Letters

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When doctors might kill their patients

Palliative care physicians always have their patients' best interests in mind

EDITOR—Gillon's editorial arising from the trial of Dr David Moor showed clear (and therefore forceful) analytical logic,[1] but I found Doyal's contribution on the same topic was disturbing because it partly missed the point.[2] Broadly speaking, the principle of double effect states that if measures taken to relieve physical or mental suffering cause the death of a patient it is morally and legally acceptable provided the doctor's intention is to relieve the distress and not to kill the patient. This is a universal principle without which the practice of medicine would be impossible. It follows inevitably from the fact that all treatment has inherent risks.

Discussions of the principle of double effect tend to focus on the care of terminally ill patients and the use of morphine to relieve pain. Regrettably, this gives the false impression that the use of morphine in this circumstance is a high risk strategy. When correctly used, morphine and other strong opioids are safe–safer than non-steroidal anti-inflammatory drugs, which are prescribed with impunity. The use of both classes of analgesic is justified on the basis that the benefits of pain relief far outweigh the risk of serious adverse effects. Indeed, clinical experience suggests that patients with cancer whose pain is relieved live longer than would have been the case if they had continued to be exhausted and demoralised by unremitting severe pain.

Most people accept that a greater risk is acceptable in more extreme circumstances. It is axiomatic, however, that effective measures that carry the least risk to life will be used. Thus although it may occasionally be necessary (and acceptable) to render a patient unconscious, it remains unacceptable (and unnecessary) to cause death deliberately.

In some quarters it is repeatedly stated that the principle of double effect is hypocritical and a smokescreen for euthanasia. Such views stem from failure to appreciate that double effect is a universal principle and the false belief that morphine usually shortens the life of a dying patient. Misleading statements that stem from such misunderstandings include "hospice doctors often kill their patients," when in practice specialist palliative care services are effectively a "euthanasia-free zone."[3]

Limiting "helping patients to die peacefully" to physician assisted suicide and euthanasia is misleading; this is the essential task of all who work in palliative care. Even at the end of life the aim of treatment must remain the relief of suffering and not the patient's intentional death.

In making decisions, health professionals balance the benefits of the treatment against its foreseen burdens and risks. They will seek to find the right balance between maleficence and beneficence and thereby integrate our dual responsibility both to preserve life and to relieve suffering. In this way, Doyal's either/or becomes both/and–both the best interests of patients and the moral character of clinicians.

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1 Gillon R. Foreseeing is not necessarily the same as intending. *BMJ* 1999;318:1431-2. (29 May.)
2 Doyal L. The moral character of clinicians or the best interests of patients? *BMJ* 1999;318:1432-3. (29 May.)
3 Farsides B. Palliative care–a euthanasia-free zone? *J Med Ethics* 1998;24:149-50.

Concept of intent is being defined inconsistently by courts

EDITOR—Gillon's editorial inspired by the acquittal of Dr David Moor brings to mind a legal anomaly, evident since the courts have acknowledged the doctrine of double effect.[1] As Gillon rightly asserts, Dr Moor was acquitted because the jury found he did not intend to kill or cause really serious harm to his patients–he therefore lacked the mental element necessary to commit murder. To lawyers, however, the narrow definition given to the concept of intent in this case, and indeed other such cases, is perplexing.

In law, there is considerable overlap between notions of intent and foresight. For example, it is uncontroversial that if I do X to bring about Y, I will be said at law to intend Y–this is the idea of intent which most people are familiar with. There is strong legal authority, however, that a jury may also infer intent if death or really serious injury is a virtually certain consequence of the defendant's actions and the defendant realised that this was the case.[2,3] Although, as Gillon suggests, this may be philosophically unsatisfactory, were the law otherwise many genuine criminals would go unpunished.

Despite this accepted legal principle, when applying the idea of double effect the courts hold that intent may not be inferred in this way.[4] In other words, a practitioner indicted for conduct such as Dr Moor's will be tried according to different rules from anyone else who has come to the attention of the prosecuting authorities; the fundamental concept of intent is being defined inconsistently by the courts.

This legal inconsistency suggests to me that the current law is not adequately equipped to deal with issues posed by modern palliative medicine. Generally, the criminal law is at its most uncomfortable regulating conduct done in good faith. Certainly, the offence of murder with its mandatory life sentence and massive stigma will, in most cases, be a wholly unsuitable charge to bring against a caring professional acting with beneficence.

To do justice, law needs to be certain, expedient, and consistent; the currently anomalous situation is unsatisfactory. The law should therefore recognise the clinical realities of end of life decisions and stop hiding behind terminological inconsistency. Until the legislature or the superior courts are prepared to deal with the issue of euthanasia openly, we may see more legally half

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hearted but nevertheless distressing murder prosecutions brought against good doctors.

