Letters

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Xenotransplantation

This new form of treatment might benefit millions

Editor—Fano has written a response in the *eBMJ* (and published here, the third letter) commenting on Vanderpool's article on xenotransplantation.[1 2] He advocates a ban on xenotransplantation, largely on the grounds of the risk of the transfer of infection. Cells taken from carefully screened pigs have been used in the treatment of patients with diabetes, certain neurological diseases, and liver failure. There has been no definite evidence of the transfer of a porcine infection to human recipients.

Nevertheless, as with almost every medical or scientific advance, it will be impossible to exclude all risk, even if this is related only to hitherto unknown pig bacteria or viruses. The ultimate decision whether to use any new therapeutic agent or procedure rests on an assessment of the risk to benefit ratio. As the potential benefits to individuals or society increase, the acceptance of slightly increased risk becomes warranted. We must not reduce our obligation to take all possible steps to minimise any perceived risk to society, but we have a moral obligation to accept a small risk to the community if the new treatment leads to great benefit to many individuals in that community.

The potential benefits of xenotransplantation are immense. Many millions of people with such diverse conditions as diabetes and degenerative brain disease may have the quality of their lives vastly improved, and in those with advanced organ failure xenotransplantation will be lifesaving. In the United States over 60 000 people currently await a human donor organ but only 20 000 organs will become available this year. At least 10 people die every day while waiting. Similar figures could be quoted for other regions of the developed world.

This new form of treatment may ultimately benefit millions of patients. Rather than calling for a ban on it we suggest that support should be given to the great efforts being made to ensure that it will be not only successful but also safe.

David K C Cooper *president, International Xenotransplantation Society*
Massachusetts General Hospital, 13th Street, Boston, MA 02129, USA
cooper@helix.mgh.harvard.edu

Carl G Groth *immediate past president, International Xenotransplantation Society*
Huddinge Hospital, Huddinge S-14186, Sweden

Ian F C McKenzie *president elect, International Xenotransplantation Society*
Austin Research Institute, Austin and Repatriation Hospital, Heidelberg, Victoria, Australia

1 Vanderpool HY. Xenotransplantation: progress and promise. *BMJ* 1999;319:1311. (13 November.)
2 Fano A. Xenotransplantation: perils and plagues. *eBMJ* 1999. (www.bmj.com/cgi/eletters/319/7220/1311#EL2).

Public health risk must not be dismissed

Editor—Xenotransplantation of organs from animals is a seductive but inherently dangerous idea. The risk is not just to the patient, who will probably die shortly afterwards; the stakes are much higher, because the entire human population is put at risk.

Viruses that inhabit animals, some of which are intrinsic to the animal's own genome, will gain a route of entry into the human population not ordinarily available. As Vanderpool notes,[1] pig DNA contains endogenous retroviruses (the same class that causes AIDS), and these infect human tissue culture cells.[2] Vanderpool doesn't mention that postmortem analyses of two patients who died 70 and 27 days after receiving baboon livers showed two simian viruses that replicated after transplantation.[3] Our state of knowledge is far too incomplete for us to breed totally virus-free animals, because we probably don't even know all the viruses that need to be eliminated.

We do know that viruses jump species even without our help, and there are enough frightening precedents—as far back as the 1918 swine influenza pandemic that killed 20 million—to scare anyone contemplating xenotransplantation. More recently, millions of chickens had to be slaughtered in Hong Kong because of the unexpected jump to humans of an avian influenza virus, and thousands of English cattle have been destroyed because of the jump to humans of bovine spongiform encephalopathy ("mad cow disease").

The spectacular advance of AIDS resulted from a virus given new routes of entry: widespread increases in certain lifestyle practices provided a conduit for efficient transmission. HIV-1 probably also resulted from a simian to human virus jump. Deadly Ebola virus is another virus transmitted to humans from primates, and there are at least another 10 primate viruses that infect humans, including a deadly form of herpes. Pigs aren't much safer: about a dozen pig viruses can be transmitted to humans, often with serious results.

Not considered by Vanderpool is the fact that better alternatives exist. These include lifestyle changes (diet and exercise) that would considerably reduce the numbers of transplant candidates and presumed consent policies for human donors, which would greatly expand the pool of available organs. Research on unwanted human embryos is much more promising as a solution, but this is held hostage to abortion politics in the United States. Instead we are absurdly rushing down a path fraught with danger. Have we learnt nothing from the AIDS epidemic?

Emanuel Goldman *professor*
Department of Microbiology and Molecular Genetics, New Jersey Medical School – UMDNJ, 185 South Orange Avenue, Newark, NJ 07103, USA
egoldman@umdnj.edu

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Research in xenotransplantation will line drug industry's pockets

EDITOR—It is naive to believe that research in xenotransplantation "is being propelled" by drug companies' desire to alleviate human suffering rather than the promise of billions of dollars in profits from the sale of "humanised" pig parts and expensive antirejection drugs.[1] There would be safer and more cost effective ways of dealing with the perceived shortage of human organs and tissue. Aggressive investment in programmes to prevent disease; the passage of "presumed consent" laws, which have increased organ donation rates in several countries[2]; and growing human tissue to provide a safer source than animals would all help.

Given the multitude of viruses lurking in animals, it will be impossible to breed germ free "donors." Public health authorities admit that xenotransplantation could transmit deadly animal viruses to humans. Known pig viruses include the porcine endogenous retroviruses that have infected human cells. In 1998-9 the Malaysian Nipah virus causing viral encephalitis jumped from pigs to humans, infected 269 people, killed over 100, left dozens brain damaged, and led to the mass slaughter of one million pigs. Pig viruses have not been extensively studied: there may be dozens, many with long latency periods, waiting to be discovered.

