

CORRESPONDENCE

e-mail submissions to correspondence@lancet.com

Suicide rates in China

Sir—The uniquely high rate of suicide in China, especially among women, described by Michael Phillips and colleagues (March 9, p 835)¹ may be partly explained by the strictly enforced birth quotas in that country.

In rural areas, couples of an appropriate age may apply to have two children. Urban couples are limited to one. The timing of births is regulated by a licensing system run by local population-control officials, who are allotted a regional birth quota. Such population control reflects a radical attempt to reverse attitudes toward procreation in a culture that has historically placed a high value on large families.²

Abortion is strongly associated with a two-fold to six-fold rise in risk of suicide.³ Record studies^{3,4} and clinical evidence⁵ show that suicidal behaviour after abortion is probably related to unresolved grief and depression rather than pre-existing psychiatric illness. These feelings may be accentuated when women consent to an unwanted abortion only because of external pressures.⁵

Chinese women face the prospect of being pressured into abortion.² Even those who manage to avoid unexpected pregnancies may experience grief over not being allowed to have as many children as they want, when they want. Moreover, the preference for boys in rural areas has led to infanticide and selective abortion of female fetuses, which may cause impacted grief and a sense of devaluation of women's self-worth.

The lower suicide rate among urban women may reflect that they are more likely to accept restricted family sizes because they are undergoing the demographic transition to lower birth rates that normally accompanies higher income, more skilled employment, and greater social opportunities. The higher rate of suicide among rural women may reflect a greater emphasis on children in rural areas, where children contribute to family labour and represent a focus for investing the parents' creative energies. Rural couples who do not proportionately share in China's economic growth may be disproportionately burdened by

denial of the opportunity to have as many children as they desire.

Given the Chinese government's commitment to reducing the population, it is unlikely to abandon its birth-quota system merely to lower suicide rates. The government fertility-regulation officials might attempt to alleviate the emotional consequences of their mandates, however, by offering appropriate grief counselling programmes for couples who have agreed to abortion or who have been denied birth permits. A study linking suicide and abortion records in China could confirm my hypothesis, but may not be feasible given the political implications of such research.

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Sir—Michael Phillips and colleagues¹ point out the association between suicide and mental disorders.

We have done a systematic review of studies in which psychiatric diagnoses of 15 629 people who committed suicide were identified, published between 1973 and 2001, all over the world. All studies refer to adults with or without history of admission to mental hospitals (53 vs 48%). We excluded studies covering only specific age-groups such as young people or the elderly, or specific disorders such as depression or schizophrenia. Diagnoses included those made while people were alive or at post mortem examinations; all diagnoses were made on the basis of the *International Classification of Diseases*, revision eight, nine, or ten, or the *Diagnostic and Statistical Manual III*,

III-R, or IV, and converted to general classifications common to both systems.

The four most frequent diagnoses were, by order of magnitude, mood disorders (30%, generally depression), substance-related disorders (18%, mainly alcohol-related), schizophrenia (14%), and personality disorders (13%). No diagnosis was noted in 2% of all cases. Associations such as comorbidity, sex, and geographical distribution of diagnoses need clarification.

Although mood disorders were the most frequent diagnosis, they did not affect even a third of the patients, which is lower than is currently believed. Should these findings be confirmed, suicide prevention strategies based solely or mostly on the treatment of people with depression might need reconsideration. On the other hand, the fact that most (98%) of people who committed suicide had a psychiatric diagnosis would clearly justify a comprehensive suicide-prevention strategy that targets mental disorders as a whole, with a clear emphasis on depression and harmful alcohol use.

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Authors' reply

Sir—David Reardon proposes China's family planning policy to explain the high rate of suicide among young women in rural China. The greater importance placed on having a male child in rural areas (to carry on the family name, inherit the family land, and be responsible for caring for elderly parents) could increase the negative psychological effects of the policy in rural areas.

To address this question, we included items about pregnancy, abortion, sterilisation, fines for exceeding the birth quota, and birth of a female child in the life-event scale we have developed as part of our continuing national psychological autopsy study of accidental deaths done in collaboration with the Chinese

Academy of Preventive Medicine. So far, the study has included 169 rural women aged 15–34 years who died by suicide and 45 controls who died by other accidents: 12 (7%) suicide cases compared with four (9%) controls had had an abortion, sterilisation or other contraceptive procedure in the year before death, or more than 1 year before death followed by continuing negative psychological effects. 34 (20%) suicide cases and six (13%) controls had any of these negative childbirth-related life events or had given birth to a daughter in the 2 years before death. By contrast, the most common negative life event—serious conflicts with spouse—had been experienced by 86 (51%) suicide cases and three (7%) controls.

Moreover, in another continuing study on attempted suicide, only four (6%) of 72 young rural women reported these childbirth-related problems. We conclude, therefore, that the social and psychological effects of the family planning policy are not important determinants of the high rates of suicide in young rural women in China.

The letter from José Bertolote and Alexandra Fleischmann raises the issue of whether or not mental illness is a necessary precondition for suicidal acts, which is relevant to the suicide-prevention programmes and current debates about euthanasia.¹ Their finding that 98% of suicide victims have diagnosable mental disorders does not match with reports from China,² Sri Lanka,³ India,⁴ and Malaysia,⁵ where substantial proportions of victims of attempted and successful suicide have no mental illness at the time.

