

CORRESPONDENCE

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Dementia and statins

Sir—The case-control observational study by Hershel Jick and colleagues (Nov 11, 1627)¹ raises some important questions over and above researchers' own caveats.

First, the diagnosis of dementia was based on a clinical assessment by family physicians, which is only a first step towards a diagnosis. Quantitative screening is needed to ascertain loss of cognition, such as the mini-mental state examination.² A score of less than 24 should lead to a more specific diagnostic assessment.³ Moreover, causes of cognitive failure other than dementia proper, should be excluded, such as pharmacologically or toxicologically induced disturbances of brain function.

Second, Jick and colleagues mention the possibility that the reduced risk for statins could be caused by characteristics of the statin recipients that are associated with a lower risk of dementia. They should have expanded this point, since they were close to touching on the fundamental weakness of the study: bias by indication. Sociological experience shows a group of intelligent, well informed, alert, mostly urban patients. If they develop hypercholesterolaemia, they frequently demand and obtain the most modern lipid-lowering agents. By contrast, other patients, generally of lower socioeconomic status, are less aware of cardiovascular risk factors and treatment trends. In the Systolic Hypertension in Europe trial,⁴ age on leaving school was a major determinant of cognitive function, measured by the mini-mental state questionnaire.

This type of preordained selection might partly explain the negative association between dementia and the use of statins, rather than a pharmacological action of this drug class.

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clinician. *J Psychiatr Res* 1975; **12**: 189–98.

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Sir—Hershel Jick and colleagues¹ found a striking inverse association between the use of statins and dementia.¹ They admit that case-control studies merely identify associations, not causal links, which could be the case in their study.

Since 87% of participants were older than 70 years, the use of statins in this population was probably affected by many factors, including state of health, quality of life, and prognosis. Healthy people in their 70s will not be denied statins. Indeed treatment in such individuals at high risk of cardiovascular events has a low number needed to treat, which suggests cost effectiveness.² Nearly all guidelines advise caution in prescribing statins to people with non-cardiovascular diseases that impair prognosis for a healthy life.³ A person who has dementia is much less likely than someone without to be prescribed statins. In Jick and colleagues' study, only 12 (4.2%) of 284 cases were receiving statins, compared with 100 (9.3%) of 1080 controls. The proportion of people receiving statins is strikingly low among cases and fairly low even in the controls.

Many randomised prospective trials of statins shed light on the effect of these drugs on the development of dementia. Jick and colleagues should nevertheless be congratulated on highlighting an important imbalance in the prescription of statins. If it is confirmed, what should be debated is whether statins should or should not be withheld from people with dementia.

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- 1 Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000; **356**: 1627–31.

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Authors' reply

Sir—In reply to W H Birkenhäger and colleagues, we point out that in another study of the effects of oestrogen-replacement therapy on the development of Alzheimer's disease we carefully assessed 80 case records of patients recorded as having dementia or Alzheimer's disease, through the General Practice Research Database. 90% met stringent criteria for the diagnosis.¹

We controlled for patients' general practice in our analysis. Although general practice provides only an indirect indicator of socioeconomic status and education, we suspect that it substantially controls for these factors, as well as for the acumen of and criteria for diagnosing dementia of the individual physicians. We suggest that specific choice of drugs, as well as the decision to treat hyperlipidaemia is not involved in any selection bias, since treatment with non-statin lipid-lowering agents had no effect on the risk of dementia.

Birkenhäger and colleagues allude to the pharmacological action of statins. However, statins have beneficial effects on vascular endothelium through the increase in activity of endothelial nitric-oxide synthase and the reduction of endothelin-1,^{2,3} and their effects in reducing heart disease and stroke^{4,5} exceed their lipid-lowering actions.

B M Y Cheung and C R Kumana seem to assume that we studied prevalent cases of dementia. We included only incident cases of dementia. Therefore the data on statin use relate only to the time before the diagnosis. The indication for use was hyperlipidaemia in all statins users. The negative association between statins and dementia was present for all durations of treatment, including 4 or more years before the date of first diagnosis. Our results provide information on the use of statins before

the diagnosis of dementia but not on the possible effect of statins in people who already have dementia.

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Sir—To answer the question of whether statins' apparent reduction in risk for dementia is also present for dementing disorders, Hershel Jick and colleagues¹ attempted to find associations between Alzheimer's type dementia and vascular dementia, but saw no differences.

Clinically, Alzheimer's type dementia and vascular dementia can hardly be differentiated. Furthermore, there is increasing evidence that atherosclerosis interacts with risk factors for Alzheimer's disease, and patients who have had strokes are at increased risk of Alzheimer's dementia.^{2–4}

On the basis of the hypothesis that cholesterol-lowering therapy with statins will slow the progression of cerebrovascular disease and will preserve cognitive function at old age, we designed a continuing double-blind, randomised, placebo-controlled trial to investigate the effect of 40 mg pravastatin in an elderly population in Scotland, Ireland, and the Netherlands.⁵ Annual neuropsychological tests are done in 5804 people to investigate the effect of pravastatin treatment on cognitive decline. In a nested substudy of 650 participants, magnetic resonance imaging of the brain is being done at baseline and after 3 years' follow-up to investigate the effect of pravastatin on the

occurrence of cerebral lesions. We also assess cytokine profiles of 450 participants to investigate the relation between cardiovascular and cerebrovascular disease and the innate immune system. The results of the study are expected in 2002.

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Sir—Hershel Jick and colleagues¹ document strikingly lower relative risk of dementia in patients taking statins. They suggest several paths by which statins might do this. I add another.

Glia synthesise tumour necrosis factor- α (TNF- α) in response to various physical or metabolic insults,² and TNF damages neurons.³ Damaged or apoptotic neurons secrete factors that activate glia to increased TNF- α production.⁴ A mutually reinforcing cycle is thus set up and believed to be part of the pathophysiology of some dementing illnesses, including Alzheimer's disease. Statins significantly suppress TNF- α synthesis,⁵ and would, therefore, be expected to dampen that glia-neuron destructive feed back cycle.

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Sir—Hershel Jick and colleagues¹ observed a lower risk of dementia in individuals aged 50 years or older who were prescribed statins. They speculate on possible mechanisms by which statins might reduce the risk of developing dementia, including effects on plasma lipids, and on the cerebral microcirculation, including endothelial cells.

We suggest that another possible mechanism through which statins improve cerebral microcirculation and lower the risk of dementia is decrease of plasma and blood viscosity.² In the West of Scotland Coronary Prevention Study, we confirmed our hypotheses that plasma and blood viscosity were predictors of coronary heart disease events (as in observational studies)³ and that pravastatin lowered viscosity (by about a quarter of 1 SD).² Plasma and blood viscosity might also be predictors of stroke,⁴ and plasma viscosity had an inverse association with cognitive performance in the Caerphilly Study of men aged 55–69 years.⁵

We agree with Jick and colleagues' conclusion that further studies of the association of statins and dementia are required. Workers in such studies should consider including viscosity measurements to test our hypothesis.

