At the time of Mrs Boyes's death the existence of paradoxical pain was recognised by only a few pain specialists. Consultants such as Dr Cox would certainly not have been expected to be aware of it. The choice presented to Dr Cox was stark: either to walk away from his patient and leave her to it or to do what he did. Mr Justice Ognall told Dr Cox that his choice was "a total betrayal of his unequivocal duty as a physician." Most doctors faced with this dilemma may consider that Dr Cox did his medical duty despite the risk to himself.

Mr Justice Devlin set out the rules for doctors in *R v Adams*. "The doctor is entitled to do all that is proper to relieve pain and suffering, even if the measures he takes incidentally shorten life," but "if the acts are intended to kill, and do in fact kill, . . . it is still murder." In practical terms doctors are allowed to assist death by giving large doses of morphine or heroin. But what if heroin, normally the strongest pain killing drug available, increases pain and there is no rationale for using other drugs? Paradoxical pain induced by heroin was not known in Devlin's time. Does his dictum need to be brought up to date?

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2 Morley JS, Miles JB, Wells JC, Bowsher D. Paradoxical pain. *Lancet* 1992;340:1045.

EDITOR,—The correspondence following the conviction of Dr Nigel Cox for attempted murder reflects the fact that suffering, including severe pain, is common in advanced disease, so that many doctors to some extent provide palliative care.¹ We suspect that the letters may also reflect the pain doctors feel when they are unable to help their patients.

We accept that not all patients in pain can be rendered pain free without drowsiness and that to suggest a specific combination of treatment that could serve as a universal panacea would be naive. We believe, however, that several important practical issues have not been covered.

The concept of "total pain" as proposed by Saunders is fundamental to the successful management of chronic pain,² yet the correspondents neglect the mental and social components of pain. Pain may be an expression of a need state³ and so may be at least as close to an emotion as to a sensation. Attempts to deal with it as a purely physical phenomenon are therefore likely to fail.

Even within the physical dimension, response to diamorphine and other opioids is often incomplete. Thus continuing pain does not necessarily imply an inadequate dose of opioids. We disagree with Lesley A M Willis's view that Lilian Boyes was "receiving a totally inadequate amount" of diamorphine.¹ Continuing severe pain despite up to 50 mg diamorphine an hour surely reflects pain that is not entirely responsive to opioids.

Like Will Tapsfield and Pat Amis,¹ we have found midazolam to be useful in controlling pain, although whether it treats physical aspects or mental aspects, or both, is unclear. Our aim is different from that of M Rosen,¹ who seems to suggest a technique of giving sedation until the patient develops a fatal bronchopneumonia. We would always aim to keep the patient comfortable but awake or at least easily aroused. To give more sedation than is necessary merely treats the staff's pain, and only in exceptional cases in which distress remains unrelieved after other expert advice has been sought would we consider aiming to achieve frank sedation.

When midazolam is used the intravenous route offers no advantages other than to achieve rapid

control when distress is acute and overwhelming. Although precise pharmacological data are not available, clinical evidence suggests that diamorphine and midazolam can be mixed in the same syringe and given by subcutaneous infusion with a syringe driver. This can be done with minimal supervision in the community as well as in hospital. We use an initial dose of 30 mg over 24 hours and then titrate according to response, the first reassessment being made within eight hours.

We hope that this broader view will help others to cope with severe pain and, perhaps, avoid another charge of attempted murder.

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1 Correspondence. Euthanasia. *BMJ* 1992;305:951-2. (17 October.)

2 Saunders C. The philosophy of terminal care. In: Saunders CM, ed. *The management of terminal disease*. London: Edward Arnold, 1978:193-202.

3 Wall PD. The pain and circumstance march. Pain in relation to behaviour. *Horizons in medicine* No 3. London: Royal College of Physicians, 1991:411-6.