A retrospective study of 160 patients exposed to living pig tissue raised concerns[3]: 30 patients who underwent splenic perfusions gave positive results when tested for porcine endogenous retrovirus DNA; 23 had pig cells circulating in their bodies 8.5 years after treatment; and four injected with pig cells produced antibodies to porcine endogenous retroviruses, suggesting a potential active infection. The study's sponsor, Novartis, insists that patients are free of infection. But virologist Stoye and coauthors have said "the absence of infectious virus in, say, the first two hundred patients does not mean it will not occur in the two hundred and first."[4]

I am baffled as to why our public health authorities, mandated to protect public health and prevent disease, are encouraging the development of xenotransplantation while simultaneously acknowledging its epidemic potential. This could become a liability for them.

In 1998 a group of physicians pointed out that global poverty (and lack of access to basic health care and sanitation) is the world's number one health problem.[5] Today, some 50 million Americans lack access to basic health care. If we invest in xenotransplantation while ignoring the fundamental needs of a majority of the world's citizens we are simply lining the drug industry's pockets.

Alix Fano *director*
Campaign for Responsible Transplantation,
PO Box 2751, New York, NY 10163, USA
alixfano@mindspring.com

1 Vanderpool HY. Xenotransplantation: progress and promise. *BMJ* 1999;319:1311. (13 November.)
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Author's reply

EDITOR—Cooper et al's letter is commendable. Research on porcine cells, tissues, and organs in xenotransplantation should continue if certain conditions are met. There should be ongoing studies of risks and increased recognition that xenotransplantation offers enormous potential for alleviating human sickness, suffering, and untimely death. To assume that xenotransplantation must be free of risk before its benefits are pursued is out of keeping with the nature of human existence and represents a preoccupation with self protection that undermines beneficence.

Goldman warns that the public health risk of xenotransplantation "must not be dismissed," which no one seems to be doing. Goldman's points about the known infectivity of simian viruses have, as my article says, already been taken to heart by the United States Food and Drug Administration, which suspended clinical research involving primate-to-human xenografts.

Goldman ends with a list of better alternatives to xenotransplants. Better for whom and how soon? Lifestyle changes would reduce the demand for transplanted organs, but they will neither end this demand nor be voluntarily and universally adopted. Presumed consent would expand the organ donor pool, but it is a form of coercion that would also not meet the great demand.

Fano expresses the party line of the Campaign for Responsible Transplantation, which he directs and which claims to represent 2.5 million members. The campaign's publications advocate an immediate ban on xenotransplantation and charge the Food and Drug Administration with "playing Russian roulette with the public's health."[1]

Fano holds that xenotransplantation is being advanced to line "the drug industry's pockets," not to alleviate human suffering. While few will quarrel with the influence, if not the necessity, of the profit motive, numerous researchers, surgeons, scientists, and regulators are additionally, and sometimes primarily, motivated by altruism, inquisitiveness, discovery, and the classic three factors in the Hippocratic oath: honour, fame, and enjoyment of life.

Fano is baffled that public health authorities are encouraging the development of xenotransplantation in the light of its epidemic potential. His evidence for this potential with respect to clinical trials of xenotransplantation is attributed to a study that does not support his fears.[2]

This study further validates other findings that persistent porcine endogenous retrovirus infection has not been detected in recipients of xenotransplants. The 30 (of a total of 160) patients that Fano refers to as testing positive for persistent porcine endogenous retrovirus evidenced microchimerism (the remaining presence of pig cells in their bodies), not persistent porcine endogenous retrovirus infection.

Harold Y Vanderpool *professor in the history and philosophy of medicine*
Institute for the Medical Humanities, University of Texas Medical Branch, Galveston, TX 77555, USA
hvanderp@utmb.edu

1 Fano A. *CRT:re Docket N. 99D-5347: precautionary measures to reduce the possible risk of transmission of zoonoses.* New York: Campaign for Responsible Transplantation, 2000:12.
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GPs can improve their hand washing habits

EDITOR—The Handwashing Liaison Group states that hand washing habits among hospital staff could be improved.[1] This statement can be extrapolated to include those working in primary care. From January to March 1999 a computer randomised sample of 230 doctors registered with the Scientific Organisation of Flemish General Practitioners was interviewed by telephone, and 200 took part. They were asked if they washed their hands after each contact with a patient. A total of 126 of those asked washed their hands after each consultation, but only 43 did so after each home visit, although they were confronted during consultation and home visit with 45 and 85 patients with infectious disease respectively. Of those who did wash their hands after consultation, 79 used water and soap. Only 21 used a towel for single use. The table shows the reasons for not washing hands.

Age and sex had no statistical influence on the frequency of hand washing. The doctors working in groups washed their hands less often than those working on their own (consultation: 22/52 (42%) *v* 104/148 (70%), P = 0.0006; home visit: 5/52 (10%) *v* 37/147 (25%), P = 0.03 (χ^2 test, Yates corrected)).

These results show that especially during home visits general practitioners have difficulties in organising hand washing, even when they know that they are treating a patient with an infectious disease. Some older patients still offer their family doctor a basin with soap and a clean towel, but this

Doctors' reasons for not washing their hands

Reasons	Consultation (n=74)	Home visit (n=157)
Too complicated to ask patients for facilities	N/A	49%
Washed hands in car or consultation room after visit	N/A	10%
No infectious contact	46%	16%
Hand washing not a habit	15%	10%
Lack of time	12%	6%
Forgotten	14%	3%
Afraid of irritation of the hands	5%	0
No idea or no answer	8%	6%

N/A=not applicable.

custom is disappearing. General practitioners working on their own may be more accustomed to include hand washing in their daily routine. The time loss is relative: during hand washing you can continue your conversation with the patient.