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- 1 Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman DA. Statins and the risk of dementia. *Lancet* 2000; **356**: 1627–31.
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Sir—The association between use of statins and lower risk of dementia reported by H Jick and colleagues¹ should be interpreted cautiously.

Only 13% of the control group were diagnosed as being hyperlipidaemic and on no treatment. This proportion is far lower than that noted for men and women (35%) with cholesterol concentrations of 6.5 mmol/L in the Health Survey for England.² This discrepancy probably arose because of underdiagnosis of hyperlipidaemia or use of a higher cholesterol concentration in the GPRD. We suspect that the former is more plausible and many patients who had true hyperlipidaemia were misclassified (perhaps up to 60%) as having normal lipids at baseline on no treatment. More surprisingly, hyperlipidaemia alone was associated with, if anything, a decreased risk of dementia, contrary to findings of prospective studies.^{3,4}

Patients of lower compared with higher socioeconomic positions might be less likely to be screened and treated with newer drug regimens. Since dementia is strongly associated with education level, the observed relation with statin use might be confounded by differential misclassification of hyperlipidaemia and treatment with statins. Jick and colleagues control for various potential confounders, but not for socioeconomic position or education level.

We assessed the effects of non-differential and differential misclassification and treatment using data from the British Regional Heart Study (BRHS)⁵ and the British Women's Heart and Health Study (BWHHS). The BRHS involves a long-established cohort of 7735 men drawn from 24 general practices throughout the UK. Participants were screened in 1998–2000 at age 60–79 years and asked about use of lipid-lowering drugs. The BWHHS is a new companion study of women aged 60–79 years in the same towns as the BRHS men, who were screened in 1999–2001. We calculated the odds ratio of no association between statin use and dementia, assuming a two-fold increased risk of dementia with hypercholesterolaemia and with fewer than 16 years of education for four scenarios of misclassification bias and

differential use of statins by educational level.

Of 3737 men and 1993 women, 7.7% and 3.6% were taking lipid-lowering drugs (91% taking statins), which is similar to the results from the Health Survey for England for men and women older than 65 years (4%).² Education level (age left education <16 vs ≥16 years) and use of lipid-lowering drugs were not obviously associated, but CI are wide; age-adjusted odds ratios: men 1.12 (95% CI 0.87–1.46) and women 0.77 (0.44–1.23). The table shows how the association between statin use and dementia can seem protective, dependent on various assumptions, even when no association exists. The non-differential misclassification of hyperlipidaemia (scenario 2) of 60%, equivalent to that which may have occurred in Jick's study, suggests a large but spurious protective effect of statins. Increasing the prevalence of hyperlipidaemia by educational level (scenario 3) made little additional difference, but differential misclassification and differential use of statins by educational level (scenario 4) generally increased the apparent protective effect of statins.

Future studies of the relation between statins and dementia risk should attempt to control for education level. Long-term follow-up of cognitive ability should be assessed in large randomised controlled trials of statin use.

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- 1 Jick H, Zornberg GL, Jick SS, Seshadri S, Drachman A. Statins and the risk of dementia. *Lancet* 2000; **356**: 1627–31.
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Deferiprone or fatal iron toxic effects?

Sir—M J Pippard and D J Weatherall (Oct 21, p 1445)¹ express reservations about the use of deferiprone as a second-line iron chelator for iron overload in thalassaemia, which is against the assessments and recommendations of the authorities in the European Community and other countries where deferiprone is registered.

They have dismissed more than 100 publications in peer-reviewed journals that show deferiprone to be an effective iron chelating drug in most patients, and instead refer to the one group of investigators whose clinical findings on possible liver fibrosis toxic effects with a single-dose regimen of 75 mg/kg daily have been questioned by an editorial in the same journal issue.^{1,2} Similarly, such findings on toxic effects have not been confirmed by other investigators, especially not by those who have treated patients with deferiprone (75–120 mg/kg daily) for more than 10 years and have seen no differences in liver fibrosis compared with patients receiving deferoxamine.³ Furthermore, the report on liver fibrosis had a fundamental error, in that the investigators, in an attempt to support their findings, referred to liver toxic effects in gerbils from the known toxic, lipophilic chelator 1,2-diethyl-3-hydroxypyrid-4-one, which has completely different in-vitro and in-vivo properties to deferiprone.^{2,4}

Deferoxamine and deferiprone can achieve negative iron balance in most patients using existing dose protocols, but comparison between the two is not yet possible because optimum therapy with deferiprone has not been established.

Assumptions	Scenario 1			Scenario 2			Scenario 3			Scenario 4		
	<16 years	≥16 years	Odds ratio	<16 years	≥16 years	Odds ratio	<16 years	≥16 years	Odds ratio	<16 years	≥16 years	Odds ratio
Proportion using statins	0.9%	0.9%	1.0	0.9%	0.9%	0.80	0.9%	0.9%	0.79	0.6%	0.9%	0.74
Proportion with untreated hyperlipidaemia	0.35%	0.35%		0.35%	0.35%		0.4%	0.3%		0.4%	0.3%	
Proportion of patients with hyperlipidaemia misclassified as normal	0	0		0.6%	0.6%		0.6%	0.6%		0.6%	0.5%	

Odds ratios for association between statin use and dementia

Pippard and Weatherall mention the possibility of commercial influence. The issue of economic and marketing wars and deals on drugs is complex. Both deferiprone and deferoxamine are viewed as orphan drugs. However, natural deferoxamine has annual sales of US\$0.5 billion, which are much higher than those for deferiprone or chemically produced deferoxamine. However, deferiprone is offered in more-developed countries at almost the same price as deferoxamine, despite its chemical synthesis and development being based on academic funding from a charity.⁴ The present price in India, where deferiprone is only eight times cheaper than deferoxamine, could further be reduced.⁴

Pippard and Weatherall do not mention what action should be taken for 90% of the thalassaemia patients worldwide, who are not currently receiving chelation therapy because of the high cost and risk of toxic effects from deferoxamine, and non-compliance with its subcutaneous administration. The use of calcium disodium pentetate, which Pippard and colleagues have previously suggested as a second-line iron chelator has not been successful.⁵

In the absence of any serious alternatives in the next 5–8 years, we believe and recommend that deferiprone should be used in iron chelation therapy in untreated patients because toxic effects from iron overload in regularly transfused patients could lead to irreversible organ damage and early death.

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- 1 Pippard MJ, Weatherall DJ. Deferiprone for thalassaemia. *Lancet* 2000; **356**: 1444–45.
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Petrou M, Modell CB. Iron chelation using subcutaneous infusion of diethylene triamine penta-acetic acid (DTPA). *Scand J Haematol* 1986; **36**: 466–72.