EDITOR,—The experience of Dr Nigel Cox¹ and the publicity surrounding it can be turned to good effect if we learn the lessons that come out of it. Though an experienced rheumatologist, Dr Cox was ignorant of the modern management of severe and intractable pain.² What this surely points to is the need for doctors of all grades, and perhaps especially consultants, to improve their therapeutic skills outside their own specialty.

Three steps toward improving pain relief and terminal care occur to me: firstly, these subjects should be emphasised more in undergraduate teaching; secondly, they should be included in a programme of mandatory refresher courses, as proposed recently by the Royal College of Physicians of Edinburgh³; and, thirdly, examples of poor terminal care should be given prominence, as in Alan Fenton's *Personal View*.⁴

I believe that in the future the reputation of our profession will hang more on how we care for those who are beyond cure than on all our brilliant successes.

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

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3 Royal College of Physicians of Edinburgh. *Continuing medical education for trained physicians*. Edinburgh: RCPE, 1992.

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Ecstasy and dantrolene

EDITOR,—The editorial by John A Henry and, more recently, an article by Henry and colleagues of the National Poisons Information Service advocate the use of dantrolene in the acute management of patients who experience severe complications after ecstasy misuse.^{1,2} Although the precise mechanism of this toxicity is not known, it is suggested that a combination of ecstasy and the circumstances in which the drug is taken is of primary importance, with direct effects on central thermoregulatory mechanisms causing a fulminant hyperthermia and heat stroke.

Dantrolene is a peripherally acting muscle relaxant with no central effects and is presumably advised because it may reduce thermogenesis associated with muscular activity and perhaps, because it contains mannitol, which may contribute towards diuresis. If this is the case then the administration of dantrolene is ill advised since a non-depolarising neuromuscular blocking agent (for example, atracurium by infusion) would

similarly reduce muscle thermogenesis while being cheaper, easier to administer, and easier to titrate. Diuretics can be given separately after rehydration. In addition, there is no real evidence of the efficacy of dantrolene in ecstasy toxicity. Among the cases of ecstasy misuse reported in the medical literature only two patients have received dantrolene, and only one patient has survived.^{3,4} Indeed the survivor had no evidence of renal or hepatic impairment or disseminated intravascular coagulation, and unfortunately concentrations of ecstasy were not documented. Experience shows that, in severe cases, biochemical and haematological variables are often abnormal on presentation; they rapidly deteriorate, and disseminated intravascular coagulation is most frequently associated with death—therefore this patient may well have survived with supportive measures alone.⁴ The patient reported to have died of ecstasy toxicity received a small dose of dantrolene (1 mg/kg); the timing of its administration was not stated, and death followed the now well described clinical scenario.¹

Dantrolene may prove to be efficacious in ecstasy toxicity, but unless an association with the neuroleptic malignant syndrome or malignant hyperpyrexia is seriously suspected, the current proposed mechanism of toxicity provides no logical reason to administer dantrolene rather than a non-depolarising neuromuscular blocking agent.

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1 Henry JA. Ecstasy and the dance of death. *BMJ* 1992;305:5-6. (4 July.)

2 Henry JA, Jeffreys KJ, Dawling S. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("ecstasy"). *Lancet* 1992;340:384-7.

3 Campkin NTA, Davies UM. Another death from ecstasy. *J R Soc Med* 1992;85:61.

4 Singarajah C, Davies NG. An overdose of ecstasy: a role for dantrolene. *Anaesthesia* 1992;47:686-7.

Confounding in epidemiological studies

EDITOR,—The clear presentation by George Davey Smith and Andrew N Phillips does not, however, provide credible support for their conclusion that "it is likely that many of the associations identified in epidemiological studies are due to confounding."¹ With a reasonable amount of scepticism and intelligence a hidden source of bias can be invoked in any epidemiological study. But empirical examples of suspected causal associations that have later been entirely attributed to a hidden confounding variable are rare. In the absence of empirical illustration of the practical importance of confounding bias it is possible to reverse their argument and say that "it is unlikely that many of the associations identified in epidemiological studies are due to confounding."

