of lipaemic serum as the normal cortisol stress response would increase lipolysis and oxidation of fat. The clinical manifestations of these underlying biochemical abnormalities are more evident in children than

adults because a relatively greater mass of drug per unit time is involved.⁵

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- 1 Parke TJ, Stevens JE, Rice A, Greenaway CL, Bray R, Smith PJ, et al. Metabolic acidosis and fatal myocardial failure after propofol infusion in children: five case reports. *BMJ* 1992;305: 613-6. (12 September.)
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EDITOR,—Prompted by T J Parke and colleagues' report describing five deaths in children in intensive care units who were sedated with propofol¹ we report our findings in a similar case, in which the outcome was favourable.

A 20 month old girl (weight 12 kg) was admitted with stridor. She was exhausted with tachypnoea and fever (39.5°C). Laryngoscopy under oxygen and halothane anaesthesia confirmed acute epiglottitis. She was intubated and sedated with chloral hydrate (400 mg four hourly down her nasogastric tube) and a propofol infusion (5-10 mg/kg/h). Ampicillin and chloramphenicol were started, and she was admitted to the intensive care unit. Chloral hydrate was stopped on day 3. The propofol infusion continued for a total of 56 hours (4980 mg total dose).

On day 3 her serum was lipaemic and she developed a metabolic acidosis (base excess -9 mmol/l). She became bradycardiac, hypotensive, and oliguric. A cranial computed tomogram and results of examination of cerebrospinal fluid were normal. Her urine was dark, and her haemoglobin concentration dropped by 40 g/l to 89 g/l over six hours. An asystolic arrest was reversed with adrenaline and dobutamine, but despite infusions of adrenaline (0.5 µg/kg/min) and calcium the bradycardia persisted. Her pupils were fixed and dilated, and because of volume overload bicarbonate infusion alone was unable to control the metabolic acidosis (base excess -17 mmol/l). Venovenous haemodiafiltration (Amikon 20 filter; blood flow 75 ml/min; dialysate flow 200 ml/h; filtrate removal 400 ml/h) was started, which allowed the 1.4% bicarbonate infusion to be increased to 200 ml/h.

Her temperature returned to normal within two hours of her starting haemodiafiltration, but bradycardia persisted for 24 hours. Her systolic blood pressure improved from 50 to 90 mm Hg overnight, and her pupils began to react by the morning of day 4. Further investigation showed a plasma lactate concentration of 2.65 mmol/l (normal 0.63-2.44), calcium 1.64 mmol/l, phosphate 2.85 mmol/l, bilirubin 38 µmol/l, serum aspartate aminotransferase 3080 U/l (5-40), and creatine phosphokinase >100 000 U/l (<170). Cardiac and abdominal ultrasound examination yielded normal results, and blood cultures were negative.

Adrenaline infusion was stopped on day 5, and she began to pass urine. By day 6 she had improved further clinically, but creatine phosphokinase remained high (74 000 U/l) and myoglobinuria persisted. Haemodiafiltration was stopped for a short while, but soon she became feverish, acidotic (lactate concentration normal), and oliguric. She developed fixed dilated pupils and for the first time had a generalised convulsion. Haemodiafiltration was restarted, and her pupils were again reactive within three hours.

On day 13 (creatinine phosphokinase 10 300 U/l) plasma carnitine concentration was normal and a muscle biopsy specimen was taken from her lateral quadriceps. This showed focal necrosis with basophilic fibres and histiocytes. The size of the muscle fibres was normal, and there was no evidence of a dystrophy or neurogenic atrophy. Histochemical examination showed normal phosphorylase, glycogen, and fat stains. Electron microscopy showed foci of necrosis with some large mitochondria and distorted cristae. Creatine phosphokinase had fallen to 3600 U/l by day 15 but again rose (to 6260 U/l) on day 16 in association with metabolic acidosis, leucocytosis, hypotension, and candidaemia, which was treated with amphotericin.