In locations where more lethal methods are frequently used, especially agricultural poisons, and where resuscitation services are limited, there are more deaths among people with a low suicidal intent, some of whom have no mental illness. Our experience in China is that most cases in which the victim has no mental illness are impulsive acts immediately after stressful life events in individuals who have no history of psychological disorders. These individuals are acutely distressed and may experience various transient psychological symptoms, but many of them do not meet the criteria of a mental disorder or personality disorder because of the short duration of their symptoms and the absence of a long-standing pattern of impaired social or occupational functioning.

In China, as elsewhere, most people who die by suicide have a mental illness, so a comprehensive suicide strategy

must—as Bertolote and Fleischmann recommend—target mental disorders as a whole, but prevention strategies must also include approaches to dealing with the subgroup of attempted and successful suicides that are impulsive acts in people without mental illnesses.

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Presentation for myocardial infarction without chest pain

Sir—It is hardly surprising that missed opportunities abound in the thrombolytic treatment of ST-segment elevation myocardial infarction (MI), as reported by Kim Eagle and colleagues (Feb 2, p 373),¹ given the fact that the UK National Health Service framework² for heart attacks emphasises the chest pain presentation of this disorder, to the complete exclusion of other presenting syndromes.

The absence of chest pain is one of the most important factors in predicting lower use of thrombolytics,³ and as many as 33% of 434 877 patients with confirmed MI in one study had this type of presentation.⁴ Perversely, subgroups with higher prevalence of MI mortality risk, such as patients with diabetes and the elderly, are the ones more likely to have painless MI.⁴

The time is long overdue for information packs for the general public and for health-care workers to be amended to stress that alternative clinical presentations of heart attacks include sudden onset of breathlessness, upper-body discomfort other than chest pain, collapse, or mental confusion.⁵ Patients presenting in this

way, within the acknowledged therapeutic time frame¹ stand a good chance of improving short-term survival benefits and having a long-term reduction in heart failure risk through timely use of thrombolytics.

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Amiodarone-induced thyroiditis

Sir—We believe the case of amiodarone-induced thyroiditis described by J Ybarra and colleagues (Jan 5, p 69)¹ requires some comment.

Amiodarone is a generally well-tolerated iodine-rich molecule that can occasionally cause hypothyroidism or hyperthyroidism, dependent on local iodine intake.² Two major mechanisms have been evoked to explain the occurrence of amiodarone-induced hyperthyroidism: the first (type 1) is due to increased hormone synthesis secondary to iodide overload;³ the second (type 2) is thought to be a so-called toxic thyroiditis. These mechanisms are not always easily distinguished in clinical practice and are sometimes associated.

Thyroid scintigraphy can show a complete suppression of radiotracer uptake in both these situations—in the first one because of iodide overload, in the second because of the inflammatory process. Contribution of scintigraphy in diagnosing the mechanism of amiodarone-induced hyperthyroidism remains controversial, but we wonder about the interest of the case reported by Ybarra and colleagues.

If their patient had a normal thyroid-

function test, which is unlikely because patients taking amiodarone frequently have slightly raised free thyroxine concentrations because of impairment of conversion of thyroxine to tri-iodothyronine, there is no need for scintigraphy. Suppressed intake in a patient taking amiodarone is not surprising and is clearly not an indication to stop the drug. The normalisation of scintigraphy is not a sign of cure but shows only that iodide overload was reversible. Euthyroid homogeneous goitre is not an indication for scintigraphy, which in this case brought clinicians to take the bad decision to stop amiodarone.

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- 1 Ybarra J, Fuster D, Martin F, Lomeña F, Torregrossa JV. Amiodarone-induced thyroiditis. *Lancet* 2002; **359**: 69.
- 2 Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. *Endocrine Rev* 2001; **22**: 240–54.

Sir—J Ybarra and colleagues¹ provide no convincing evidence to support their diagnosis of amiodarone-induced thyroiditis. The presence of a faint thyroid is systematically seen in euthyroid patients chronically treated by amiodarone.²

This drug causes iodine overload because amiodarone contains 75 mg iodine per 200 mg tablet, of which around 10% is released as free iodine each day.³ The very low thyroid uptake of technetium-99m-labelled sodium pertechnetate or radioiodine is due partly to isotope dilution but also to a direct inhibitory effect of iodine on sodium/iodide symporter mRNA synthesis and protein expression.⁴

A few months after amiodarone treatment is discontinued, the thyroid uptake reverts to normal. Therefore, based on the information provided by Ybarra and colleagues, amiodarone-induced thyroiditis is certainly not the most likely explanation for the suppressed thyroid uptake in their patient.