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2 R *v* Moloney [1985]1 All ER 1025.
3 R *v* Nedrick [1986] 3 All ER 1.
4 Re J [1990] 3 All ER 930.

Patients must never be left to suffer so that doctors "stay out of trouble"

EDITOR—Neither of the authors of the editorials on when doctors might kill their patients has addressed the central problem: deciding how much analgesia or other treatment is enough to resolve pain (or symptoms) and how little is likely to shorten a patient's life.[1 2] These can only be based on experience and judgment; certainly no trial will give us evidence based medicine to rely on in court.

I have given what I thought would be a final dose of diamorphine to a terminally ill patient and found him next day distressed more at the result of the Cup Final. I myself have suffered considerable pain despite the effects of frighteningly large doses of intravenous morphine. Who can write down clear instructions for a safe as well as an effective dose, applicable in every situation?

There are times when doctors have to be trusted to make such decisions in what they see as the best interests of their patients. To do this properly they must dare to risk being wrong, because anything less will mean doing too little. Perhaps Dr Moor paid the price for us all when the public checked up on his morality, and perhaps he called his trouble on himself a little by speaking out. But let us never leave patients to suffer in the cause of following guidelines whose principle is "stay out of trouble."

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Moral character of clinicians and best interests of patients cannot be separated

EDITOR—Doyal argues that the doctrine of double effect is part of "a code of ethics that places the moral integrity of the individual clinician above his duty when there may be conflict between them."[1] He would prefer to see emphasis placed on conformity to the "independent standards" of the "broader professional environment." Such a change would have the effect of removing the legal and moral responsibility that now rests with the individual doctor looking after a terminally ill patient and placing it, probably, in the hands of some kind of local consensus group basing its decisions on published clinical and legal guidelines.

The moral decision in individual cases cannot be avoided by the use of such criteria. Consequences are not the only ethically important aspects of actions. The law has always recognised the paramountcy of personal responsibility, and doctors who are not doctrinaire utilitarians would surely agree that this is also a vital moral consideration. Even if these procedural changes were introduced the distinction between foreseen and intended actions would have to be made. The effect would be not only to remove responsibility from the patient's personal physician but also, by making decisions impersonal and objective, to disguise and undermine their moral importance.

Doyal provides three hypothetical cases to illustrate possible problems with double effect. Two are rather puzzling choices in that they describe what would clearly be legally and morally unjustifiable management of patients who were not terminally ill. In the third example a physician decides to prolong a patient's life, even while agreeing that this is against his best interests, because she is unsure of the purity of her intent. This is indeed a problem, but the difficulty does not lie with the doctrine of double effect itself; it lies in the question of who takes responsibility. It is possible that a consensus group would be at least as likely to allow a patient to suffer unnecessarily as an individual who knows the patient.

Individuals' decisions will inevitably err on occasions, but to preserve what is arguably one of the most valuable things we can offer a terminally ill patient–a relationship with a caring and personally responsible physician–this is surely a price worth paying.

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Increased mortality from liver cancer in England and Wales is not related to hepatitis C

EDITOR—We were surprised to read the letter from Harris and colleagues disagreeing with our findings on mortality from liver cancer since their data and conclusions are similar to our own.[1 2] We are agreed that death rates in England and Wales from all causes of malignant tumours of the liver are increasing (ICD-9 (international classification of diseases, ninth revision) code 155) and that they are a poor indicator of previous infection with hepatitis C virus. We also pointed out that this ICD classification includes mortality data not only from hepatocellular carcinoma (ICD-9 155.0), which may be aetiologically related to hepatitis C virus, but also from intrahepatic cholangiocarcinoma (ICD-9 155.1) and primary and secondary tumours of uncertain aetiology (ICD-9 155.2),[3] where there is no proved link with hepatitis C infection.

We expected to find that the increase in mortality for all liver tumours during 1979-94[2] was accounted for by an increase in death rates from hepatocellular carcinoma, which in some southern European countries has been causally linked with pre-existing hepatitis C infection.[4] However, further analysis of data from the Office for National Statistics showed that age standardised mortality for hepatocellular carcinoma over this 15 year period remained relatively static,[2] unlike the case in France, Italy, and the United States.[4 5]

Instead, we found that age standardised mortality for tumours of the intrahepatic bile ducts (ICD-9 155.1) has increased in England and Wales over this period and seems to be largely responsible for the increase in mortality we observed for all liver tumours.[2] Whether this trend represents improved diagnosis and case ascertainment or a real increase in the incidence of bile duct cancers remains to be established. Further epidemiological studies are now required to determine the cause of the observed increase in mortality from cholangiocarcinomas.