General practitioners must become more aware of their role in transmitting infections from one patient to the other and must train themselves to make hand washing a routine action. Students should practise this early during their medical education in order to learn good hand washing practice.[2] During home visits patients can help by reminding the doctor or offering him or her the opportunity for hand washing after the examination.[3] Alcohol gel can be used as a good alternative to decontaminate the hands after a home visit.[4] It is effective (if the hands are not dirty), quick, and easy to use. Irritation of the skin or dermatitis can be prevented by using hydrating soap formulas, hand cream, or gloves.[5]

Barbara Michiels *general practitioner*
michiels.rombouts@village.uunet.be
Dirk Avonts *professor*
Paul van Royen *professor*
Joke Denekens *professor*
Centre for General Practice Antwerp, University of Anwerp, B-2610 Antwerp, Belgium

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System to detect tuberculosis in new arrivals to UK must be improved

Editor—The news item on the global spread of drug resistant tuberculosis raised the issue of screening new arrivals to the United Kingdom who come from countries with a high incidence of tuberculosis.[1] One group of new arrivals in which such communicable diseases are an issue are refugees and asylum seekers.[2]

These people may have arrived from areas of war or famine, where medical systems have broken down, and may be incompletely immunised. Last year thousands of people arrived from tuberculosis hotspots at port health units (mainly Gatwick and Heathrow airports) claiming political asylum.[3] Regulations state that these people, and indeed anyone planning to live in the United Kingdom for over six months who arrive from areas where tuberculosis is common (40 cases/100 000 population), should be screened by chest radiography at the port of entry as part of the tuberculosis screening programme.[4] But port health units no longer have the resources to deal with the many asylum seekers and other immigrants arriving every day.

According to the regulations, the consultant in communicable disease control in the health authority in which the asylum seeker plans to live is contacted. It is up to him or her to contact the asylum seeker and carry out follow up tests to find people positive on skin testing and those requiring vaccination, and to initiate chest radiography for those who did not have it at port health units. Most health authorities, however, have insufficient resources to offer comprehensive contact tracing and screening of newly arrived asylum seekers.

In the absence of a national reception policy, and with a tuberculosis screening programme that is not detecting all people at risk, general practitioners have to deal with the health concerns of these new arrivals. General practitioners, however, do not seem to be initiating screening either. In a recent study of 58 general practitioners in Ealing, Hammersmith, and Hounslow Health Authority, most of whom had refugees on their lists, only four referred asylum seekers to a chest clinic for tuberculosis screening; 48 were unaware of the tuberculosis screening programme.[5] Most thought that some screening should take place.

Although screening for tuberculosis at ports of entry is limited in detecting active cases, follow up in the community or reception centre needs to be organised. Tuberculosis and drug resistant tuberculosis are not only personal concerns but, potentially, major public health issues. The number of asylum seekers coming to the United Kingdom has sharply increased in the past few years; the system to tackle the spread of tuberculosis in the United Kingdom therefore requires attention.

Sally Hargreaves *researcher*
Department of Infectious Diseases, Imperial College of Science, Technology, and Medicine, Hammersmith Hospital, London W12 0NN
shargreaves@hotmail.com

1 Hopkins Tanne J. Drug resistant TB is spreading worldwide. *BMJ* 1999;319:1220. (6 October.)
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Antibiotic prophylaxis after percutaneous endoscopic gastrostomy insertion

All encompassing study is needed

Editor—Preclik et al reported an incidence of 65% peristomal infection in their control group.[1] This is considerably higher than in previous studies, where rates vary from 19% to 29.4%.[2–4] This discordance can be explained by considering the indications for gastrostomy insertion. This feeding method is used in five broad categories of patients—cerebrovascular disease, neurodegenerative conditions, malignancy (primarily oropharyngeal or oesophageal), dementia with anorexia, and head injuries. In the previous studies malignancy represented 14.8-21.1%,[2–4] whereas in Preclik's cohort it is 65%.

Previous studies have implied that patients with underlying malignancy are more susceptible to peristomal infection.[2] This may explain the high infection rate in the controls of this study and therefore the benefit of antibiotics in this particular patient subgroup. This, however, cannot necessarily be extrapolated to other indications for gastrostomy insertion. The British Society of Gastroenterology has indicated that this is an area requiring further evaluation.[5] We require a similar study encompassing all the conditions for which gastrostomies are inserted in the United Kingdom to resolve this issue.

D S Sanders *gastroenterology research fellow*
M J Carter *gastroenterology research fellow*
MartynCarter@compuserve.com

Gastroenterology and Liver Unit, Royal Hallamshire Hospital, Sheffield S10 2JF

1 Preclik G, Grune S, Leser J, Lebherz W, Machka K, Holstege A, et al. Prospective, randomised, double blind trial of prophylaxis with single dose of co-amoxiclav before percutaneous endoscopic gastrostomy. *BMJ* 1999;319: 881-4. (2 October.)
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Widespread routine use of prophylactic antibiotics might predispose to increased risk of resistant organisms

Editor—In their paper Preclik et al conclude that antibiotic prophylaxis reduces infections after percutaneous endoscopic gastrostomy insertion as recommended by the American, European, and French societies of gastrointestinal endoscopy.[1] We believe that this paper does not provide the evidence required to introduce such a practice in the United Kingdom, a position supported by the 1996 guidelines from the British Society of Gastroenterology.