First, amiodarone-induced thyroiditis (type 2 amiodarone-induced thyrotoxicosis) was described in patients with hyperthyroidism, which was not present in this case. This diagnosis may be suspected in patients with amiodarone-induced thyrotoxicosis in the case of a normal thyroid associated with raised serum interleukin 6, decreased thyroid blood flow on colour flow doppler sonography, and

heterogeneous pattern on ultrasonography.⁵ These criteria are not documented by Ybarra and colleagues. Therefore, this clinical picture illustrates only a faint thyroid due to iodide overload as was described more than 40 years ago by Saxena.⁵

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Authors' reply

Sir—Although amiodarone is viewed as a highly effective antiarrhythmic agent, its use may lead to alterations in thyroid gland function, thyroid hormone metabolism, or both more than rarely. 14–18% of amiodarone-treated patients have overt thyroid dysfunction, either amiodarone-induced thyrotoxicosis or amiodarone-induced hypothyroidism, as shown by Martino and colleagues, who Bernard Goichot and colleagues and Rodrigo Moreno-Reyes and Bernard Corvilain both cite. In the USA, amiodarone-induced hypothyroidism occurs in up to 20% of patients, whereas hyperthyroidism is far less common. These differences are attributed to increased ambient iodine.¹

Bogazzi and colleagues² reported colour-flow doppler sonography's ability to rapidly differentiate the two types of amiodarone-induced thyrotoxicosis. Although this ability can be crucial in choosing the right treatment (methimazole and potassium perchlorate *vs* glucocorticoids), its use in thyroid iodine overload—our case report—is unnecessary, as well as the measurement of serum interleukin 6.

We agree on the evoked mechanisms underlying amiodarone-induced hyperthyroidism and the difficulty in ascertaining which is the predominant

one in clinical practice. On the other hand, we believe that the teaching point of this case has been misunderstood. We are not recommending the practice of thyroid scintigraphy in amiodarone-induced thyroid dysfunction. Additionally, there were no clear indications to do thyroid scintigraphy in our patient. The patient was looking for a second opinion and the first image had already been obtained. We simply recorded the reversibility of the iodide overload in a patient with euthyroid homogeneous goitre by doing thyroid scintigraphy every 6 months.

Additionally, we bring to your attention the normality of the thyroid hormone concentrations: free thyroxine 15 pmol/L (normal range 9–28), total thyroxine 134 nmol/L (58–161), tri-iodothyronine 0.01 nmol/L (0.01–0.03), reverse tri-iodothyronine 0.45 nmol/L (0.23–0.6), and thyrotropin 1.1 mU/L (0.25–5.0). The typical increase in serum thyroxine and reverse tri-iodothyronine, and a decrease in serum tri-iodothyronine concentrations, mainly related to the inhibition of 5'-deiodinase activity, resulting in the generation of tri-iodothyronine from thyroxine and a decrease in the clearance of reverse tri-iodothyronine was not found in this case. Laboratory data were not included in the original manuscript due to space limitations.

However, we agree that iodine overload was probably the underlying cause for the initially minimal thyroid uptake; nevertheless, clinical examination of the patient's neck revealed a tender goitre. Her neck discomfort completely disappeared 3 months after amiodarone withdrawal.

Whenever qualifying a certain medical decision as good or bad one has to be indeed alert and keep in mind the full clinical context of the individual patient. Amiodarone has several systemic effects including pulmonary, ocular, skin, and hepatic toxicity which must not be overlooked. Additionally, our patient's atrial fibrillation has been under good control under treatment with warfarin, propranolol, and digoxin. Moreover, amiodarone treatment can be discontinued in those cases with absence of thyroid abnormalities.³

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Necrotising infections and group G streptococcus

Sir—Deepali Humar and colleagues (Jan 12, p 124)¹ in their report, and Stephen Gillespie, in his accompanying Commentary,² draw attention to group G β -haemolytic streptococcal infections. We report such an infection in a patient who developed extensive cellulitis (without necrotising fasciitis) and subsequent multiple-organ failure.

A man aged 32 years presented with malaise, right-sided pleuritic chest pain, and dyspnoea of 1-day duration. He had type I chylous reflux syndrome, characterised by chronic lymphoedema of the lower limbs and concomitant capillary haemangioma of the skin. A therapeutic embolisation of the right common iliac vessels had been attempted during childhood and had led to an above-knee amputation after gangrenous complications. He had also undergone surgical ligation of the megalymphatics of the aorta and inferior vena cava, and persistent chylothorax had been partly treated by chemical pleurodesis some years previously.

On admission, the patient was pyrexial (39°C) and cardiovascularly stable, but had signs of consolidation of the right lung. Within 4 h, cellulitis of the right thigh and abdomen had developed, extending to the flanks with associated blistering. White blood-cell count and renal function were normal. Despite intravenous antibiotics (benzylpenicillin and flucloxacillin) he worsened over the next 24 h. In the following 6 h he developed multiple-organ failure secondary to septic shock, and mechanical ventilation and inotropic support were started and progressively increased (epinephrine and norepinephrine). A pulmonary artery flotation catheter confirmed hyperdynamic circulation consistent with septic shock.

Clindamycin and gentamicin were added to antimicrobial treatment. Blood cultures grew group G streptococcus sensitive to benzylpenicillin. Despite all supportive

treatment he continued to deteriorate, his cardiovascular state became increasingly labile, he required 100% oxygen, and developed a disseminated intravascular coagulopathy. Cardiovascular instability prevented renal dialysis for worsening acute renal failure. Intravenous steroids (hydrocortisone) were introduced when he developed cardiovascular collapse unresponsive to increasing doses of inotropes, but to no effect. He died shortly afterwards. Postmortem investigation confirmed changes associated with multiple-organ failure together with the presence of extensive cellulitis but without necrotising fasciitis.