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2 Taylor-Robinson SD, Foster GR, Arora S, Hargreaves S, Thomas HC. Increase in primary liver cancer in the UK 1979-94. *Lancet* 1997;350:1142-3.
3 World Health Organisation. *International classification of diseases. 1975 revision.* Vol 1. Geneva: WHO, 1977.
4 Nousbaum JB, Pol S, Nalpas B, Landais P, Berthelot P, Brechot C. Hepatitis C virus type Ib[11] infection in France and Italy. Collaborative study group. *Ann Intern Med* 1995;122:161-8.
5 El Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. *N Engl J Med* 1999;340:745-50.

Effectiveness of rivastigmine in Alzheimer's disease

Improvements in functional ability remain unestablished

EDITOR—Two recent reports on rivastigmine in Alzheimer's disease[1 2] provide further proof that cholinesterase inhibitors produce modest improvements in cognitive testing and in clinical impression of change. The new claim is of improved functionality with rivastigmine, which, if true, would be an important advance in the management of Alzheimer's disease.

Unfortunately, however, these studies do not establish that functional ability is improved. Both studies rated functionality using the progressive deterioration scale, which was developed to assess quality of life not activities of daily living.[3] It contains considerable duplication (for example, four

questions on handling finances), and only two items relate peripherally to the basic activities of dressing and eating. It cannot be concluded, therefore, that improved scores equate to improved functionality.

Moreover, Rösler et al misrepresent the small improvement in progressive deterioration score seen with rivastigmine (2.8 on a 100 point scale) by citing in the discussion that one third of patients taking higher dose rivastigmine attained at least a 10% improvement in score without noting that 20% of placebo patients also improved to this extent. The benefit was actually only 13% (33% *v* 20%), which is reduced to 10% (29% *v* 19%) on more appropriate intention to treat analysis.

The intention to treat analyses are also potentially biased because of non-random drop outs: 77 (32%) of 243 higher dose rivastigmine patients did not have a 26 week assessment compared with 31 (13%) of the 239 placebo patients. Alzheimer's disease is progressive and so replacing missing data by carrying forward values obtained earlier in the trial underestimates natural deterioration. No improvements in progressive deterioration score were seen in the lower dose rivastigmine group, which had the same drop out rate as the placebo group.

Thus it remains unclear whether cholinesterase inhibitors produce sufficient benefit in Alzheimer's disease to justify their widespread use. Clearly, any delays in progress to severe dependency or institutionalisation would be worth while both clinically and economically. Improved functionality, fewer neuropsychiatric symptoms, and reduced burden and stress on carers would also be important. But none of these has been reliably established for rivastigmine or donepezil. Longer term placebo controlled trials addressing these outcomes are urgently required.[4] One such study, the national AD2000 donepezil trial, has recently opened and already includes 150 patients. To resolve current uncertainties about the best use of cholinergic agents, widespread support—from clinicians and purchasers—for studies such as AD2000 should be encouraged.

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1 Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al on behalf of the B303 Exelon study group. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial [commentary by Bayer T]. *BMJ* 1999;318:633-9. (6 March.)
2 Corey-Bloom J, Anand R, Veach J for the ENA 713 B352 Study. A randomised trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Ger Psychopharmacol* 1998;1: 55-65.
3 DeJong R, Osterlund OW, Roy GE. Measurement of quality of life changes in patients with Alzheimer's disease. *Clin Ther 1989*;11:545-54.
4 Stein K. *Rivastigmine (ExelonTM) in the treatment of senile dementia of the Alzheimer type (SDAT).* Bristol:NHS Executive South and West; 1998. (Development and evaluation committee report No 89.)

Authors' reply

Editor—We agree with Sellwood et al on the need for longer term trials (≥2 years) to assess economic and disease specific outcomes. However, such trials cannot be performed until efficacy is proved in six month studies and can be performed only once the drug is registered.

It should be noted that items in the progressive deterioration scale are based on a comprehensive evaluation of activities performed in day to day life by patients with Alzheimer's disease and were selected following input from carers[1]: those who deal with patients on a day to day basis and best know their activities. Therefore the scale meaningfully reflects patients' functional ability. Although some items seem to cover similar activities, this was done deliberately as an internal cross check to ensure the validity of information provided by the carer.

Our data show clearly that the functional ability of patients treated with rivastigmine improves over six months. Also, significantly more patients treated with rivastigmine experience a highly clinically relevant improvement in activities of daily living (≥10% improvement on the progressive deterioration scale) compared with placebo. In comparison, clinical studies have shown that untreated patients worsen consistently.[2 3] Although the change reported in our study may not seem large, any stabilisation or reduction in loss of functional ability results in important clinical benefits in this progressive and debilitating disease. Furthermore, in a pooled analysis of phase III studies with rivastigmine, clinically and statistically significant improvement was noted for 22 of these items compared with placebo.[4]

We agree that an intention to treat analysis is not appropriate for a disease characterised by progressive worsening. Indeed, an observed case analysis also showed significant clinical benefits for rivastigmine (29% *v* 18% for placebo; P = 0.012).