From day 17 her condition steadily improved. On day 21 she underwent general anaesthesia for insertion of a peritoneal dialysis cannula, and on day 28 she received propofol for induction of anaesthesia for insertion of a tracheostomy tube. Neither procedure was associated within an untoward event. Haemodiafiltration was continued until day 26 and then replaced by peritoneal dialysis until day 44. She was discharged from the intensive care unit on day 46 and went home on day 54 with normal renal function. Follow up at six months showed no neurological deficit.

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EDITOR,—T J Parke and colleagues' paper demonstrates some of the pitfalls of extrapolating data on the safety and efficacy of drugs from adults to infants and children.¹ The failure of the pharmaceutical industry and clinicians to cooperate in the evaluation of drugs in children frequently leads to unlicensed use by clinicians seeking therapeutic benefits for their patients. The resulting case reports and small series showing a therapeutic effect^{2,3} are soon followed by reports of therapeutic misadventures, often with attendant publicity from the non-medical press.^{1,4} Although the precise background to reports of adverse reactions is often unclear and drug use may have been speculative, a new agent with potential therapeutic benefits may thus be condemned.

Much comment has been made recently on the status of infants and children as "therapeutic orphans."^{5,6} We believe that clinicians, pharmaceutical companies, and government agencies must collaborate to ensure that data on drug disposition in children are obtained where the potential for therapeutic benefit exists.

What of the use of propofol in paediatric intensive care? It currently stands condemned through lack of structured data on efficacy and safety. As with other recent reports of adverse sequelae associated with propofol infusion, the critically ill children in the series reported by Parke and colleagues seem to have received relatively high doses of propofol, with infusion rates approximating to twice the maximum rate recommended for sedation of adult patients receiving intensive care.

In a pilot study we gave propofol infusions to 20 children after cardiac surgery, in addition to intravenous morphine by infusion. The median propofol infusion rate required to sedate these children was 2.7 mg/kg/h, a much lower rate than that reported by Parke and colleagues. We were not aware of any adverse effects related to propofol infusion, although we limited the maximum infusion rate in our patients to 6 mg/kg/h. Further-

more, we have used propofol in 100 selected children after cardiac surgery without adverse effects, again limiting the maximum infusion rate as in our pilot study.

We believe that the potential therapeutic advantages of propofol to critically ill children ought to be evaluated rigorously and that enough data exist from several centres, including our own, to justify this. It would be regrettable if the initial reluctance of ICI to evaluate propofol in paediatric intensive care and the recent sporadic reports of problems during its uncontrolled use condemned a potentially valuable drug and reinforced the status of children as therapeutic orphans.

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AUTHOR'S REPLY,—All the cases that we reported occurred at last a year ago. Details of cases 1-3 were presented at the spring meeting of the Paediatric Intensive Care Society in March this year. The discussions that ensued yielded cases 4 and 5, and we were encouraged to publish the cases in a journal with a wide readership, as many children are cared for in adult intensive care units, which may not have been represented on this occasion. Though warning against the use of propofol infusions in children in intensive care units, the bulletins issued by the Committee on Safety of Medicines and ICI, which were triggered partly by these cases but also by many others, contained no clinical details; we thought that clinicians should be aware of the events behind the advice given.

The points identified by S Cook are debatable but do not alter the fact that children who should otherwise have done well deteriorated dramatically during propofol infusion and that this deterioration contributed to their death. The letter from K Barclay and colleagues, case reports sent to us since publication of our paper, and information from ICI on further similar reports worldwide enhance our view that there is an association between viral infections such as croup, high dose propofol infusion, and metabolic acidosis, which is neither rare nor idiosyncratic but real and often fatal. It may well be that lower dose infusions in combination with other sedative agents, as Duncan Macrae and Ian James suggest, are both safe and preferable to other regimens, but, until the appropriate uses of the drug are clear, uncontrolled use of propofol infusions should be avoided.

The question of how to ensure that drugs are fully evaluated in children, or, for that matter, adults, is difficult. A recent letter in the *Lancet* suggests that propofol or its lipid vehicle should be avoided in adults taking cyclosporin,¹ but evaluating every agent in all its likely clinical uses and in every disease before its release is surely impossible. Therefore anecdotal reporting of untoward occurrences will remain the only way of informing colleagues of concerns over drug safety, and if this should render it more difficult to conduct trials