This patient fulfilled the clinical criteria for streptococcal toxic-shock-like syndrome, which is rarely reported in group G streptococcal infections.³ Several important points for management of group G streptococcal septicæmia arose from this case. First, our patient had a long-standing predisposing disorder, a chronic venous and lymphatic syndrome.⁴ Second, despite adequate antibiotic therapy and intensive support, this disorder may progress to multiple-organ failure and death.⁴ Third, there seems to be two groups of patients with group G streptococcal infection—fast responders and slow responders.⁵ Benzylpenicillin has been the mainstay of treatment, although slow responders may need a second antibiotic, such as clindamycin or gentamicin,⁵ and require further investigation for undrained abscesses. Aggressive surgical intervention may have a place in treatment, but in our patient this approach was deemed impossible because of the extensive spread of cellulitis and his overall physiological instability. Finally, adjuvant treatment with corticosteroids was unsuccessful.

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Decline in surgical training

Sir—Lewis Spitz and colleagues (Jan 5, p 83)¹ will have done UK medicine an enormous service if their comments reopen the debate on consultant training in the UK.

Although the difficulties they describe apply particularly to surgery, in which it is difficult to see any alternative to hands-on experience, similar issues exist in all medical disciplines, in which clinical training cannot possibly be completed without clinical experience.

10 years ago, Brearley² pointed out that in the UK, where specialist practice is done almost exclusively by consultants in the National Health Service, training is designed to produce individuals with the skills, knowledge, and experience necessary for appointment as consultants. He notes that most other countries have a social security system, under which most specialists are in private practice outside hospitals, are approached directly by patients, provide mainly an outpatient service, and recoup their fees through the system. Such an arrangement requires less training than the UK system because the responsibilities of specialists are different.

Against this background, it is difficult to understand why there was a consensus in favour of the Calman proposals, designed apparently to replace UK consultants with European-style specialists. It seems unlikely that Britain's pathetically small medical workforce can provide specialists on the continental model and old-style UK consultants. Instead, we are likely to see increasing centralisation of medical facilities, as specialists in smaller centres become unable to cope with the breadth of work handled by their predecessors. Public protest may draw political attention to the issue, but by then it will be too late.

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- Brearley S. Medical education. In: Richards T, ed. *Medicine in Europe*. London: L BMJ Publishing, 1992.

Sir—Lewis Spitz and colleagues¹ described their concerns about the future direction of surgical training in the UK. They mention several areas that will be affected by the new regulations, such as a decline in the continuity of care, and that the residents will not be exposed to a sufficient

number of cases to attain a certain degree of competence.

I submit that in the US a similar phenomenon is occurring in surgery and other specialties. For example, most residency programmes are mandated to give their residents a certain number of days off per month. This results in the aforementioned difficulties.

Furthermore, some primary-care programmes limit the number of patients that a resident can admit while he or she is on call, and there are night float systems, for which a selected resident takes all of the calls in the middle of the night so the other residents on call can sleep uninterrupted.

The deeper issue that I have noted as a resident is the decline in the old fashion apprenticeship model of training, which I too feel is invaluable and produces the most qualified and experienced physicians. It seems that, in the world of managed care, physicians now have to see two or three times as many patients as before and have less time to teach.

In the current litigious society of the USA, attending physicians are less inclined to allow residents (and medical students) to take a more active role in patients' management and in doing procedures. Ultimately, these two issues may lead some residents to feel that they are inadequately trained at the end of their residencies (especially in procedure-intensive fields) and lead them to pursue a fellowship for additional training.

I am well aware of the good intentions of trying to limit the number of hours that residents spend working; there will be no-one to limit their hours when they have completed their training. Being a physician requires mastery of a large amount of information and the ability to deal with the demanding lifestyle. Yet it seems that medical education is being diluted. Whether the roots of these changes in the USA are an effort to decrease the risk of litigation, a result of the pressures of managed care, or from the endless complaints that come from residents that feel that they are all overworked, is unclear.

The way in which residents and medical students are clinically educated is strikingly different from that seen as little as 10 years ago. Like Spitz and colleagues, I think that we are producing a generation of ill-equipped physicians, through no fault of their own.

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Albumin and hypovolaemia

Sir—In his response to the Viewpoint on quality of evidence on albumin and hypovolaemia, Ian Roberts (Jan 5, p 72)¹ comments on activities of the plasma products industry to which we respond.

Since the publication of the Cochrane report on the issue of albumin,² there have been many questions about the strength and validity of the findings.³

The Plasma Products Therapeutics Association (PPTA) has an obligation to provide the medical community with science-based evidence about the appropriate use of albumin. Therefore, the PPTA has started several activities to provide this evidence. We cannot agree with Roberts's statement that none of these activities help to resolve our uncertainty about albumin. We believe exactly the opposite.

In May, 2001, an article was published in which the safety of albumin based on spontaneous serious (fatal and non-fatal) events was reported. These data covered around 100 million doses of albumin administrations from January, 1990, to December, 1997.⁴ This method is widely accepted to show safety. The study provided evidence that non-fatal and fatal serious adverse events in albumin recipients are very rare. Currently this report is being updated to include all albumin used until the end of 2000.

Wilkes and colleagues⁵ concluded, in a meta-analysis, that postoperative blood loss is significantly lower in cardiopulmonary bypass patients exposed to albumin than in those exposed to hydroxyethyl starch.