Predictive testing for Huntington's disease

Sir—Michael Hayden's Dec 9 commentary¹ is a timely report on the experience of almost 15 years of predictive testing for Huntington's disease. In addition to the factors he mentions for the low uptake of prenatal testing is an issue of identity between the parent who carries the mutation and an affected fetus. A decision to terminate such a pregnancy involves destroying a fetus that is in the same genetic situation as that parent. Some of the people in families that carry the disease feel this dilemma acutely.

Our evidence supports Hayden's point that parents are reluctant to use prenatal testing for various late-onset disorders. In a questionnaire survey of students and adult women, 98% of our sample thought prenatal testing should be offered for disorders such as Tay Sachs's disease or cystic fibrosis, but 80% thought so for Huntington's disease and inherited breast cancer syndromes (unpublished data).

Men and women may differ in their response to information about health risks. More women than men request predictive genetic testing or carrier detection testing, which could relate to the position that women hold in families as being the so-called genetic housekeepers. Typically women have most knowledge of family medical history.² Work with women who have an inherited risk of breast or ovarian cancer shows that many perceive themselves as having a responsibility to their kin (past, present, and future generations) to establish the magnitude of the risks to themselves and family members, and to act on this information by some form of risk management.³

The acknowledgment of genetic responsibility for kin seems part of this same typically female role.

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- 1 Hayden MR. Predictive testing for Huntington's disease: the calm after the storm. *Lancet* 2000; **356**: 1944–45.
- 2 Richards MPM. Families, kinship and genetics. In: Marteau T, Richards MPM, eds. *The troubled helix*. Cambridge: Cambridge University Press, 1996: 249–73.
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Treatment of oxygen-induced hypercapnia

Sir—P M A Calverley, in his Nov 4 commentary,¹ describes the conventional treatment for patients with oxygen-induced hypercapnia, but clinical data to support this approach are lacking. Although respiratory acidosis and narcosis are important complications in patients with chronic obstructive pulmonary disease, the belief that they arise because of abolition of hypoxic respiratory drive is not well established.

In a prevalence study of respiratory acidosis in acute exacerbations of chronic obstructive pulmonary disease Plant and co-workers² showed only a weak correlation between arterial oxygen tension and pH in hypercarbic patients. The frequency of carbon dioxide narcosis was similar in reports by Bone and colleagues³ and Campbell,⁴ although patients were treated with controlled oxygen therapy in the former study and uncontrolled oxygen therapy in the latter, which suggests that controlling oxygen therapy offers little advantage.

We know of no controlled data to support Calverley's opinion that maintaining an arterial saturation of 87–92% in patients with chronic respiratory disease is the safest treatment goal. Although titration of oxygen therapy to this degree of saturation might prove to be the best approach, Calverley's call for widespread adoption of such an approach should be tempered by an acknowledgment of the sparseness of supporting data.

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- 1 Calverley PMA. Oxygen-induced hypercapnia revisited. *Lancet* 2000; **356**: 1538–39.
- 2 Plant PK, Owen JL, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbations of COPD: implications for the provision of noninvasive ventilation and oxygen administration. *Thorax* 2000; **55**: 550–54.
- 3 Bone RC, Pierce AK, Johnson RL. Controlled oxygen administration in acute respiratory failure in chronic obstructive pulmonary disease: a reappraisal. *Am J Med* 1978; **65**: 896–902.
- 4 Campbell EJM. The J Burns Amberson Lecture: the management of acute respiratory failure in chronic bronchitis and emphysema. *Am Rev Respir Dis* 1967; **96**: 626–39.

Sir—P M A Calverley¹ expresses more truth than he realises about the necessity for each generation to repeat the errors of its predecessors. Although he claims that McNichol and

Campbell² were the first to appreciate the risk of oxygen in severe hypercapnia in 1965, he is probably unaware that this phenomenon was well known in the Bellevue Hospital Chest Service, New York City, USA, at least as early as the late 1950s.

Arterial blood gases were measured in the cardiopulmonary laboratory under the direction of Andre Cournand. Patients were treated with a high degree of success with intermittent positive-pressure breathing (Bird or Bennet) via non-invasive masks. During this period, the Chest Service was headed by J B Amberson,³ whose named lecture Calverley cites as his reference 3. On the basis of research in Cournand's laboratory, the cause of the hypercapnia was thought to be perfusion ventilation imbalance. Amberson and Cournand deserve recognition for their seminal work.

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- 1 Calverley PMA. Oxygen-induced hypercapnia revisited. *Lancet* 2000; **356**: 1538–39.
- 2 McNichol MW, Campbell EJM. Severity of respiratory failure: arterial blood-gases in untreated patients. *Lancet* 1965; **1**: 336–38.
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Author's reply

Sir—S Ramsay and colleagues note the lack of control data to support the views of Plant and colleagues. I tried to balance the different strands of evidence suggesting that suppression of hypoxic drive to breathing was an important mechanism in these patients, although I think that the work by Robinson and colleagues¹ suggests that this mechanism is a factor in some people. Ramsay is incorrect in suggesting that uncontrolled oxygen was used in the study reported by Campbell. He gave a detailed account of the treatment approach in his lecture, and it is clear that patients were initially managed on 24.5% oxygen.

The physiological principles outlined 33 years ago remain just as relevant today and the need for close monitoring of these patients and avoidance of unnecessary carbon dioxide retention and acidosis are still relevant. This point is emphasised by a review of practice in our University Teaching Hospital.² Poor management of acute chronic respiratory failure due to chronic obstructive pulmonary disease is still occurring. Worryingly, patients who develop oxygen-induced hypercapnia seem to have worse mortality, despite similar previous

pulmonary function, than those in whom this complication has been avoided. This review falls short of a controlled clinical trial, but the ethics of such investigations and the need to obtain informed consent makes data of this type particularly difficult to obtain.

L Cohen correctly reminds me that the Cornell group were pioneers in this field. However Campbell and colleagues published the first systematic observations about the effects of oxygen therapy in this area, and I defend my choice of reference. Campbell has pointed out that I inaccurately equated his data with low-flow controlled oxygen therapy. He used a high-airflow oxygen entrainment system that achieves controlled oxygen administration in a different way to current controlled oxygen masks. I am delighted to have this opportunity to put the record straight.