There is an omission in Smith and Phillips's paper that may explain why they were led to overemphasise the importance of confounding. Their argument does not take into consideration the magnitude of the bias that may result from unadjusted confounding. The size of the confounding effect varies with at least three factors: the strength of the relation between the confounders and outcome; the strength of the association between confounders and studied exposure; and the prevalence of the confounders in the studied population. Those elements must be taken into consideration when invoking a potential bias due to unadjusted confounding. It is unlikely that a strong confounding effect due to a factor highly related either to exposure or to disease, or frequent in the population compared to prevalence of the studied exposure, would remain undetected. It is also unlikely that a confounding bias would nullify

a large true association. In contrast, a weak confounding effect is hard to detect and can plague weak associations—that is, associations with relative risks smaller than 2.0. It can either produce spurious associations or mask true associations.

Therefore, the warning against confounding bias raised by Smith and Phillips applies really to the study of weak associations. It is certainly true that weak associations should be interpreted with caution because there is no certainty that all confounding effects have been neutralised. Nevertheless, as long as the menace of confounding bias remains a purely theoretical exercise, there is no ground to give more credit to sceptical debunking of a suspected relative risk rather than to a postulated biological mechanism supporting its plausibility.

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1 Smith GD, Phillips AN. Confounding in epidemiological studies: why "independent" effects may not be all they seem. *BMJ* 1992;305:757-9. (26 September.)

Distinguishing inhalers to aid blind people

EDITOR,—Martyn Partridge points out the confusion engendered by the colour of a new asthma inhaler.¹ Consideration should also be given to those who have partial or no sight and are therefore unable to distinguish any colour at all on their inhalers.

Drug manufacturers at present pay little regard to this problem. The Ventolin inhaler has a V embossed on its side to help distinguish it from Becotide. Pulmicort and Bricanyl Turbohalers can barely be distinguished by small concentric rings embossed at their bases (and how blind asthmatic patients may realise when the Turbohaler is empty is not apparent). Other inhaler "pairs," such as Ventidisks and Becodisks, Aerolin and Aerobec, Ventolin and Becotide Rotacaps, and Bricanyl and Pulmicort metered dose inhalers, seem to have no obvious distinguishing features for blind people at all. In addition, not all practitioners agree that inhalation devices that combine both a bronchodilator and a steroid are useful in managing asthma.

Practical solutions to this problem may be devised, such as wrapping an elastic band around one of the devices to distinguish it from the other, or keeping the inhalers in containers of different shapes. It would be more appropriate, however, if the Department of Health and drug manufacturers were to agree on a common standard solution, such as simple embossed symbols or Braille lettering.

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1 Partridge M. Coloured inhalers. *BMJ* 1992;305:890. (10 October.)

Changes in drug treatment after discharge from hospital

EDITOR,—Rachel Ann Cochrane and colleagues examine why 45 out of 50 patients had their drugs changed after discharge from hospital.¹ They do not, however, discuss the problems of general practitioners having a prescribing policy. For example, in my practice we use the loop diuretic frusemide with monitoring of the potassium con-

centrations. Patients are discharged from our local hospital taking frusemide, co-amilofruse, or bumetamide, depending on the consultant they have been under. As soon as they come out of hospital they go back on frusemide.

The authors say that patients are discharged with five days' supply of drugs. They do not report having studied how many days it takes for a general practitioner to get the full discharge report. This is necessary for the general practitioner to plan how to merge the patient's existing drug treatment with the new treatment from the hospital; a brief list on a form is not enough. The best way to prevent interruption to the patient's treatment is to make sure that the patient is discharged with enough days' treatment to last until the general practitioner has received the necessary information.

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1 Cochrane RA, Mandal AR, Ledger-Scott M, Walker R. Changes in drug treatment after discharge from hospital in geriatric patients. *BMJ* 1992;305:694-6. (19 September.)