Preclik et al found a significantly higher infection rate in the control group, with an astonishing overall infection rate of 65% representing peristomal and other infections.[1] Even when only the most clinically significant wound infections were considered, the infection rate among the control group was 26%. This figure is considerably higher than in our experience and that of Gossner et al, also from Germany.[2]

We performed a retrospective audit in a single unit and found a peristomal infection rate with no prophylactic antibiotics of only 4.4%, with no severe infections. Furthermore, the case mix in the German studies consisted predominantly of patients with cancer (65%), the remainder having neurological disease. The reverse is true in most British units. This was also not a large study

as claimed by the authors, with only 84 patients evaluable out of 106 randomised in six centres, and ambulatory healthy patients were excluded because of short follow up. They found mainly streptococci and coliform bacteria but only one case of *Staphylococcus aureus*, whereas our predominant organism was methicillin resistant *S aureus*, usually detected before or long after gastrostomy insertion.

Their experience clearly differs from that of most district general hospitals in the United Kingdom with respect to case mix, organisms cultured, and the severity and frequency of stomal infections.

We believe that widespread routine use of prophylactic, broad spectrum antibiotics might predispose to an increased risk of resistant organisms such as methicillin resistant *S aureus*. As stated by others,[2] antibiotic prophylaxis is only of relevance in hospitals with a high incidence of wound sepsis related to percutaneous endoscopic gastrostomy, which might be preventable by more careful attention to the insertion technique.

I Mohammed *specialist registrar*
B J M Jones *consultant gastroenterologist*
B.J.M.J@btinternet.com

Department of Gastroenterology, Russells Hall Hospital, Dudley DY9 ODT

1 Preclik G, Grune S, Leser J, Lebherz W, Machka K, Holstege A, et al. Prospective, randomised, double blind trial of prophylaxis with single dose of co-amoxiclav before percutaneous endoscopic gastrostomy. *BMJ* 1999;319:881-4. (2 October.)
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Long acting antibiotic is superior in reducing systemic complications

EDITOR—The paper by Preclik et al is the second recently published to investigate whether antibiotic prophylaxis in patients with percutaneous endoscopic gastrostomy is efficacious in reducing local infections.[1 2] In both papers the subgroup of patients with underlying neurological disease is in the minority. These patients are at high risk of systemic infections, especially pneumonia. Preclik et al state that prior selected patients with cancer are at high risk of infections after percutaneous endoscopic gastrostomy, which has not been proved yet. These patients might have been having chemotherapy or radiotherapy, a concomitant procedure—for example, bougienage—might have been performed, or a drug—for example, an immunosuppressant—might have been given during percutaneous endoscopic gastrostomy, which might also lead to higher rates of infection. In most studies and in clinical practice local infections after percutaneous endoscopic gastrostomy rarely necessitate treatment with antibiotics. Infection is mostly controlled by intense local treatment.[2 3] Systemic infections are a serious problem and necessitate using antibiotics; they mostly occur in patients with neurological disease.[4] These patients are at high risk of aspiration, which is sometimes caused by a feeding protocol using large boluses.

In our final results of 216 (106 patients taking ceftriaxone prophylactically) standardised procedures of percutaneous endoscopic gastrostomy including care before and after the intervention, 145 of the patients had a neurological disease.[3] Patients with tumours were scored positive for local infection on day 10 after the intervention without and with antibiotic prophylaxis in 12 (31.0%) *v* 1 (3.7%) ($P < 0.05$) respectively, whereas in patients with neurological disease the infection rate was 17 (20.3%) *v* 9 (11.4%) respectively ($P > 0.05$). Out of 39 patients scoring positive for peristomal infection, six (all patients without prophylaxis) received antibiotics for this reason. Systemic infections affected 13 patients without and two patients with antibiotic prophylaxis ($P < 0.05$). Pneumonia affected seven patients without and one with prophylaxis, all with neurological disease ($P < 0.05$), and one patient with a tumour but who did not take prophylaxis. All incidences of pneumonia occurred within 96 hours after percutaneous endoscopic gastrostomy.

Preclik et al state that the choice of prophylactic regimen is unlikely to account for differing results. These data are based on local infection, but no data are available for systemic infection in which a prolonged interval of antibiotic coverage or short term treatment could be more effective.[2 3] Our data indicate that a long acting substance such as ceftriaxone is superior in reducing systemic complications.

Arno J Dormann *consultant*
Medical Clinic, Klinikum Minden, D-32427 Minden, Germany
arno.dormann@debitel.net

1 Preclik G, Grune S, Leser J, Lebherz W, Machka K, Holstege A, et al. Prospective, randomised, double blind trial of prophylaxis with single dose of co-amoxiclav before percutaneous endoscopic gastrostomy. *BMJ* 1999;319: 881-4. (2 October.)
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Author's reply

EDITOR—Previous double blind studies of antimicrobial prophylaxis in percutaneous endoscopic gastrostomy have reported wound infection rates of 29%,[1] 32%,[2] and 19%[3] in placebo groups. In the study reported by Jain et al all wound infections required treatment with antibiotics and can therefore be considered as clinically significant.[2] In our study, the wound infection rate among placebo recipients was 26% (clinically important) or 44% (including minor, score defined "infections") to correct the figure Sanders and Carter erroneously caught from the paper. We believe that these reported incidences among patients not given antibiotics are comparable. Considering the fact that not all infections were clinically important, rates from open studies (30%[4]; 10%[5]; 25%[6]) seem to have been slightly lower—reasons may be patient selection, definitions used, or chance. Nevertheless, most studies came to a similar conclusion.