A thorough meta-analysis by Wilkes and Navickis³ could not support the findings of the Cochrane article, but showed no increase in mortality in patients receiving human albumin.

In addition, the PPTA has and will continue to support research activities that help us to better understand the role and value of albumin in clinical practice. Results of these preclinical and clinical trials are and will be presented and published.

That is in our view what needs to happen, in parallel with further meta-analysis that uses consistent criteria for selecting the articles similar to the process used by Wilkes and colleagues.³

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1 Roberts I. Albumin and hypovolaemia: times to move on and generate new evidence. *Lancet* 2002; **359**: 72–73.

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Arterial-wall thickness and impairment in ABCA1-driven cholesterol efflux

Sir—In their report on cholesterol efflux and arterial-wall thickness, Marjel J van Dam and colleagues (Jan 5, p 37)¹ predict the ages of reaching an intima-media thickness at the upper limit of normal (0.80 mm) in individuals with ATP-binding cassette A1 transporter (ABCA1) mutations and unaffected controls. However, I think there are some flaws in the study design and question their results.

First, the prediction does not take into account the individual characteristics by which the association is affected. As described in the results, smoking and HDL cholesterol concentrations were significantly correlated with intima-media thickness. Therefore, based on van Dam and colleagues' findings, the predicted age of reaching the upper of normal intima-media thickness should be different for smokers and non-smokers, and for individuals with different HDL cholesterol concentrations.

Second, the age distributions in the two study groups differ. 15 (50.0%) patients with *ABCA1* mutations and about the same number of controls are aged 30–60 years; however, a significantly lower proportion of controls (13.6%, n=15) was selected in this age range. Therefore, without specifying the matching criteria (such as within an age range or the frequency matching) in the study design, and relying only on the statistical non-significance in the mean ages, the differing age distributions violated the matching prerequisite of this study.

The change of intima-media thickness with age should be assessed in a longitudinal study to assess changes over a period of time. Van Dam and colleagues used only one data point from each individual. Therefore, without evidence to describe and

support the relation within each individual, the estimated trend is meaningless and misleading.

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- 1 van Dam MJ, de Groot E, Clee SM, et al. Association between increased arterial-wall thickness and impairment in ABCA1-driven cholesterol efflux: an observational study. *Lancet* 2002; **359**: 37–41.

Author's reply

Sir—Yen-Hong Kuo's remarks are highly relevant. It is true that our main result on the upper limit of normal intima-media thickness is a global one, not discriminating between smoking and non-smoking individuals, and those with other risk factors. Since smoking and risk factors such as HDL cholesterol are associated with intima-media thickness, the upper limit will be reached later in life for non-smoking individuals and earlier for smokers. But since our controls are more or less randomly selected, our result is applicable for a random person from our population. We do not attempt to specify strata in our study since there are many risk factors, and our dataset is simply not large enough for that purpose.

We used only global matching for selecting controls to compare with individuals with *ABCA1* mutations to ensure the mean age was similar. Otherwise the age-distributions were not entirely similar, but our estimated regression line is still valid because age was the independent variable. Moreover, we did not select the unaffected controls on the basis of their intima-media-thickness values.

Kuo touches on the hidden premise in our analysis that the changes within individuals are supposed to be similar to the changes of the means; this assumption is basic to any cross-sectional study.

We have no longitudinal intima-media-thickness measurements as yet (we are sampling these), and we cannot, therefore, confirm this assumption. The rate of intima-media-thickness change due to ageing will probably vary between individuals because of the effect of risk factors, but we believe that the average intima-media-thickness change pattern will be similar to our results, as illustrated in figure 3 in the report.

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Treatment of severe autoimmune thrombocytopenic purpura

Sir—In their report, Bertrand Godeau and colleagues (Jan 5, p 23)¹ elegantly show that intravenous immunoglobulin is more effective for the acute treatment of severe autoimmune thrombocytopenic purpura than methylprednisolone. However their use of a platelet count less than $50 \times 10^9/L$ as a surrogate marker for bleeding risk is slightly misleading. Bleeding risk is strongly correlated with age, the highest risk being patients older than 60 years,² of whom their study only included small numbers.

In fact a platelet count of more than $30 \times 10^9/L$, rather than more than $50 \times 10^9/L$ is associated with an extremely low risk of haemorrhage.³ No mention is made of the difference in cost between these two treatments (around US\$1228 vs \$105 for a 70 kg patient), or the small but significant risks associated with intravenous immunoglobulin (anaphylaxis, haemolytic anaemia, aseptic meningitis).

Thus, to recommend intravenous immunoglobulin and prednisone as first-line treatment for patients of all ages with severe thrombocytopenia (platelet count $< 20 \times 10^9/L$) will lead to substantial treatment-related expense and expose some patients to potential risks when their risk of fatal haemorrhage is very low.

The treatment does work, but is it needed for everyone?

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- 1 Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; **359**: 23–29.
- 2 Cohen YC, Djulbegovic B, Shamai-Lubovitz O, Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. *Arch Intern Med* 2000; **160**: 1630–38.
- 3 Cortelazzo S, Finazzi G, Buelli M, Molteni A, Viero P, Barbui T. High risk of severe bleeding in aged patients with chronic idiopathic thrombocytopenic purpura. *Blood* 1991; **77**: 31–33.