Finally, Sellwood et al will be pleased to note that a placebo controlled study with a duration of treatment and follow up of three years is under way to examine the delay to diagnosis of Alzheimer's disease with rivastigmine in an at-risk patient population. In addition to cognitive, behavioural, and pharmacoeconomic measures, this trial (which includes 900 subjects from 12 countries) will examine the effect of rivastigmine on reducing the rate of brain atrophy using quantitative magnetic resonance imaging.

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Competing interests: Four of the authors of the paper are employed by Novartis.

1 DeJong R, Osterlund OW, Roy GW. Measurement of quality of life changes in patients with Alzheimer's disease. *Clin Ther* 1989;11:545–54.
2 Knapp MJ, Knopman DS, Solomon PR Pendlebury WW, Davis CS, Gracon SI. A 30-week randomised controlled trial of high-does tacrine in patients with Alzheimer's disease. *JAMA* 1994; 271:985–91.
3 Corey-Bloom J, Anand R, Veach J for the ENA 713 B352 Study. A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. *Int J Geriatr Psychopharmacol* 1998;1:55–65.
4 Schneider LS, Anand R, Farlow MR. Systematic review of the efficacy of rivastigmine for patients with Alzheimer's disease. *Int J Geriatr Psychopharmacol* 1998;1(suppl 1):S26–34.

Patients' view on quality of life should be assessed

Editor—In commenting on the recent paper showing efficacy and safety of rivastigmine in patients with Alzheimer's disease,[1] Flicker refers to a modest improvement in carer rated quality of life.[2] There is no consensus, however, on how to assess quality of life in dementia and no quality of life instrument used in clinical trials to date has been satisfactory.[3] The progressive deterioration scale, which was used in this trial, is regarded as a measure of functional ability (activities of daily living) and not quality of life. Patients with mild to moderate dementia are, however, able to describe and rate their quality of life, and their views on treatment should be taken into consideration.

In a study of patients starting on adjunctive antiepileptic drugs we found that side effects and adverse events were important indicators of quality of life. Indeed, some patients who became completely free of seizures opted to stop taking the adjunctive drugs because of unwanted side effects, notably weight gain.[4] Without objective data we cannot know how patients with dementia would balance small improvements in cognition or activities of daily living against side effects such as nausea, vomiting, and diarrhoea. Similarly, we have few data to guide us on how changes in the various domains assessed in dementia trials relate to quality of life from the patients' perspective.

Assessment of quality of life in dementia is in its infancy and raises many technical and ethical issues. Several measures of patient self report have, nevertheless, been developed and are now becoming available. In future, clinical trials of antidementia drugs should incorporate measures of patient-reported quality of life alongside proxy measures.[5]

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1 Flicker L. Acetylcholinesterase inhibitors for Alzheimer's disease. *BMJ* 1999;318;615-6. (3 March.)
2 Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al on behalf of the B303 Exelon study group. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial [commentary by Bayer T]. *BMJ* 1999;318:633-9. (6 March.)
3 Selai C, Trimble MR. Assessing quality of life in dementia. *Aging and Mental Health* 1999;3:101-11.

4 Selai CE, Smith K, Trimble MR. Adjunctive therapy in epilepsy: a cost-effectiveness comparison of two AEDs. *Seizure* 1999;8:8-13.
5 Whitehouse PJ, Winblad B, Shostak D, Bhattacharjya A, Brod M, Brodaty H, et al. First international pharmacoeconomic conference on Alzheimer's Disease: report and summary. *Alzheimer Dis Assoc Disord* (in press). (http://dementia.ion.ucl.ac.uk/harmon/)

Guidelines do not ignore clinically relevant end points

EDITOR—In his commentary on the European rivastigmine study[1] Bayer states that the absence of measures of neuropsychiatric outcome and the burden on carers is unfortunate but that the choice of these end points was governed by requirements of regulatory authorities rather than the aim of measuring the real impact of the illness on the lives of patients and their families. He says that the need for clinically relevant outcome measures should now be better appreciated.

However, the European guideline on medicinal products in the treatment of Alzheimer's disease recommends that improvement of symptoms should be assessed in the following three domains: cognition, as measured by objective tests (cognitive end point); activities of daily living (functional end point); and overall clinical response, as reflected by global assessment (global end point).[2] Efficacy variables should be specified for each of the three domains. Two primary variables should be stipulated, one evaluating the cognitive end point and the other the clinical relevance of the improvement in cognition. The protocol should specify this second primary variable and to which domain (global, or preferably functional) it is related. Moreover, the instruments which measure burden on carers and activities of daily living should have been validated for Alzheimer's disease. The study should be designed to show significant differences in at least two of the primary variables. If this is achieved, then the overall benefit (response) should be assessed in individual patients, and the effect of treatment should be illustrated in terms of the proportion of patients who achieve a meaningful benefit (responders).