Other aspects need to be considered. Firstly, in two studies wound infection rates among patients ineligible owing to prior antibiotics were very low (0/52 and 2/54, respectively).[2 3] Secondly, reporting solely wound infection rates may underestimate the effect of prophylaxis. Control patients are likely to receive more often therapeutic antibiotics for non-wound infections that, in turn, will influence the development of wound infection. Ours and other studies that included assessments of any infections after percutaneous endoscopic gastrostomy[4 6] avoid or minimise this potential bias. Most retrospective analyses of peristomal wound infections after percutaneous endoscopic gastrostomy did not differentiate patients with prior antibiotics given for pre-existing illness, patients given therapeutic antibiotics for non-wound infections, and others. They almost inevitably underestimate the true wound infection risk associated with percutaneous endoscopic gastrostomy. This may explain (at least to some extent) a seemingly low complication rate as seen in the unit of Jones and Mohammed.

With regard to the risk of bacterial resistance, the calculation of defined daily doses of antibiotics (given for prophylaxis as well as for treatment of any infection) in control and treatment groups in our study revealed increased total exposure to antibiotics in the no-prophylaxis group, implying an impact on resistance development that should be negligible if not in favour of prophylaxis. No big difference in the total exposure to antibiotics (or consumption) is probably the reason why the cost for antibiotics in Dormann et al's interesting trial[6] was similar in both groups, leading those investigators to state that the reduction in morbidity by using prophylaxis is very likely to be cost effective. Dormann et al report non-wound infection rates of 17% and 6% in the no-prophylaxis and prophylaxis groups, respectively, using ceftriaxone. These can be compared with the rates in our study, using co-amoxiclav: 21% *v* 7% respectively (intention to treat population). A single dose of either drug (and probably of other antibiotics) works.

Winfried V Kern *associate professor*
Department of Medicine, University Hospital and Medical Center, D-89070 Ulm, Germany

1 Jonas SK, Neimark S, Panwalker AP. Effect of antibiotic prophylaxis in percutaneous endoscopic gastrostomy. *Am J Gastroenterol* 1985; 80:438-41.
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Honesty about new screening programmes is best policy

Editor—Austoker's editorial on gaining informed consent for screening is timely.[1] The National Screening Committee has commissioned two pilot sites for screening for bowel cancer, and there has been hot debate about what information should be given to potential participants and how.

If we follow past practice we would give very general information aimed at encouraging an invited age group to attend. "Screening for bowel cancer is effective; thousands of lives can be saved; the test is painless and free and can be done in the privacy of your home; cancers can be picked up early when they are easy to treat." We would measure success by the uptake, and we would reassure those outside the invited group that screening is not important for them. If there is a downside to screening it is a price worth paying for the lives saved; mentioning it could deter people from attending and thus deprive them of the chance of benefit. So why the hot debate?

The screening committee held a workshop in 1998, where the consequences that an individual contemplating screening might need to be aware of were discussed.[2] These were based on results of the Nottingham[3] and Danish[4] randomised controlled trials. Of the 178 cases of cancer among 100 000 people during a screening round, 35 have their life expectancy prolonged (representing the 15% reduction in mortality in the trials) (figure). Around 70 people have cancers that are not detected or have complications from investigation. Unless these 70 know in advance that these consequences are just as much a feature of screening as the lives saved then they will justifiably conclude that the screening programme is a shambles and may seek legal redress.

A relatively large group have adenomas detected by screening, most of whom if left unscreened would never develop a problem. Unless they know in advance that the discovery of benign and uncertain abnormalities is a feature of screening they are likely to credit the screening programme with having saved them from cancer. This boosts the popularity of screening but creates the myth that all dysplastic lesions are life threatening and must be found and eradicated. This can lead to the treatment of potential precancer (most of which would not cause a problem) becoming a bigger industry than the care of the sick.

The workshop was left with a dilemma. If you tell people all the consequences before they have a screening test then maybe it would deter them. If you do not tell them then you end up with expectations that are impossible to meet. Honesty is the best policy.

A E Raffle *consultant in public health medicine*
Avon Health Authority, Bristol BS2 8EE

1 Austoker J. Gaining informed consent for screening. *BMJ* 1999;319:722-3. (18 September.)
2 National Screening Committee. *Second colorectal cancer screening workshop. Information pack.* Leeds: NHS Executive, 1998.
3 Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW. Randomised controlled trial of faecal-occult blood screening for colorectal cancer. *Lancet* 1996;348:1472-7.
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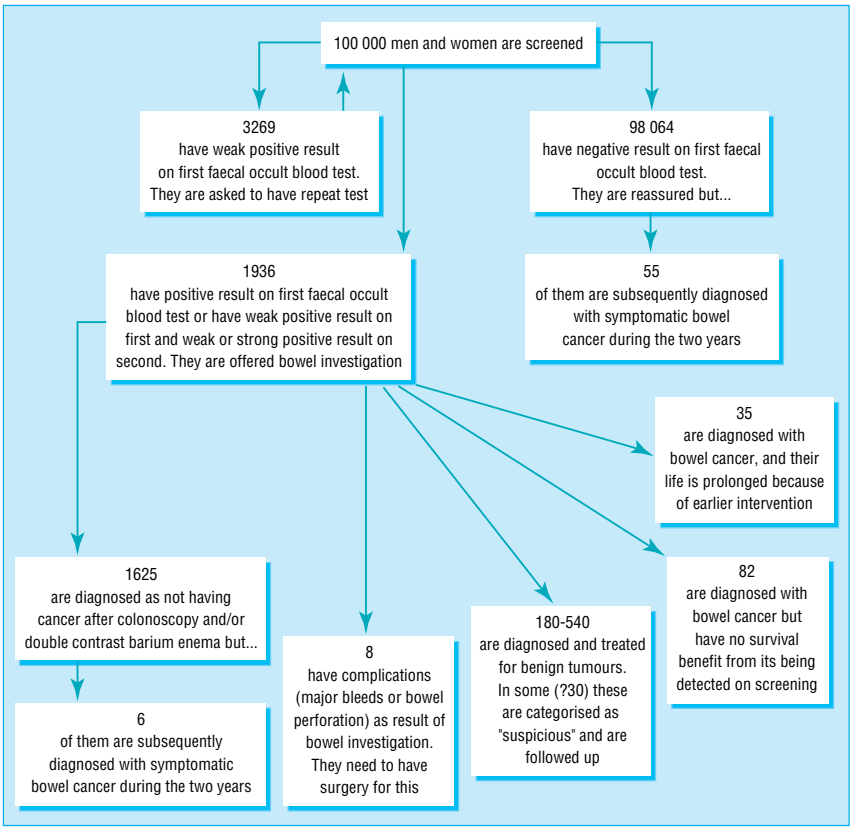