Sir—We wonder why the primary outcome of Bertrand Godeau and colleagues' trial¹ was the number of days with platelet count more than $50 \times 10^9/L$. It seems clear from the data that a platelet count at this concentration was of no real clinical use, especially in patients with no evidence

of bleeding. Indeed the risk of fatal haemorrhage is extremely low even with a platelet count lower than $30 \times 10^9/L$.²

The so-called wet autoimmune thrombocytopenic purpura group, which is at an increased risk of haemorrhage, was excluded. Physicians need definitive answers in patients with severe autoimmune thrombocytopenic purpura, especially in those who have bleeding episodes. Unfortunately, Godeau and colleagues do not answer that question for intravenous immunoglobulin or high-dose methylprednisolone. These two treatments seem equally effective in patients with severe autoimmune thrombocytopenic purpura and no sign of haemorrhage.

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- 1 Godeau B, Chevret S, Varet B, et al. Intravenous immunoglobulin or high-dose methylprednisolone, with or without oral prednisone, for adults with untreated severe autoimmune thrombocytopenic purpura: a randomised, multicentre trial. *Lancet* 2002; **359**: 23–29.
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Authors' reply

Sir—We agree with the remarks of Duncan Carradice and Rama Balaraman that the use of a platelet count lower than $50 \times 10^9/L$ as a surrogate marker for bleeding risk could be misleading. However, we show that the median number of days with platelet counts higher than $20 \times 10^9/L$ (and two-fold the baseline value) between day 1 and day 21 after treatment was started is significantly higher in patients assigned intravenous immunoglobulin at randomisation than in those assigned high-dose methylprednisolone. The proportion of patients who have platelet counts greater than $20 \times 10^9/L$ between day 2 and day 5 is also significantly higher in the intravenous immunoglobulin group.

The number of days with platelet count greater than $20 \times 10^9/L$ also differs significantly in patients receiving intravenous immunoglobulin plus prednisolone and those receiving high-dose methylprednisolone plus prednisolone. Thus, we clearly show that intravenous immunoglobulin acts more rapidly, more frequently, and for a longer time than high-dose methylprednisolone.

As we note in the discussion, however, we are aware that clinical trials of autoimmune thrombocytopenic purpura should ideally focus on the effect of treatment on risk of severe bleeding or death, although these events are very rare. Thus, with these outcomes, we would need to enrol more than 1000 patients to show a clinical benefit, which is not feasible. We therefore chose platelet count as the primary outcome measure because it is a relevant and simple surrogate marker.

We also agree that other considerations, such as the cost of the treatment, should be taken into account for the choice of treatment. As Carradice states, we show that intravenous immunoglobulin works and, contrary to the suggestion of Balaraman, that intravenous immunoglobulin is better than high-dose methylprednisolone. However, to the question of Carradice of whether it is needed for everyone, we answer in our report that, in our opinion, only patients with the most severe forms of autoimmune thrombocytopenic purpura should receive intravenous immunoglobulin and prednisone.

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Unsterile injections and emergence of human pathogens

Sir—Ernest Drucker and colleagues (Dec 8, p 1989)¹ raise the valid concern that unsafe injection practices may have contributed to the emergence of HIV infection in sub-Saharan Africa.

A scientific hypothesis should be formulated together with a definition of the type of study that could prove it or disprove it. Unfortunately, Drucker and colleagues' definition of the type of study they have in mind is vague, and it is unlikely that any study could test the role of unsafe injections in HIV emergence in the 20th century.

Ecological and descriptive studies have generated hypotheses about large-scale transmission of hepatitis C virus (HCV) through unsafe injections in the past,² but no cohort or case-control study has tested these hypotheses. By contrast, evidence suggests that unsafe injections currently transmit hepatitis B virus, HCV, and HIV.³ Today, this burden of disease can be measured epidemio-

logically and efficiently prevented.

In response to this evidence, WHO scaled up its injection safety activities with the Safe Injection Global Network (SIGN).⁴ Communicating the risk of HIV infection associated with unsafe health-care injections is now a core activity of any HIV programme. WHO's Department of Essential Drugs and Medicine Policy promotes rational use of drugs, including injections, through research, normative work, and capacity building, and works to increase access to safe injection equipment. The Department of Protection of the Human Environment has created a working group to ensure that contaminated sharps are not reused. The Department of Vaccines and Biologicals has given immunisation safety priority.

Drucker and colleagues' statement that WHO still recommends reuse of sterilisable syringes in vaccination programmes is misleading. The referenced product information sheet is not a policy document; it provides general information for equipment selection and technical and purchasing data. The document clearly refers to the WHO, United Nations Children's fund, and United Nations Population Fund 1999 joint statement on the use of autodisable syringes in immunisation services, which specifies that such syringes are the equipment of choice for administration of vaccines and urges countries to use only those by the end of 2003.⁵ In June 2001, the board of the Global Alliance for Vaccines and Immunization endorsed this policy, with support from the Vaccine Fund. A switch to autodisable syringes, cannot, however, take place overnight. As long as sterilisable equipment remains in use, WHO needs to recommend quality equipment and develop clear guidelines for its proper use.