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- 1 Robinson TD, Freiberg DB, Regnis JA, Young IH. The role of hypoventilation and ventilation-perfusion redistribution in oxygen-induced hypercapnia during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; **161**: 1524–29.
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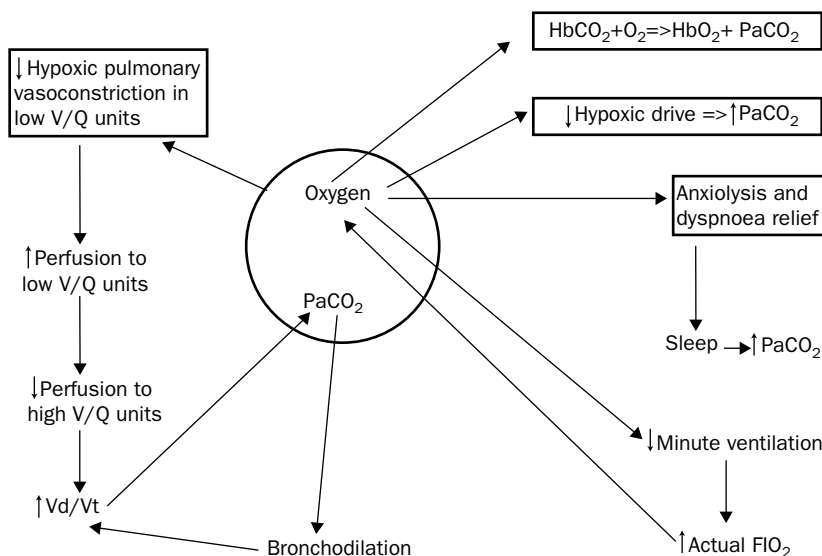
Sir—We agree with P M A Calverley's interpretation of the available data on oxygen-induced hypercapnia. We wish to suggest potential additional mechanisms for hyperoxic hypercapnia in acute exacerbations of chronic

obstructive pulmonary disease (COPD) to those discussed.

Although rare, the occasional patient with acute exacerbations will develop severe acute on chronic respiratory acidosis (partial pressure of carbon dioxide [PaCO_2] >20 kPa) when given oxygen. We believe that there are five distinct mechanisms that could underlie hyperoxic hypercapnia (figure).

First, the Haldane effect refers to the reduction in haemoglobin affinity for CO_2 with the binding of oxygen to haemoglobin. The CO_2 that is released from haemoglobin leads to a small increase in PaCO_2 . Second, the increase in oxygen tension in lung units with low ventilation/perfusion (V/Q) ratios can blunt hypoxic pulmonary vasoconstriction in these low V/Q lung units, thus diverting perfusion away from high V/Q lung units (effectively increasing dead space in these latter lung units, ie, worsening CO_2 elimination).² CO_2 -induced bronchodilation might contribute to this mechanism.² Third, data on PCO_2 recruitment threshold in intubated patients with chronic obstructive pulmonary disease (COPD) persuasively support a change in sensitivity of the central nervous system to CO_2 during hyperoxia, compared with normoxia.³ Fourth, we believe that some patients with acute exacerbations of COPD are especially susceptible to the development of severe hypercapnia due to sleep deprivation that is common in acute illness before clinical presentation. Patients with underlying obstructive sleep apnoea might be particularly susceptible since they are acutely and chronically sleep deprived.⁴

In acute exacerbations of COPD, oxygen may have anxiolytic and



Various proposed mechanisms important in development of hyperoxic hypercapnia

Vd/Vt=valve-dead space; FIO₂=fraction of inspired oxygen; V/Q=ventilation/perfusion; Hb=haemoglobin.

antidyspnoeic effects that allow the onset of sleep in people with high sleep drive. Therefore, the observed hypoventilation could be secondary to a reduced hypercapnic ventilatory response (sleep deprivation⁵); the loss of the wakefulness drive to breathe at the time of sleep onset; and the elimination of hypoxic drive. Previous sleep deprivation also increases the subsequent arousal threshold. Therefore, the development of CO₂ narcosis could, in fact, be triggered by the onset of sleep.

Fifth, during non-invasive oxygen administration, the actual fractional oxygen concentration delivered is dependent on minute ventilation and inspiratory flow demand. Therefore, as patients undergo a gradual reduction in minute ventilation by the above mechanisms,² the actual fractional oxygen concentration delivered gradually increases, despite no change in the oxygen flow rate from the source. The result can be a vicious cycle of increasing fractional oxygen with worsening hypercapnia, leading to severe respiratory acidosis in some patients.

We believe that all five of these mechanisms might be relevant to acute exacerbations of COPD. We agree with Calverley's recommendations to judiciously limit fractional oxygen concentration in COPD patients with acute or chronic respiratory acidosis. Although most patients experience a small increase in PaCO₂ with oxygen administration, the occasional patient might enter one of the cycles we describe and develop life-threatening hypercapnia.

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Animal testing in India

Sir—In his Oct 21 news item,¹ Dinesh Sharma reports on the current regulations for animal testing in India. I am a member of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and believe that his statement that the Chairperson, Mrs Maneka Gandhi, has secretly amended the rules governing animal experimentation is not based on fact.

Most experiments in India involve small laboratory-bred animals and are approved by the Institutional Animal Ethics Committee (IAEC) of the organisation doing the experiments. These committees are formed as per the guidelines of the Indian National Science Academy, and include a nominee of the CPCSEA. Many meetings were being called at short notice, and, therefore, the meeting notice, along with the research protocol, must now be sent to the members of the IAEC at least 30 days before the meeting.

CPCSEA nominees have no veto powers, but to ensure that they are not bulldozed into agreeing with IAEC members, they can refer points to other CPCSEA members. Most organisations in India have formed their IAEC only since the start of 2000, and many still have to do so. With the exception of the CPCSEA nominee, all the other members are generally employees of the institution or organisation and cannot question their superiors or peers.

Although a few private laboratories and government organisations maintain their animal houses well, fewer than a dozen of the roughly 5000 laboratories in the country have been certified to conform to good laboratory practices requirements.

For almost 50 years, scientists have been able to do as they please in their laboratories. For the first time in 1998, rules governing animal care were formulated. These rules are in line with, but less stringent than, those in force in the UK and the USA. Jawharlal Nehru, India's first Prime Minister, set up a string of scientific institutions. He called them the temples of modern India and described the scientists working there as the high priests of these temples. Probably the discontent of some of these scientists being asked to follow rules is due to their taking Nehru's statement too literally.

The scientists on the CPCSEA are nationally renowned and it would be unfair to accuse them of keeping quiet if Mrs Gandhi had done what Sharma reports. The current rules, decided in April, 2000, are that IAECs can allow

experiments only on small laboratory-bred animals—guinea pigs, rabbits, rats, mice, hamsters, and invertebrates. For all other animals, permission must be sought from a subcommittee of the CPCSEA, consisting of P K Dave, Director of the All India Institute of Medical Sciences; O P Asthana of the Central Drug Research Institute, Lucknow; and Vasantha Muthaswamy, Deputy director general, Indian Council of Medical Research (Animal Users All). To speed permission, CPCSEA nominees contact subcommittee members as early as possible by fax, e-mail, and so on, and communicate the decisions quickly. Appeals can be made to the CPCSEA if organisations disagree with the decision or if the proposal is refused by the CPCSEA nominee on their IAEC.