In our view these recommendations show that the emphasis of regulatory authorities is on clinically relevant end points, and the Committee for Proprietary Medicinal Products guideline stresses the need to develop these. Therefore, the statement that the choice of the outcomes in clinical drug trials in dementia was governed by the requirements of regulatory authorities is not justified.

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2 Committee for Proprietary Medicinal Products. *Note for guidance on medicinal products in the treatment of Alzheimer's disease (CPMP/EWP/553/95).* London: European Agency for Evaluation of Medicinal Products, 1995. (www.eudra.org/emea.html)

Screening and mortality from cervical cancer

Does screening really reduce mortality?

EDITOR—We were rather non-plussed to read that the conclusion of the paper by Quinn et al on screening for cervical cancer[1] is not supported by their data, and we wonder whether so called political correctness had anything to do with it. The statement "800 deaths might have been prevented in 1997" is based on a projected mortality of a completely arbitrarily (alas, not randomly) selected part of a subset of graphs showing trends in mortality. The opposite conclusion may be reached using the same graphs. For example, in women aged 35-44 mortality fell from 10 per 100 000 to 5 per 100 000 in the period 1960 to 1975, and it should have approached zero by 1997 assuming that the trend had continued. Similarly, with the same age groups as in the original paper, in women aged 25-34 mortality fell from 2.5 per 100 000 to 1.1 per 100 000 in the period 1955 to 1965, so by 1997 it should have again approached zero. Since the only new intervention has been screening, and the mortality is excessive at 5 per 100 000, screening may have caused up to 2900 extra deaths in 1997—by the same logic.

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Authors' reply

EDITOR—The conclusions in our paper are not based solely on the analysis of mortality. We presented strong evidence that the introduction of national call and recall and of incentive payments to general practitioners led to a dramatic fall in the incidence of cervical cancer in women in all age groups from 30 to 74 and in all regions of England. Other evidence confirms the expected shift towards detection of earlier stages of disease. There is no other plausible explanation for these patterns. If women do not get cervical cancer, they will not die from it. In addition, it has been recognised for over 30 years that mortality from cervical cancer shows very strong cohort trends (reflecting those in incidence)[1] and so Vaidya and Baum's simple extrapolation of age specific trends is totally inappropriate. We extrapolated the cohort rates for the relevant age groups. Our analysis and conclusions are supported by a similar study in Scotland[2] and by the results from formal age period cohort models.[3]

We remain deeply concerned about the many well known problems with cervical screening which we mentioned in our paper: cervical cancer is a comparatively rare disease and its natural course is not well understood; the smear test has both low sensitivity and low specificity; many tests are technically unsatisfactory and the proportion of such tests varies widely across the country; the mix of three and five year screening intervals is inequitable; too many smear tests are opportunistic; and the programme costs four times as much as breast screening. Nevertheless, there is now conclusive evidence that cervical screening has markedly reduced both incidence and mortality.

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1 Hill GB, Adelstein AM. Cohort mortality from carcinoma of the cervix. *Lancet* 1967;ii:605-6.
2 Walker JJ, Brewster D, Gould A, Raab GM. Trends in incidence of and mortality from invasive cancer of the uterine cervix in Scotland (1975-1994). *Public Health* 1998:112:373-8.
3 Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ* 1999;318:1244-5. (8 May.)

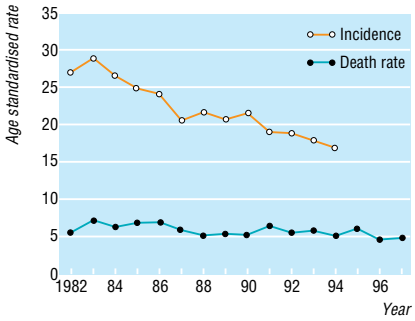
Study shows importance of centralised organisation in screening

EDITOR—The paper by Quinn et al reporting the effects of screening on incidence of and mortality from cervical cancer in England[1] highlighted the characteristics of successful programmes elsewhere[2 3] and showed that the national screening programme had been effective.