Outcome during two-year screening round when 100 000 men and women aged 50-69 are screened for bowel cancer according to national pilot protocols

Higher rate of organ procurement can be achieved in UK

Editor—Berry's personal view on the shortage of organ donors in the United States[1] and Davis's editorial on meeting the demand there[2] highlight the growing disparity between those waiting for transplantation and the number of organs available. Sadly, the situation in the United Kingdom is little different. A report by the Royal College of Surgeons in 1999 highlighted the need for transplant services to develop a wider national strategy and for organ procurement to be put on a sounder professional basis[3] in line with the recent recommendation of the United Kingdom Transplant Coordinators Association.[4]

One other step could be undertaken in the United Kingdom, in line with the experience in North America. As Berry said, Pennsylvania introduced an act requiring hospitals to notify coordinators and organ procurement organisations of a potential donor and allow the procurement coordinators to make the first approach to the family and become the "first requester."

The increase of nearly 40% in organ donation that resulted in Pennsylvania was followed by a national increase, with a wider introduction, of just over 5%. Such a relatively simple step might have a considerable impact in the United Kingdom as well. The evidence in other countries suggests that, with the skill, experience, and sympathy of organ procurement coordinators, it results in far fewer refusals and a higher rate of organ procurement.

P McMaster *professor of hepatobiliary surgery*
Queen Elizabeth Hospital, Birmingham B15 2TH
Paul.McMaster@university-b.wmids.NHS.UK

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Eugenics debate

Eugenics principles are there

EDITOR—Eugenics is defined in the *Oxford English Dictionary* as the science of improving the (especially human) population by controlled breeding for desirable inheritable characteristics. Stated in this way there is no doubt that the coercion of controlling breeding together with the subjectivity of desirable characteristics makes eugenics morally difficult to defend.

Caplan is really putting the case for gene manipulation.[1] Manipulation of somatic cells has been considered to pose no new ethical challenges, but manipulation of germ cells raises ethical issues as an alteration in the germ cell line affects future generations. The same criticisms can be levelled against manipulation of germ cell genes as were made against eugenics. Coercion is still a problem. Although we hope that parents can take decisions in the best interests of their child, this cannot be guaranteed and is similar to the problem with society coercing individuals to make inappropriate choices. The child has the right to be treated as an autonomous individual.

The social dimension of the subjectivity of perfection should not be forgotten. If society decides that a particular trait is beneficial this does not mean that it is morally right—for example, colour of skin. Admittedly, however, some traits may be globally regarded as beneficial.

Can equality be guaranteed by a programme of social initiatives to compensate for differences in biological endowment? It is always possible that rich people will purchase the technology. The other problem is that if people do not use the technology or do not use it well enough they may be ostracised by society. There seem to be moral uncertainties when examining these individual principles. If we consider what the business of health is we might get a better idea. Seedhouse defines the business of health as the removal of obstacles.[2] Modifying genes is a spectrum, from interventions that definitely remove obstacles to those that do not remove obstacles but may improve an individual's genetic make up towards a subjective ideal.

Perhaps clinical trials are needed to ascertain whether or not modifying genes is beneficial. Until then, can we condone the possible use of resources on "designer children" as opposed to using the resources to treat illness? Perhaps the principles of beneficence, non-maleficence, and justice can guide us through this maze.

Rupert Suckling *specialist registrar public health*
Rotherham Health Authority, Rotherham, South Yorkshire SG5 2QU
rupert.suckling@exs.rotherhm-ha.trent.nhs.uk

1 Caplan AL, McGee G, Magnus D. What is immoral about eugenics? *BMJ* 1999;319:1284-5. (13 November.)
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Other slippery slopes become apparent

EDITOR—I am writing with reference to Caplan et al's editorial on eugenics.[1] Eugenics has been vilified because of its abuses during the early 20th century, particularly Germany's choice to murder people with perceived disabilities. But the origin of eugenics was simply a desire to increase the odds that a child would be born healthy. Today we consider such measures as prenatal care, eating sensibly during pregnancy, avoiding use of alcohol or other drugs, and choosing your partner carefully to be the minimum that the pregnant woman should do and that the healthcare system should offer. Yet these practices are the very basis of "eugenics."