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- 1 Sharma DC. India's animal experimentation

Author's reply

Sir—Chinny Krishna's letter should be read in the context of the continuing controversy about animal experimentation rules in the past 2 years.

After the uproar by the scientific community over the rules, which required that all animal experiments be cleared by the centralised CPCSEA, headed by the social justice minister and animal welfare activist Mrs Maneka Gandhi, the process of giving permission for animal experimentation was decentralised. The Indian National Science Academy had proposed in its guidelines that animal experiments be approved by IAECs instead of the CPCSEA to cut down delays. This proposal was accepted and IAECs, with CPCSEA nominees, were allowed to approve animal experiments on small laboratory-bred animals.

The amended CPCSEA rules, decided in the April 6 meeting, clearly state in agenda item 6 that whenever a CPCSEA nominee in any IAEC disagrees with a proposal for experimentation on animals, the IAEC will not be empowered to give permission for pursuing that experiment. If one member of the IAEC does not agree, the decision of the rest of the members is invalidated. Krishna does not believe that this procedure amounts to veto power.

Second, Krishna mentions the three-member experts subcommittee to which institutions can appeal if they

disagree with the CPCSEA nominee's decision. He has, however, conveniently forgotten to mention that, irrespective of the expert committee's verdict on any institution's appeal, the CPCSEA decision will be final. Therefore, not only is there one veto at IAEC level, but the expert committee verdict can also be vetoed by the CPCSEA.

The veto power has been exercised by CPCSEA nominees on some IAECs. In one leading institution's IAEC, the nominee from CPCSEA once "completely forgot" to attend a meeting. A few months later, she telephoned to say that she would be unable to attend another meeting because she had sprained her ankle. All decisions taken at the two meetings by other committee members were declared invalid by the CPCSEA.¹

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1 Researchers say that projects are under a stranglehold—Animal Kingdom. *Telegraph* (Calcutta) 2000; **Oct 8**: 11.

Trends in use of positron emission tomography

Sir—M J O'Doherty and colleagues' Nov 18 commentary¹ outlines the clinical validity of and current trends in positron emission tomography (PET) scanners and investigations, especially in oncology. Because of its extremely high costs, reimbursement for clinical investigations done and the high costs of delivery systems of radiopharmaceuticals should be discussed.

Reimbursement is a rate-limiting factor for wider use of PET. For example, the number of PET scans done in the USA increased strikingly after public-health insurance began to reimburse hospitals for oncology

PET.² The table shows the number of scanners per population in various countries.

In Belgium and the UK, public support for clinical PET studies exists. In Germany, private health insurance companies, which supply about 50% of the health budget, have agreed to support almost all clinical PET investigations. Public-health organisations are still debating whether or not to fund the procedure.

Delivery of short-lived radioactive pharmaceuticals has become popular in Germany, and ¹⁸F-fluoro-deoxyglucose (FDG) is transported by car and airplane nationally and to nearby European countries. Because of the frequency of radiopharmaceutical delivery, more than 65% of PET sites are supplied with FDG from nearby cyclotrons in Germany.^{3,4} The sharing of cyclotrons saves money that would otherwise be spent on the installation of new cyclotrons, and is also practical because one cyclotron can supply up to ten PET sites.

In Japan, however, all PET sites have their own cyclotrons. This arrangement is not cost effective, but insurance organisations have not yet approved reimbursement for FDG PET. Most PET sites in university hospitals can charge the patient for a part of the cost (Advanced Medicine System) of their treatment. This system is meant to be a temporary answer before full payment from health insurance organisations can be arranged. Unfortunately, patients have only limited budgets and this system has not worked well. Furthermore, a rise in the number of elderly people in Japan has led to higher medical costs. Insurance organisations are, therefore, increasingly unlikely to become involved.

Additionally, regulations for the handling of radioactive material are strict and its transport is expensive. These factors limit wider distribution of PET in Japan (table). The strict regulations might be partially

attributable to the past tragedies caused by two atomic bombs, and to an accident in Tokai-mura. There might be a kind of nuclear-phobia in Japan. We believe that it will take years before PET becomes a routine clinical investigation in this country.

There are wide differences between countries in the distribution of PET and in socioeconomic situations. Reimbursement and radiopharmaceutical transportation issues have a big effect on the spread of PET use.

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Subarachnoid haemorrhage

Sir—I found in the conclusion of Alfonso Ciccone and colleagues (Nov 25, p 1818)¹ that oral contraceptive use was the only known risk factor in a woman aged 36 years who had stroke unusual, since she smoked around 20 cigarettes a day.

In my 40 years' work as a general surgeon, the young women I saw with a stroke or different serious vascular lesion all took oral contraceptives and were heavy smokers. Perhaps I saw in total about five or six such cases. They always made a deep impression on me.

To not mention the heavy smoking of the patient as a risk factor in this case of Ciccone and colleagues is an error in my opinion. These case reports should be good examples you can learn something from.

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- 1 Ciccone A, Citterio A, Santilli I, Sterzi R. Subarachnoid haemorrhage treated with anticoagulants. *Lancet* 2000; **356**: 1818.

Country	Number of PET scanners	Population (million)*	PET scanners per million†
USA	108	274	0.4
Germany	73	82	0.9
Japan	37	126	0.3
China	12	1262	0.01
UK	11	58	0.2
Belgium	9	10	0.9
Russia	9	147	0.1
Italy	9	57	0.2
Canada	8	31	0.3
France	7	59	0.1

*Taken from UN Population Division, Department of Economic and Social Affairs. Population of the Countries of the World, 1998.

†Number of PET scanners extracted and revised from a list supplied by Siemens Company, 1998.

Number of PET scanners per 1 million population by country

Fetal microchimerism and inflammatory myopathies

Sir—Carol Artlett and colleagues (Dec 23/30, p 2155)¹ and Ann Reed and colleagues (Dec 23/30, p 2156)² report the presence of microchimerism of maternal origin in male patients with juvenile idiopathic inflammatory myopathies. Microchimerism can induce graft-versus-host disease (GVHD) and polymyositis as a manifestation of chronic GVHD.³

To find out whether fetal chimeric cells play a part in the pathogenesis of idiopathic inflammatory myopathies, we analysed the presence of male DNA by amplifying, with PCR, a specific region of the Y chromosome in peripheral blood cells from 18 Spanish women (mean age 51·7 years [range 25–86]) who had male children, selected from patients with idiopathic inflammatory myopathies. 11 of the women had dermatomyositis, six had polymyositis, and one was diagnosed as having inclusion body myositis. No disease was related with malignant disorders or other connective-tissue diseases. As a control we included 18 healthy Spanish women (mean age 48·7 years [32–65]) who had male children.