The situation in Hong Kong, where there is no systematic population based cervical screening programme, shows the importance of central organisation. Hong Kong is a generally affluent community with a better health profile than most developed countries. Infant mortality is low (4.6 per 1000 live births in 1995, compared with 6.2 in the United Kingdom), and life expectancy is high (81.5 years at birth for women, compared with 79.4 years in the United Kingdom). Women in Hong Kong are at lower risk of developing many common cancers, such as those of the breast and lung, than are their counterparts in most Western countries yet the reverse is true for cervical cancer.[4]

The figure shows the trend in the incidence of and mortality from cervical cancer standardised to the European standard population (for age bands of five years). Although incidence has reduced gradually over time, it has not fallen dramatically as in the United Kingdom after organised screening achieved a coverage greater than 70%, and the death rate has changed little. The standardised incidence of 16.9 per 100 000 for invasive cancer in 1994 was higher than the baseline rates of disease before organised screening started in the United Kingdom. Cervical cancer is the fourth most common newly diagnosed cancer and accounts for 4% of deaths from cancer in local women, compared with 2% in the United Kingdom.

One of us (PA) recently found that 56% of nearly 1800 women aged between 20 and 75 in Hong Kong had never had a cervical screening test.[5] Coverage was lowest among



Age standardised incidence of invasive cervical cancer and mortality from cervical cancer, Hong Kong, 1982-7

older women (72% of women over 50 had never been screened) and those in the lower socioeconomic groups. Less than a quarter of all women were screened regularly, and these were generally screened yearly or more often.

The current screening system in Hong Kong is therefore inequitable, wastes resources, and results in avoidable cases of cervical cancer. It may also cause unnecessary harm by overscreening women at lower risk. The study by Quinn et al provides further support for centralised organisation in any screening system and is a message that should not be ignored by any country with a developed health care system.

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2 Laara E, Day N, Hakama M. Trends in mortality from cervical cancer in the Nordic countries; association with organised screening programs. *Lancet* 1987;i:1247-9.
3 ICRF Coordinating Committee on Cervical Screening. Organisation of a programme for cervical cancer screening. *BMJ* 1984;**289**:894-5.
4 Adab P, Hedley AJ. Preventing avoidable death: the case of cervical cancer in Hong Kong. *Hong Kong Med J* 1997;3:427-32.
5 Adab P. Screening for cervical cancer in Hong Kong [abstract]. Fifth Hong Kong international cancer congress, Hong Kong, February 1998.

Use of guidelines should be evaluated in randomised controlled trials

Editor—It remains to be proved whether implementing guidelines for the prevention of corticosteroid induced osteoporosis will be of benefit overall. The editorial by Lips[1] encouraging the adoption of the UK Consensus Group's guidelines[2] is based on the assumptions that following these guidelines will have no adverse effects, will achieve the benefits the group envisaged mostly by extrapolation of the results from limited studies, and will be worth the costs entailed.

On the contrary, it is easy to imagine that advice to take regular calcium and vitamin D, to review lifestyle, and to take bisphosphonates (or hormone replacement therapy or calcitriol) will add important problems of adherence to an otherwise simple regimen of glucocorticoid treatment for example, 10 mg once a day for the early management of polymyalgia rheumatica.

Assertions that guidelines (even those which are well thought out) can be implemented without the potential for adverse outcomes and additional economic costs should not be accepted. The introduction of guidelines is seldom tested in randomised controlled trials,[3] yet this is what is required if they are to be evaluated adequately.

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1 Lips P. Prevention of corticosteroid induced osteoporosis. *BMJ* 1999;318:1366-7. (22 May.)
2 Eastell R, Reid DM, Compston J, Cooper C, Fogelman I, Francis RM, et al. UK Consensus Group on management of glucocorticosteroid induced osteoporosis: an update. *J Intern Med*;244:271-92.
3 Balint G, Szebenyi B, Kirwan JR. The use of guidelines for managing and treating osteoarthritis. *Disease Management and Health Outcomes* 1998;3:11-142.

Cognitive therapy is no better than supportive counselling in schizophrenia

Editor—Minerva is wrong to state that cognitive behaviour therapy can improve symptoms in people with schizophrenia,[1] based on the findings of the latest study by Tarrier and colleagues.[2] In fact, the results they present are similar to those that they published recently in the *BMJ*.[3] They found that although cognitive behaviour therapy was significantly superior to "routine care," there was no significant difference between cognitive therapy and non-specific "supportive counselling." (In fact, some of my patients receive such supportive counselling as part of their routine care.)

As I pointed out in a letter regarding the earlier study,[4] cognitive behaviour therapy is more expensive than supportive counselling. There seems to be a growing assumption that cognitive behaviour therapy is beneficial for patients with schizophrenia. The assumption is based on very little evidence, and it is unhelpful for Minerva to contribute to this trend. Larger studies need to be done to determine whether cognitive behaviour therapy actually has any specific effect other than the effects due to an increased quantity of therapeutic contact.