Drucker and colleagues also refer to the injection of substances such as heroin, cocaine, and amphetamines as a major contributor to unsterile injections. This contribution is well recognised. WHO is promoting evidence-based policies and strategies that prevent the transmission of HIV associated with injecting drug use, including improved access to sterile injecting equipment, community outreach to drug users, and expansion of drug-dependence treatment services.

In addition to preventing injection-associated infections, safe and appropriate use of injections saves costs wasted in unnecessary injections, introduces standards of care, develops

infection control cultures, and strengthens health systems.

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- 1 Drucker E, Alcabes PG, Marx PA. The injection century: massive unsterile injections and the emergence of human pathogens. *Lancet* 2000; **358**: 1989–92.
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Xenotransplantation trials

Sir—At the 6th Congress of the International Xenotransplantation Association held in Chicago, October, 2001, a presentation was made on a clinical trial involving the treatment of diabetic children in Mexico City using pig islets introduced into the peritoneal cavity. The islets had been prepared in New Zealand and transported to Mexico for the clinical trial.

Transnational clinical trials raise an important issue. We believe that effective national and international regulation of clinical trials of xenotransplantation need to be developed. If clinical xenotransplantation trials are done without rigorous regulations, they could be brought into disrepute in the view of the general public. We are not aware that this trial was perceived as being inadequately regulated. However, we see a trend for future clinical trials being planned in a similar way.

Questions have been raised about the potential for the transfer of porcine infectious agents into the human population. Porcine endogenous retroviruses have perhaps received most attention, but there are several other micro-organisms that are of potential concern. In the absence of regulatory authorities, clinical trials may place patients at risk, and raise the possibility of risk to the general population.

Although such trials may provide a limited amount of information on the outcome of xenografts, we suggest that clinical trials done outside an

internationally accepted regulatory framework will prove harmful to the development of xenotransplantation as a treatment.

We believe that organisers of transplantation meetings and editors of journals should, before acceptance, insist on presentation or publication of verification of adherence to internationally acceptable guidelines. We urge academic centres and companies involved in xenotransplantation research not to pursue clinical trials unless supervised by a nationally or internationally recognised regulatory body.

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Sir—The association between simian virus 40 (SV40) and tumours, especially lymphoma, are highlighted in the report of Regis Vilchez and colleagues (March 9, p 817).¹ This animal-derived virus seems to have infected millions of people through inadvertent contamination of poliovirus vaccines between 1955 and 1963. However, people born after 1963 have also been infected, which implies human-to-human transmission.²

What we now know about SV40 should serve as an important warning. We need to be extremely vigilant so that a similar situation does not arise with other animal viruses. Such vigilance is particularly relevant to xenografts.

The SV40 experience shows that viruses in animal tissue can be transmitted to human beings via medical procedures, can cause disease that manifests many decades after initial infection, and have the potential to be spread from person to person. Viruses can be part of an animal's genome, such as porcine endogenous retrovirus, and, therefore, impossible to remove. Other viruses, including some currently undiscovered, are probably likely to be present in xenografts. SV40 was not known to be present in the early poliovirus vaccines when they were manufactured.

Xenografts have a poor record of success to date, yet many are vigorously espousing the potential benefits of this procedure. We need to remember that many of the epidemic infections that cause continuing difficulties to human beings were

initially derived from animals (eg, HIV, hepatitis B, influenza).² We should, therefore, be very circumspect before embarking on procedures such as xenografts anywhere in the world.

Some proponents of xenografts are trying to circumvent the regulations in countries such as New Zealand by doing xenografts in the Cook Islands.³ If a new infection developed in under-resourced countries, the infection would probably not be identified and constrained if human to human transmission occurred.

People carrying a new infection can easily move around the world. Therefore, what happens with xenografts and especially in a remote corner of the globe should be a concern to us all.

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- 2 Collignon P, Purdy L. Xenografts: are the risks so great that we should not proceed? *Microbes Infect* 2001; **3**: 341–48.
- 3 Archer K, McLellan F. Controversy surrounds proposed xenograft trial. *Lancet* 2002; **359**: 949.

Sir—Your March 16 news item¹ on the controversy in New Zealand over a proposed clinical trial of xenotransplantation includes comments made by the past president of the International Xenotransplantation Association (IXA), David Cooper, relating to a clinical trial of islet xenotransplantation currently being done in our institution. We think that the remarks need clarification because they were made without proper knowledge of the investigation or the regulations governing clinical research in Mexico.

Mexico has a general health law, that regulates the conduct of all experimental investigations in human beings. This law also regulates organ and tissue transplantation, and on May 26, 2000, it was amended to include rules governing xenotransplantation.

The protocol for our clinical trial was approved by the research, ethics, and biosafety committees of our institution and of the National University of Mexico Medical School. Of prime concern was the safety of the patients; the protocol followed the US Food and Drug Administration guidelines for xenotransplantation.

We recruited adolescent college students with better than average

education. We held several meetings with the patients and their parents to explain in detail the procedure and its potential risks. After reflection time the patients and parents signed an extensive informed consent form that conformed to international requirements.