We used more than five samples per woman. The results showed Y-chromosome-specific DNA detected in peripheral blood cells from only one patient with idiopathic inflammatory myopathies, but not in the 18 healthy controls. Southern blotting confirmed the identity of the Y-chromosome-specific product in the positive sample. The two groups did not differ significantly for findings.

During pregnancy, a transfer of cells is bidirectional between mother and fetus, which could explain the presence of fetal microchimerism and chimerism of maternal origin.⁴

Whether the presence of fetal or maternal chimeric cells has different pathogenic implications in patients with autoimmune diseases is an issue that needs to be explored. Our results suggest that the presence of microchimerism is not enough to induce disease, and that other genetic and environmental factors are probably involved.

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Pain in Anderson-Fabry's disease

Sir—F Peters and colleagues (Jan 13, p 138)¹ describe a woman in her 60s who had Anderson-Fabry's disease, with associated skin, cardiovascular, renal, and ophthalmological signs. In addition, she had a 10–12 year history of episodic pain in her hands and feet, described as acroparaesthesia, a known feature of the classic and atypical forms of the disease that can occur in heterozygotes.

These unusual subjective symptoms of the extremities might be the only clue to this uncommon disease. We saw a girl aged 11 years who presented with a 4-year history of recurring pain in both hands.² The attacks of severe burning pain lasted for 4–10 days and were relieved partially by cold objects, with no neurological deficit during or after attacks. We suspected Anderson-Fabry's disease, and we confirmed her carrier status through a mean α -galactosidase A enzyme concentration of 2·3 μ mol/L (normal range 3·3–20·3).

In the classic form, 90% of affected boys younger than 15 years might have excruciating acral pain crises.³ However, most female carriers are symptom-free and only 10% have an intermittent pain of the extremities, generally starting at a later age than in male hemizygotes.¹

Our patient had no other skin or systemic features on screening and has had no further attacks requiring any treatment. Such pain might be the presenting and only symptom in young women carriers.

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Invasive brain tumour after radiosurgery

Sir—John S Yu and colleagues (Nov 4, p 1576)¹ report on a patient treated for an occipital meningioma, who developed a glioblastoma in the region of her therapeutic radiation 7 years later. Unfortunately they calculate the risk of this occurring by coincidence as one in 1–5 billion and use this number to prove that radiation is the cause.

If we ignore the possible common aetiological factors, the chances of the patient developing such a tumour are at least 100 000 times more likely than stated. In the USA, the age-specific yearly incidence rate for invasive brain tumours for women in their early sixties is 11 per 100 000 population.² For any woman age 63 years living for 7 years, therefore, the odds of this event are more than one in 15 000. Many tumours of the size shown in Yu and colleagues' figure 1 would be expected to occur adjacent to any given 4 cm diameter area (such as the treated area in their case).

Since many tens of thousands of patients have received radiosurgery, the chance occurrence of one subsequent invasive tumour is feasible and might not be the confirmation of radiation-induced malignant disease Yu and colleagues claim.

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- 1 Yu JS, Yong WH, Wilson D, Black KL. Glioblastoma induction after radiosurgery for meningioma. *Lancet*. 2000; **356**: 1576–77.
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Authors' reply

Sir—We calculated the joint probability of independent events occurring together as the product of their individual probabilities: $P(A \text{ and } B) = P(A)P(B)$, which in the case of developing a primary brain tumour in 7 years would be one in 1–5 billion. However, dependent on whether woman already has the primary brain tumour, and with use of the SEER data to estimate the incidence of primary brain tumours for women in their early 60s, we concur with Bydder that the probability of our patient developing a primary brain tumour in 7 years is more than one in 15 000.

We disagree that many tumours would be expected to occur adjacent to a 4 cm area of the meningioma. Glioblastomas have frontotemporal

predominance, which may reflect the larger tissue mass in this region.¹

According to Cahan's criteria, a latent period must elapse after radiation for the tumour to be classified as radiation induced. Because of the requirement for a latency period and for the tumour to be in the irradiated field, the risk of a tumour with these requirements would be substantially less than the calculated risk.

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- 1 Davis L, Martin J, Goldstein SL, et al. A study of 211 patients with verified glioblastoma multiforme. *J Neurosurg* 1949; 6: 33–44.

Anonymous testing for HIV in tuberculosis cases and contacts

Sir—Frances Bowen and colleagues (Oct 28, p 1488)¹ report a study of anonymous testing for HIV seroprevalence among patients with culture-proven tuberculosis in a south London, UK, cohort.

Guy's and St Thomas' Hospitals, also in south London, serve the communities of Lewisham, Lambeth, and Southwark, a population of around 750 000. Since 1993, 8% of all UK immigrants have lived in this area, and 25% of the local population are from ethnic minority groups. In 1998, about 350 new cases of HIV were diagnosed and notification rates for tuberculosis

Characteristics	n (%)
Sex (M/F)	29 (58%)/21 (42%)
Infection	
First infection	45 (90%)
Recurrent infection	5 (10%)
Age range	
16–34	31 (62%)
35–54	9 (18%)
≥55	10 (20%)
Country of origin	
Outside UK	32 (64%)
UK	18 (36%)
Ethnic origin	
White	17 (34%)
Black African	23 (46%)
Indian	6 (12%)
AfroCaribbean	2 (4%)
Other	2 (4%)
Time of arrival in UK	
<5 years	34 (68%)
≥5 years	16 (32%)
Site of disease	
Pulmonary	32 (64%)
Extrapulmonary	16 (32%)
Both	2 (4%)

Demographic and clinical data on 50 patients with culture-proven tuberculosis

were higher than 30 per 100 000, the seventh highest in the UK.

With ethics approval, from December, 1999, to November, 2000, we aimed to establish the prevalence of concurrent HIV infection among patients diagnosed with culture-proven tuberculosis. In our chest clinics we displayed a Department of Health poster which said that, after blood tests, leftover blood could be anonymised and HIV tested. We collected the following information on smear-positive patients or patients with presumptive tuberculosis: first infection or recurrent disease, age range, sex, place of origin, year of arrival in the UK, and site of infection. When microbiological samples became culture positive and were speciated as *M tuberculosis*, we assigned them random numbers and anonymised them by unlinking all identifiers before HIV testing. No patient refused blood tests.

166 patients with mycobacterial disease were diagnosed: 96 had culture-positive tuberculosis and 47 mycobacteria other than tuberculosis. 23 cultures were contaminated or still outstanding. Among the patients with culture-positive tuberculosis ten were known to be HIV seropositive, three were diagnosed at necropsy, and three attended chest clinics outside our Trust's catchment area. 80 patients with culture-confirmed tuberculosis were regular attendees at chest clinics and 50 (62.5%) anonymised blood samples were available for HIV antibody testing (Microparticle enzyme immunoassay [MEIA], Abbott AxSYM system). Reactive samples were confirmed by a Wellcozyme HIV-1 specific competitive ELISA (Murex Biotech Ltd) and an HIV-1-specific gel particle agglutination assay (Serodia, Fujirebo Inc). The relevant information on patients tested for HIV is summarised in the table.