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1 Minerva. *BMJ* 1999;318:1708. (19 June.)
2 Tarrier N, Wittkowski W, Kinney C, McCarthy E, Morris J, Humphreys L. Durability of the effects of cognitive-behaviour therapy in the treatment of chronic schizophrenia: 12-month follow-up. *Br J Psychiat* 1999;174:500-4.
3 Tarrier N, Yusupoff L, Kinney C, McCarthy E, Gledhill A, Haddock G, et al. Randomised controlled trial of intensive cognitive behaviour therapy for patients with chronic schizophrenia. *BMJ* 1998;317:303-7.
4 Curtis D. Intensive cognitive behaviour therapy for chronic schizophrenia. *BMJ* 1999;318:331. (30 January.)

Door to needle times of 12 minutes are possible in one emergency department

Editor—Several correspondents have discussed call to needle times after acute myocardial infarction.[1] Rapid door to needle times are possible in accident and emergency departments with the use of appropriate protocols and the availability of cover by senior medical staff on the floor 24 hours a day.

In the emergency department of this hospital all adult patients with chest pain are taken immediately to a cubicle by nursing staff; before they see a doctor oxygen treatment and electrocardiographic monitoring are started and an intravenous line is inserted. A 12 lead electrocardiogram is taken to the attending emergency doctor even before it is labelled. When an acute myocardial infarction is diagnosable from this first electrocardiogram the door to needle times are around 12 minutes. Thus thrombolysis is routinely administered in this emergency department.

The key points are that the nurses do not require medical authorisation to instigate their protocol and that the first doctor to read the electrocardiogram has the competence to interpret it correctly and the authority to instigate thrombolysis.

This hospital has a tertiary cardiac surgical service, and its cardiologists envisaged from the outset that the emergency department would function in this way.

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1 Correspondence. Call to needle times after acute myocardial infarction. *BMJ* 1999;318:1553-4. (5 June.)

Early trials of angiogenic factors have not targeted patients most at risk of ocular disease

Editor—In his clinical review on therapeutic angiogenesis Henry discusses the potential benefits of this treatment in relation to myocardial and limb ischaemia.[1] Vascular endothelial growth factor, fibroblast growth factor, and the angiopoietin receptors have already been evaluated in disease models and small clinical trials and shown to be beneficial. The use of these agents highlights a paradox of subspecialty medicine.

Henry briefly mentions the danger of pathological angiogenesis in other tissues, and this is of particular relevance to ocular disease. Vascular endothelial growth factor, fibroblast growth factor, and angiopoietin have been implicated in the pathogenesis of proliferative diabetic retinopathy, ischaemic central retinal vein occlusion, retinopathy of prematurity, and exudative age related macular degeneration.[2 3] Ocular neovascularisation is common to all these conditions, and visual loss results from vitreous or subretinal haemorrhage, retinal detach-

ment, or neovascular glaucoma. Any systemic treatment involving these factors, whether designed to promote angiogenesis for myocardial and limb ischaemia or to inhibit angiogenesis for ocular disease, may have an adverse pathological effect elsewhere.[1 2]

Much of the ocular disease involving neovascularisation is characterised by prolonged hypoxia and chronic exposure to higher levels of vascular endothelial growth factor, fibroblast growth factor, and angiopoietin than found normally.[4 5] It is difficult, therefore, to quantify the ocular risk resulting from the single, direct application of an angiogenic factor to a target organ or from sustained production by a virus vector. In the healthy eye the blood-retinal barrier will prevent access of these angiogenic factors to the ocular tissues and the risk is likely to be small.

However, with the breakdown of the blood-retinal barrier in proliferative diabetic retinopathy, ischaemic central retinal vein occlusion, retinopathy of prematurity, and age related macular degeneration,[2] these angiogenic factors will have ready access to ocular tissues; they may then become sequestered in the vitreous cavity and other extravascular spaces. In these diseases the vascular endothelial cells are likely to have been primed by hypoxia and there will have been limited breakdown of the existing extracellular matrix. The risk of stimulating endothelial cell proliferation and tube formation and of causing pathological angiogenesis in the eye will be maximal.

By excluding either all diabetic patients or those diabetic patients with retinopathy the early clinical trials of angiogenic factors have failed to target those patients most at risk of ocular disease.

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1 Henry TD. Science, medicine, and the future: therapeutic angiogenesis. *BMJ* 1999;318:1536-9. (5 June.)
2 Schlingemann RO, van Hinsbergh VWM. Role of vascular permeability factor/vascular endothelial growth factor in eye disease. *Br J Ophthalmol* 1997;81:501-12.
3 Takagi C, Takagi H, Matsumura M, Koyama S, Otani A, Honda Y. Expression of angiopoietins and Tie-2 in retinal proliferative diseases. *Invest Ophthalmol Vis Sci* 1999;40:3706.
4 Boulton M, Foreman D, Williams G, McLeod D. VEGF localisation in diabetic retinopathy. *Br J Ophthalmol* 1998;82:561-8.
5 Smith G, McLeod D, Foreman D, Boulton M. Immunolocalisation of the VEGF receptors FLT-1, KDR and FLT-4 in diabetic retinopathy. *Br J Ophthalmol* 1999;83:486-94.