Cholesterol lowering treatment and mortality

EDITOR,—U Ravnskov's paper shows again that reducing coronary mortality with cholesterol lowering treatment does not result in a reduction in total mortality despite the considerable proportionate mortality of coronary heart disease and the high statistical power of a meta-analysis of 22 trials.¹ Because death from coronary heart disease accounts for a large proportion of total mortality (36% on the average in the primary prevention studies, 77% in the secondary prevention studies) the failure to reduce total mortality may suggest a lack of any net benefit of cholesterol lowering treatment.

Total and coronary mortality has been published for 22 of the 27 trials listed in table 1 of Ravnskov's paper. This allows the calculation of the "non-infarct mortality" (mortality from causes other than coronary heart disease—that is, "all deaths" minus "fatal coronary heart disease"). The figure displays the odds ratios and 95% confidence intervals of these 22 trials. The mean weighted odds ratio for all trials shows a significant increase in the non-infarct mortality (odds ratio=1.09 (95% confidence interval 1.02 to 1.17); $p=0.007$); this increase is even more significant in a separate analysis of only the trials that used drugs (odds ratio=1.27 (1.20 to 1.35); $p=0.00009$). The overall increase in non-infarct mortality seems to

be the result of drug treatment alone as it is not observable in the studies that used diet (figure).

Table 1 shows a striking consistency in this increase in non-infarct mortality in all subgroups of the drug trials. Trials that used modern drugs as well as those that used obsolete drugs show this highly significant adverse increase in non-infarct mortality. The increase in non-infarct mortality

Odds ratios and 95% confidence intervals (logit method) for mortality other than that from coronary heart disease (non-infarct mortality) in all trials, grouped into drug and diet trials, and mean weighted odds ratios (Mantel-Haenszel method)

*Confidence intervals and p value approximate (χ^2 test for number of events < 5)

CDP=Coronary drug project. MRFIT=Multiple risk factor intervention trial

TABLE 1—Mortality from causes other than coronary heart disease (non-infarct mortality). Mean weighted odds ratios and confidence intervals* in all trials and subgroups of trials

	No	Odds ratios (95% confidence interval)	p Value
All trials	22	1.09 (1.02 to 1.17)	0.007
Unifactorial	18	1.19 (1.13 to 1.24)	<0.001
Multifactorial	4	1.02 (0.97 to 1.08)	>0.5
Primary prevention	12	1.07 (1.00 to 1.14)	0.08
Unifactorial only	8	1.18 (1.03 to 1.35)	0.017
Drugs only	5	1.42 (1.13 to 1.78)	0.003
Secondary prevention	10	1.20 (1.04 to 1.38)	0.012
Drugs only	8	1.22 (1.06 to 1.41)	0.006
Drugs	13	1.27 (1.20 to 1.35)	<0.001
Modern drugs only†	8	1.26 (1.09 to 1.45)	0.002
Excluding nicotinic acid	6	1.35 (1.14 to 1.61)	<0.001
Obsolete drugs only†	5	1.31 (1.06 to 1.63)	0.014
Primary prevention only	5	1.42 (1.13 to 1.78)	0.003
Secondary prevention only	8	1.22 (1.06 to 1.41)	0.006
Diet	8	1.03 (0.96 to 1.10)	0.5
Duration ≤ 5 years	15	1.17 (1.02 to 1.33)	0.022
Drugs only	9	1.30 (1.08 to 1.57)	0.006
Duration > 5 years	7	1.07 (0.99 to 1.16)	0.07
Drugs only	4	1.25 (1.07 to 1.47)	0.005

*Mantel-Haenszel method. Test for heterogeneity: $p \geq 0.08$ for all analyses.

†Modern drugs: clofibrate, anion exchange resins, nicotinic acid, gemfibrozil. Obsolete drugs: oestrogen, dextrothyroxine.