One (2%) patient of 50 tested HIV-1 antibody positive, which differs significantly from Bowen and colleagues' findings of 23 (11.4%) of 202 patients. Overall, the prevalence of HIV and tuberculosis co-infection was similar at 11 (11.3%) of 97.

The study is continuing, and the final analysis will include 150 patients. Our preliminary data suggest that the occurrence of undiagnosed HIV-1 infection among patients with culture-positive tuberculosis attending chest clinics in south London is rare. Although the possibility of HIV co-infection should always be considered, our preliminary findings do not suggest that all patients with *M tuberculosis*, irrespective of back-

ground, should be urged to have an HIV test.

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- 1 Bowen EF, Rice PS, Cooke NT, Whitfield RJ, Rayner CFJ. HIV seroprevalence by anonymous testing in patients with *Mycobacterium tuberculosis* and in tuberculosis contacts. *Lancet* 2000; 356: 1488–89.

Authors' reply

Sir—We note the low seroprevalence for HIV reported by Mark Melzer and colleagues. We believe the rate of HIV and tuberculosis co-infection might vary widely within London, according to local population demographics. Such differences are shown by the results of three different studies.

Melzer and colleagues' co-infection rate of 2.0% differs from 4.6% in 1993 in a London-wide PHLS study,¹ 24.8% in 1999 in a west London study,² and 11.4% in our southwest London study.³ So far Melzer and colleagues have included only six patients of Indian origin, compared with 97 in our study. In this subgroup of patients we saw a surprisingly high seroprevalence rate.

At the final analysis, Melzer and colleagues' extra demographic data, such as first or recurrent infection, site of disease, and date of arrival in the UK, will help to further understanding of the epidemiology of HIV and tuberculosis co-infection. We are concerned, though, that an interim analysis of 50 patients with such detailed demographic data could lead to the deductive disclosure of the HIV-positive individual.

Although HIV seroprevalence rates might vary widely across London in people with tuberculosis, trying to predict who is HIV positive from cultural background is an error of judgment, and we still believe that all patients with tuberculosis should be urged to have an HIV test.

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- 1 Kumar D, Watson JM, Charlett A, et al. Tuberculosis in England and Wales in 1993: results of a national survey. *Thorax* 1997; 52: 1060–67.
- 2 Marshall BG, Mitchell DM, Shaw RJ, et al. HIV and tuberculosis co-infection in an inner London hospital prospective anonymized seroprevalence study. *J Infect* 1999; 38: 162–66
- 3 Bowen EF, Rice PS, Cooke NT, Whitfield RJ, Rayner CFJ. HIV seroprevalence by anonymous testing in patients with *M tuberculosis* and their contacts. *Lancet* 2000; 356: 1488–89

Electrocardiography first for reducing cot death

Sir—The Italian Superior Council of Health has suggested offering, free of charge, electrocardiography for all neonates for the prevention of sudden infant death syndrome (SIDS). The incidence of this syndrome in Italy is estimated to be 0.07% of liveborns (378 of 540 000).¹ This conclusion is the result of Italian research that has provided important evidence that the deaths of about half of SIDS infants is associated with an extended QT interval (>440 ms, 97.5 percentage value among all liveborn).²

This intervention applied to the whole population of Italian neonates can be expected to have a potential cost of at least 12 billion lire (UK£3.7 million) for electrocardiograms, and organisational difficulties for guaranteeing adequate technical procedures. With diagnosis in all national birth places, 13 500 neonates with the defined extended QT would be identified.³

In other countries, where this decision is only a hypothesis, many physicians argue against the initiative, especially about the efficacy and effectiveness of the intervention.⁴ The Italian health authority has recommended treatment with β -blockers for at least the first 6 months of life in all infants with a long QT interval. This approach is more than questionable, given that efficacy has to be proven, that the drugs would be used in an unlicensed or off-label way, and that side-effects need to be taken into account.

We are also concerned with the decision about the public-health approach. Many factors affect the risk of SIDS, including attitudes such as those about sleeping position, co-sleeping, and parental smoking. Attitudes can be changed with information campaigns. These changes can effectively lower SIDS incidence.⁵ Although this type of intervention should be a priority, nothing systematic, continuous, and country-wide has yet been done in Italy.

We randomly interviewed, close to the authoritative decision date, 100 mothers of healthy infants aged 1–3 months about their attitudes to and knowledge of SIDS risk factors. 16% of infants slept in a separate room and 4% were co-sleeping. Parental smoking concerned 4% of mothers and 14% of fathers. 91% of infants were given pacifiers, especially to induce or during sleep. Only 38% of infants slept on their back at night and at naptime; 24% of mothers had never received instructions about the best sleep position for their child, and 42% received suggestions to

put the baby on his or her side by health professionals. Furthermore, only 52% of infants were exclusively breastfed.

The population size was small, but primary health priorities and preventive interventions at the national level seem to need to, move in other directions before routine neonatal electrocardiographic screening is warranted.

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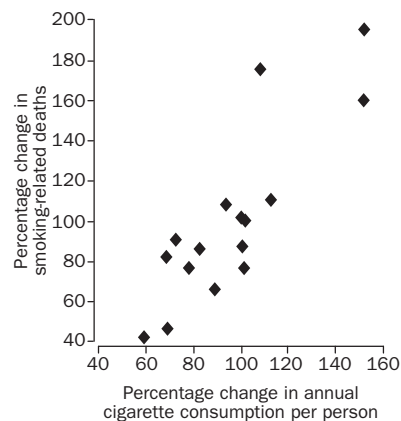
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Redefining goals for tobacco control

Sir—In Denmark we have two ambitions for tobacco control. The Ministry of Health aims to lower the prevalence of smoking by 1% per year in the new public-health programme, from 1999 to 2008. The Ministry of Taxation wishes, because of increasing border trade after changes in European Union regulations in 2003, that Denmark should lower tax on cigarettes by 25%. This reduction should raise consumption of cigarettes by 4% and provide the Ministry with an additional UK£30 million per year.

The two goals might seem incompatible, but are not mutually exclusive. From 1950 to 1980, prevalence of smoking in adult Danish men declined from more than 80% to less than 50%. Meanwhile, consumption of cigarettes in Denmark increased from 1×10^9 to 7×10^9 per year. The incidence of lung cancer was probably related to the consumption of cigarettes 15 years earlier, which would explain the paradox of a rise in lung-cancer incidence in a period of declining prevalence of smokers.