If we decry genetic engineering because of its potential to lead us down a slippery slope to potential force or compulsion, the imposition of arbitrary standards, or inequities that might result, we must also decry medical care in general. It leads to making people who cannot obtain it second class citizens with shorter, more unpleasant lives. It provides unfair advantages to those with the money and power to get more of it. The antibiotics that save one person's life may lead to antibiotic resistance that will harm others. Are we ready to say that medical care should be banned on these grounds? What other human endeavours would be banned if these standards were applied?

Our own version of eugenics today includes offering pregnancy termination to a woman carrying a fetus that seems to have a condition producing disability, such as Down's syndrome. Just the offer of a triple screen to a pregnant woman has implications for what she "should" do if an abnormality is found. This "standard of care" practice in obstetrics today is remarkably similar to Germany's rationale for murders in the name of eugenics. Widespread use of the triple screen implies that it is moral to murder your child if it is defective. Surely it must also be moral to improve the health of your child using genetic engineering?

Genetic engineering offers the potential to dramatically reduce the burden of disease and disability. Stem cell technology may produce cures for Alzheimer's disease; vascular growth factors may enable the body to produce its own cardiac bypasses; and the elimination of metabolic derangements may cure phenylketonuria and diabetes. My hope is that we will use science and technology to continue improving lives and health rather than regressing into Luddite technophobia.

Susan Root *vice president, medical affairs*
Institute of Genetics Education, Santa Fe, NM 87505, USA
sroot@gened.org

1 Caplan AL, McGee G, Magnus D. What is immoral about eugenics? *BMJ* 1999;319:1284-5. (13 November.)

What is immoral about the eugenics article?

EDITOR—Reading Caplan et al's article about eugenics[1] I can understand the fear and the threat that genetic engineering is to many people. The article is centred on the belief that parents have the right to choose the best for their offspring, and if a decision is made without coercion it should be accepted by society.

I understand medicine as the art of healing, and genetic engineering is a potentially wonderful tool to eradicate genetic illnesses that mankind, because of its supremacy over the environment, carries around without any option for natural selection.

I do not understand how choosing to increase any other attribute of a human being can benefit our society. Firstly, if there is a gap between rich and poor, with the former being able to improve the odds of their children by investing not only in better education but in "better" genetic material, this gap can only increase further, leading to a society where the weak will have no chance to improve their social status. Secondly, if parents look for the best genoma, pressure will be increased to raise the standards that could be achieved, leading eventually to a different subspecies of human beings, perhaps more "perfect" but by no means stronger, as nobody can predict the ultimate consequences and possible mutations and DNA ageing that can happen if DNA changes are pursued to the limit. Thirdly, diversity will be lost as more people are created to have similar attributes, and the chance of natural improvement by aleatory combination of varied genes with or without spontaneous mutations will be lost as any cell with unknown genes would be eliminated before it can manifest itself.

Parents should not be allowed to favour a specific sex (as already happens nowadays) or attribute in their children. Parents are looking for the best not for their children but for themselves. They want their offspring to have what they would like to have themselves, and they want their offspring to succeed where they didn't. Life is about living, not about setting goals to achieve. Life is about chances, not about rigid protocols. Life is diversity and spontaneity, and it should not be spoiled by grandiose ideas.

Pablo Millares-Martin *general practitioner*
The Surgery, Leeds LS12 5AZ

1 Caplan AL, McGee G, Magnus D. What is immoral about eugenics? *BMJ* 1999;319:1284-5. (13 November.)

The changing doctor-patient relationship

Diagnoses are made from careful history and examination

EDITOR—I welcome the improved use of resources already available to us, but I must point out some facts to Weed and Weed.[1] When we are medical students we are taught that more than 80% of diagnoses can be made on the basis of a careful history and physical examination. We are therefore taught to focus on individual symptoms and signs from which a differential diagnosis is formed and appropriate investigations are requested. I was certainly not taught to "focus on general knowledge about large populations." Doctors in the United Kingdom

undertake a period of general professional training and have to complete a difficult and highly competitive examination, before specialisation. The Weeds' case was from the United States, and many specialists were involved in the patient's care, which may have been a contributing factor to the delay in diagnosis.

You cannot damn the whole of the medical profession on the basis of one case report. Addison's disease was top of my differential diagnosis by line four of the article, as would have been a Synacthen test to diagnose it.

Vincent McAulay *research fellow*
Royal Infirmary of Edinburgh, Edinburgh EH3 9YW
vmcaulay@yahoo.com

1 Weed LL, Weed L. Opening the black box of clinical judgment: how the doctor-patient relationship is changing with new technology. *BMJ* 1999;319:1279. (13 November.)

Authors' reply

EDITOR—The medical profession remains in denial, judging from the responses of McAulay and Reinecke.[1] By denying the limitations of the human mind, the profession only worsens the impossible burdens placed on it.

McAulay indicates that British medical students are taught that most diagnoses can be made by focusing on individual symptoms and signs drawn from a "careful" history and physical examination. We do not question that British (and American) medical students are taught this. Our point is that in practice what they are taught cannot be consistently achieved—unless medical practice changes fundamentally. The reality for most patients is that their doctors are not given the opportunity to conduct a truly careful history and physical examination or to analyse thoroughly the resulting mass of data. And even when doctors have that opportunity, they still may err. Their personal store of knowledge may be insufficient, they may be unable to apply their knowledge correctly to an actual patient, or that "knowledge" may itself be fallible and incomplete. Isolated fragments of general knowledge about large populations can easily mislead, for example, because doctors are unable to combine detailed patient data with the myriad fragments of knowledge relevant to complex, unique problems.