The overriding safety issue for xenotransplantation is zoonosis, especially the theoretical possibility of cross-species transmission of pig endogenous retrovirus (PERV). Current evidence from many exposures of patients to porcine tissue suggests that transmission does not occur.^{2,3} In addition the source herd for the clinical trial is co-culture negative for PERV. Nevertheless, we are fully aware of the responsibility we have to monitor our patients closely. We have carefully followed up all 12 patients for up to 2 years and have noted no sign of infection. Blood samples are sent routinely to an independent virologist to be tested for seroconversion and for latent or active PERV infection by PCR and reverse transcriptase PCR, respectively.

The xenotransplantation technique was developed in Mexico after extensive animal experimentation. The cells are transplanted into a vascularised collagen tube; they are not encapsulated as you report. The technique requires no immunosuppression of the recipient. After 2 years our patients are free from evidence of any infection, and one has stopped taking insulin.

As you mention, we presented our preliminary results at the IXA congress last year. Several colleagues voiced their concerns and we were happy to explain our processes and procedures. We hope we have now clarified these issues. We believe that the benefits that insulin independence can bring through islet xenotransplantation to patients with type 1 diabetes far outweigh the risks involved. We hope for the support of the IXA in our efforts to gather the data.

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The need for independent scientific peer review of Biobank UK

Sir—The UK Medical Research Council (MRC) and the Wellcome Trust have recently made a decision on the proposed funding, originally suggested at UK£60 million, for the genetic research project, Biobank UK. The proposed project aims to link blood samples and genetic and lifestyle data with the National Health Service records of 500 000 volunteers aged 45–69 years.

Biobank UK has already proved highly controversial and some serious criticisms of its scientific validity have been published.¹ Consultations by the project's backers, with medical professionals, scientists, and the public, have also highlighted a wide range of concerns.

Funding for Biobank UK was agreed in principle by the MRC and Wellcome Trust in 1999. Yet the peer review process is also being managed, and the outcome considered, solely by these bodies. This allows them to select their own reviewers and potentially to sideline any scientific criticisms when making their decisions.

A major concern expressed by the public in workshops on the proposal was the unclear benefits to individuals and society. A key aim of Biobank UK is to develop genetic tests to predict future disease, with a view to giving medicines to healthy people before they get the predicted illness. This approach to disease prevention is of doubtful scientific validity and dubious benefit to health. Genetic test results could also be misused by others, such as insurers or employers, and there is a lack of legal safeguards to protect the public.

A much more open decision-making process is therefore essential before substantial public funds are spent. As MRC's Chief Executive, Professor Sir George Radda, has noted, the quality of peer review is key to the excellence of UK science, and there is an obligation on those using it to strive to make practices "fair, transparent, effective, and rigorous".² A new peer review process of the Biobank's scientific protocol should be undertaken by a body independent of the MRC, Wellcome Trust, and Department of Health, with an open debate of the issues raised. This should be followed by an independent appraisal of the project's value for money and a House of Commons debate. Family physicians need to be

confident before recruiting their patients that the Biobank is likely to be of benefit to health and not a waste of public time and money.

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- 1 Clayton D, McKeigue PM. Epidemiological methods for studying genes and environmental factors in complex diseases. *Lancet* 2001; **358**: 2001.
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Reply from Biobank UK

Sir—The MRC, Wellcome Trust, and Department of Health are going ahead with the UK Biobank project, and have announced initial funding of £45 million. This decision was based on the outcome of a lengthy period of consultation with various stakeholders, and on thorough peer review done according to well established principles.

Reviewers were selected solely on the basis of their expertise in relevant scientific areas and without previous knowledge of their views on the project. There was a deliberate decision to ensure that most of the 12 reviewers were from overseas, and none of them had had any previous involvement in the development of the project nor any connection with organisations likely to participate directly. We therefore reject Helen Wallace's suggestion that a second peer review process is required because of conflict of interest. Indeed we find it unworkable and unrealistic that any other group, with no responsibility for managing our financial resources, should be tasked with MRC or Wellcome Trust funding decisions.

Scientific differences of opinion are inevitable with such a large and complex project, and the development of the draft protocol^{1,2} to date has intentionally involved widespread consultation with UK scientists, including a workshop in April, 2001, attended by more than 150 experts. Most debate has been about the detail of the approach rather than the project rationale. The 16-member Protocol Development Committee was responsible for drawing these views together and making the difficult decisions necessary to develop a workable, scientifically valid, and affordable study design. There will be further widespread consultation over the project's development once a coordinating centre has been established and the regional centres that will participate in recruitment have been identified.

Consultation with the public and other stakeholders has also been an important feature of the development of the plans for the UK Biobank, since a project of this scale cannot succeed without widespread public support. We were pleased to note that the Human Genetics Commission recommendations for governance of genetic research databases³ closely match our approach in establishing an independent oversight body. This strategy was developed at a very early stage to address concerns raised in the first phase of public consultation.^{4,5} Stringent measures will be put in place to safeguard the security and confidentiality of personal information.

The primary aim of the UK Biobank is to provide the resource necessary for research into the combined effects of genes and environment in common diseases of major public-health importance. Over the next few years, research in the commercial and the academic sectors will undoubtedly lead to a plethora of claims for links between different genetic variations and disease risk or treatment response. The UK Biobank will be an invaluable resource for identifying the real predictive value of these variations and working out which are likely to be useful in decisions about treatment or preventive interventions. We expect the UK Biobank to make a major contribution to a revolution in health care.

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