The general trend in western European countries in 1970–95 supports the importance of



Change in consumption of cigarettes and death rates for smoking-related at age 35–69 years, 1970–95, in western European Countries

consumption of cigarettes for the development in tobacco-related deaths.^{1,2} Some countries, such as Finland and the UK, had almost a 50% reduction in consumption, with a corresponding decrease in deaths among men aged 35–69 years. Consumption of cigarettes and death rates were stationary in most other countries. Consumption of cigarettes, however, increased by 50% in Portugal and Greece and the respective death rates doubled (figure). A third of deaths in men aged 35–69 in western Europe are from tobacco-related diseases.

Better use of findings might help in public-health planning in western European countries. We show that reduction of the consumption of cigarettes is possible in a country and is more important than a reduction in prevalence of smoking to decrease burden of premature deaths. A reduction in consumption is, however, harder to obtain than that in prevalence of smoking. The UK and Finland had had strong concerns about smoking-related deaths since the 1950s but differed in approach to tobacco control. More knowledge about these countries' approach might lead to similar redefinition of goals and implementation of appropriate measures to obtain a 50% reduction in smoking-related mortality in other countries.

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- 1 Peto R, Lopez AD, Borcham J, Thun M, Heath C. Mortality from smoking in developed countries, 1950–2000: indirect estimates from national vital statistics. Oxford: Oxford University Press, 1994.
- 2 Corrao MA, Guindon GE, Sharma N, Shokoohi DR. Tobacco control country profiles. Atlanta, Georgia: American Cancer Society, 2000.

Fake antimalaria drugs in Cambodia

Sir—During 1998–99 the European Commission-Cambodia Malaria Control Project (EC-CMCP) carried out surveys on malaria-treatment-seeking behaviour in four malaria-endemic areas in Cambodia. More than 90% of the population in the normally remote communities obtained their first-line treatment from local informal-sector health providers. The treatments were invariably inadequate, containing no malaria drugs at all or only a small part of the complete regimen recommended for mefloquine and artesunate. Although a single dose of mefloquine was the officially recommended treatment, artesunate was the most popular. The local health providers obtained the drugs from drug vendors and small pharmacies based in nearby market places. These vendors and pharmacies were in turn supplied by wholesale pharmacies based in Phnom Penh.

Because of suspiciously low prices and claims about strong and poor qualities of malaria drugs, samples were collected in June and July, and sent for analysis in August, 1999, to the drug analysis division of the Department of Medical Science, Ministry of Public Health in Thailand. The results were double-checked in the laboratories of the supposed manufacturers of mefloquine in Australia and of artesunate in Guilin, China. Most of the bottles with Mefloquine tablets and about half of the artesunate blister packs sampled seemed to be fakes. For mefloquine and artesunate, two different varieties of fakes were found: a first-generation fake that was easy to distinguish from the genuine product, and a second-generation fake that much more closely resembled the genuine product.

A survey to assess the availability of fake drugs across the country was carried out at the end of 1999 by a team of two investigators posing as relatives or colleagues (forest workers) of a malaria patient. A total of 242 drug vendors and pharmacies were mapped in 12 market places, and 133, about half in each market place, were selected at random for investigation. Fake artesunate was sold by 71% (86% sold the genuine product) and fake mefloquine by 60% (61% sold the genuine variety). The fakes were frequently preferred by patients and village health providers because of the lower price. Given their widespread use, the fake malaria drugs are probably a major cause of mortality and morbidity due to malaria in Cambodia.

Cambodia lacks companies with pharmaceutical packaging facilities and although almost all drugs, including fakes, are imported from neighbouring Vietnam, it is not clear in which country the fake drugs are manufactured. Analysis of samples collected by the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, has confirmed that the fake artesunate is common in other countries in the Mekong region.

Stronger regulation of the private or informal sector in poor areas with weak government structures will be counterproductive if not complemented by other measures. An information campaign aimed at protecting consumers and combined with measures to improve availability of quality-assured drugs through a social marketing programme of prepackaged antimalaria drugs is the most effective strategy.

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Women in advertising

Sir—I am sure *The Lancet* would not champion the idea that to rise to the top in medicine you should be a man. Yet, a quick review of the (blue) full-page advertisements suggests otherwise.

Unimaginatively, women appear as the beautiful bride or holding up the queue for *The Lancet*, or with the regulation bouncing bosom. Men are portrayed as old-school fogies, but they are innovative, witty, and, yes, generally on their way up.

Although I wish *The Lancet* well with its advertising, I would be grateful for (and attracted by) more ingenious images of women readers.

Rosalind Coleman

C/o 92 Alderney Street, London SW1V 4EZ, UK

Sizing up research

Sir—There is a message for scientific journals hidden in newspaper headlines, which rely on size to signal the importance of the news. I think it is time for journals to adopt and extend this approach, by printing articles in a font size proportional to the importance of the work, as judged by the editors.

Editors at prestigious journals claim to turn away many fine papers for a lack of sufficient space. I suspect that some of these papers are solid but duller than

the US tax code. So why not publish them in the small-print type size used for the tax code? High-priority articles could be printed in a bold 12 point font. Smaller gradations of font sizes could be used accordingly for articles of lower priority, down to microscopic. Three or four low-priority reports might then fit a single 10-column page. Busy readers could save precious reading time simply by noting the editorial priority reflected in the font size.

Some journals already use a rudimentary version of this approach, by using small font sizes for appendices. Many journals also shift to a small font size for the methods section of papers, which conveys the message that the description of what was actually done in a study is low-priority information, barely worth publishing. A better implementation of this scheme is to apply the message in the font size to the entire paper. The table of contents could mirror the font size used in each article, thereby directing readers first to the most important material.

Perhaps the biggest obstacle would be the unfair burden placed on those who are visually challenged. The editors of the Oxford English Dictionary solved this difficulty by including a magnifying glass with each copy of their compact edition. A more elegant approach might be to offer a premium to journal subscribers, such as a binocular microscope with a shelf designed to hold the journal.

Should the editors care to give this scheme a try, I suggest that they might begin with this letter. I am hoping for at least a double-digit font size, but it would not surprise me if you needed to borrow a microscope to read it.

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DEPARTMENT OF ERROR

Classification of drug-resistant tuberculosis—In this Correspondence letter by Pamela Sonnenberg and colleagues (Dec 2, p 1930), the first sentence of the third paragraph should read “In the Cape Town study, [van Rie and colleagues](#) defined a cluster as ‘a group of two or more drug-resistant isolates.’”

Renal-dose dopamine: will the message now get through?—In this Commentary by Helen F Galley (Dec 23/30, 2000, p 2112) the low or “renal” doses of dopamine referred to in the second paragraph should have been “0.5–2.0 µg/kg per min”.

Pain expression and stimulus localisation in individuals with Down's syndrome—In this Article by M Hennequin and colleagues (Dec 2, p 1882), Prof J S Feine should also have been affiliated to the Faculty of Dentistry, McGill University, Montreal, Quebec, Canada H3A 2B2.