Smoking by parents of asthmatic children

Sensitive counselling may still be worth while

EDITOR—Reducing exposure of asthmatic children to parental smoking is important, but without more information the paper by Irvine et al provides no foundation for evidence based practice.[1] The reader can safely conclude that something made no difference but is given no useful description of what that something was. The paper supplies only two of the five elements that Windsor et al suggest as an adequate description of an intervention—namely, counselling content, theoretical framework from which methods are derived, duration of each patient contact, frequency of intervention components, and training of intervention counsellors.[2] It is sad that journals which take commendable steps to ensure that the outcomes are adequately reported still do not apply similar standards to the reporting of the intervention.[3]

A further cause for concern is the context of the study. What was the nature of the families' consent? If they were given adequate information it is likely that the control group was appreciably contaminated, and if they were not the ethics of the study are debatable. What previous advice and support had been given to these families? I hope we can assume that all practices in the study routinely advised all such parents of the possible connection between their smoking and their child's asthma, in which case the additional intervention sounds marginal.

I would also question whether the intervention was in accord with best practice. The use of a research nurse unknown to the family and apparently unconnected with the patient's practice does not use the practice-patient relationship. The use of the phrase "telling patients what to do" in the discussion raises concern about the counselling style.

Certainly we need more effective methods of helping smokers cut back or quit, and the intervention used in this study was apparently ineffective. However, this paper should not be interpreted as indicating that sensitive counselling by primary care teams of parents who smoke and have asthmatic children is not worth while.

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1 Irvine L, Crombie IK, Clark RA, Slane PW, Feyerabend C, Goodman KE, Cater JI. Advising parents of asthmatic children on passive smoking: randomised controlled trial. *BMJ* 1999;318:1456-9. (29 May.)
2 Windsor RA, Boyd NR, Orleans CT. A meta evaluation of smoking cessation intervention research among pregnant women: improving the science and art. *Health Educ Res* 1998;13:419-38.
3 Speller V, Learmonth A, Harrison D. The search for evidence of effective health promotion. *BMJ* 1997;315:361-3.

Authors' reply

EDITOR—Kemm raised several important issues. He was concerned that the intervention was not described in enough detail. The extent of reporting was restricted by the word limit, but we take this opportunity to give more details. The intervention was designed so that it could be easily used in the clinical situation, if found to be effective. It was brief, based on the method first described by Russell et al.[1] Parents were visited once, and the nature of the intervention is described in the paper. Information given at the time of the consultation was reinforced in leaflets. The duration of contact with the parents was about one hour, although the actual intervention took around 10 minutes. The intervention was delivered by research nurses, who were not trained counsellors. This was intentional, the purpose of the study being to test an intervention which could be delivered by any nurse.

Kemm was also concerned about the ethics of our study. Providing enough information about a study to obtain informed consent without contaminating the control group is a problem for all studies designed to change behaviour. Parents were told that the study was being carried out to look at ways of reducing passive smoking in children with asthma and gave written consent to participation. However, the full details of the study design were not disclosed. The issue of informed consent was discussed in detail with the Tayside committee on medical ethics before the start of the study. We were satisfied that parents were given sufficient information.

Kemm assumes that clinicians routinely advise all parents of the possible connection between their smoking and their child's asthma. Several studies have shown that many clinicians do not give such advice routinely,[2 3] and some are uncertain about the effect of counselling smokers at every opportunity.[4]

Finally, he queried the use of research nurses unknown to the study participants. The alternative, using practice staff to deliver the intervention was not a realistic option. The size and complexity of the study and the large number of practices involved made it impracticable for the intervention to be delivered by practice staff. Furthermore, we believe that the quality of large trials depends on rigorous data collection by staff dedicated to the project. We remain confident that our study showed that a brief intervention given to parents is of no benefit to children with asthma.

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1 Russell MAH, Wilson C, Taylor C, Baker CD. Effects of general practitioners' advice against smoking. *BMJ* 1979;2:231-5.
2 Goldstein MG, Niaura R, Willey-Lessne C, DePue J, Eaton C, Rakowski W, et al. Physicians counselling smokers. *Arch Intern Med* 1997;157:1313-9.
3 Frankowski BL, Weaver SO, Secker-Walker RH. Advising parents to stop smoking: pediatricians' and parents' attitudes. *Pediatrics* 1993;91:296-300.
4 Coleman T, Wilson A. Anti-smoking advice in general practice consultations: general practitioners' attitudes, reported practice and perceived problems. *Br J Gen Pract* 1996;46:87-91.

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