Perhaps some readers believe that such conclusions do not apply to highly trained doctors who, like McAulay, sometimes can quickly recognise the correct diagnosis when reading a case report. Yet many talented doctors "find that the skills that allowed them to excel in the classroom, and even as house officers, are of little use … when they are faced with a flood of information" in a typical medical practice.[2] Moreover, even if some doctors believe that they experience no such difficulties, what is to be done for the patients of other doctors, or for people without access to doctors?

Contrary to Reinecke's view,[1] we do not "totally discount" the experienced doctor's intuition. On the contrary, Reinecke's description of what contributes to that intuition—years of training; intimate and confidential contact with the patient; the combination of visual, aural, and sensory functions of the brain; telephone conversations and chance remarks in passing—buttresses our thesis. Reinecke's own description shows that sound medical decision making depends on coupling detailed data with comprehensive medical knowledge. And his description shows that present approaches to that coupling process, such as "chance remarks in passing," are insufficient.

Software tools do not replace the doctor's intuition; they empower it. If doctors find help in telephone conversations and chance remarks from colleagues, then they can find enormous help in software that illuminates the connections between data from individual patients and medical knowledge in every encounter with patients. Practitioners who have used knowledge coupling software have written of how much more gratifying medical practice becomes with such a tool.[3 4]

Lawrence L Weed *president*
PKC Corporation, Chace Mill, Box A-8, One Mill Street, Burlington, VT 05401, USA
llw@pkc.com

Lincoln Weed *attorney*
Groom Law Group, Chartered, 1701 Pennsylvania Avenue NW, Washington, DC 20006, USA
ldw@groom.com

1 Reinecke L. A black day for clinical judgment. *eBMJ* 1999. (www.bmj.com/cgi/eletters/319/7220/1279/DC1#EL2)
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Choice is a gift from the patient to the doctor, not the other way around

EDITOR—I agree with Taylor that many patients are happy to let their doctor have the ultimate decision about treatment, and rightly so, based on their doctor's years of training and experience.[1] This may especially be the case in Taylor's highly technical specialty, anaesthesia. All that most patients want of their anaesthesia is not to feel any pain and to still be alive and well afterwards. But there are many areas of medicine that allow for more negotiation.

It is not in any way politically incorrect to make a decision for the patient if that is what the patient wants. It is a valid route for a patient to relinquish their right to a choice, and none of the consumer groups that I have worked with would deny this. But it should be done only after the patient has been given as much information as they want.

Knowing from experience that the patient may say, "What would you have, doctor?" does not mean that the choice should not be offered in the first place. For many patients, the emotional onslaught of illness can be relieved in part by some feeling of choice in their own care, even if they then hand that choice over to an expert.

Sadly, some doctors use their patients' deference to them as an excuse not to give any genuine options. As one doctor admitted to me, "I can usually tell it in such a way that the patient chooses what I want." It seems likely that other doctors also use this strategy, and many would defend this as being in the interests of the patient. As Taylor acknowledges, the patients who hand their choice to him are intelligent and motivated. But whether they are or not, they deserve the chance of some control over their treatment. Choice is a gift from the patient to the doctor, not the other way around.

Ailsa Harrison *chief officer*
South Buckinghamshire Community Health Council, High Wycombe HP13 5DR
ailsa.harrison@gymail.demon.co.uk

1 Taylor I. Some patients are happy for doctors to make decisions. *BMJ* 2000;320:58. (1 January.)

Continuity of supply of drugs is critical

EDITOR—I do hope that the House of Commons health select committee considers more than the price of generic drugs.[1] Continuity of supply is the real issue.

My own specialty, anaesthesia, depends on 10 or so drugs, of which about half a dozen could be considered essential. All surgery depends on these drugs as well. Almost all of them are old drugs, long off patent, and are items that do not make much profit for their manufacturers, who therefore have little motivation or scope for investment to ensure continuity of supply.

Over the past few months methohexitone (the induction agent of choice for brief procedures) has not been available, nor will it be for the foreseeable future, and thiopentone (the induction agent of choice for many anaesthetics) has been severely rationed. The most serious shortage has been of suxamethonium, a neuromuscular blocker indicated in most emergency procedures. This was in critically short supply for several weeks, which threatened wholesale disruption of emergency and elective surgery (in the event, unrealised).

There is an international anaesthesia internet discussion group.[2] Observation of this group suggests that the United Kingdom is not alone in having these shortages and that it may only be a matter of time before there is a world shortage of a crucial drug, seriously impairing our ability to conduct any surgery.

We need a mechanism whereby manufacturers of these drugs are rewarded not only for the work of making them but also for the reliability of supply for certain drugs. For anaesthesia, this is particularly urgent.

Andrew Skinner *consultant anaesthetist*
St Helens and Knowsley Hospitals, Liverpool L35 5DR
skinner@summerfld.demon.co.uk

1 Beecham L. MPs say the market for generic drugs is "ripe for manipulation". *BMJ* 2000;320:7.
2 Global Anesthesiology Server Network. http://gasnet.med.yale.edu/HomePage.html (accessed 9 March 2000).

Training for NHS Direct staff needs funding

EDITOR—Tyrer in his editorial on the national service framework for mental health and its wish lists is perpetuating several myths about NHS Direct that seem to be held by doctors who feel threatened by the new service.[1]

Firstly, NHS Direct is not a counselling service, and the qualified nurses who answer the telephones are not counsellors.

Secondly, general practitioners should have no problem with NHS Direct "splitting care" since NHS Direct does not provide care. It is an advice giving and signposting service. It does not seek to undermine the relationships between general practitioner and patient—exactly the reverse.

A substantial proportion of those who telephone NHS Direct will have a mental health problem, and a need for training has been identified. At the Depression Care Training Centre, we have been working with another organisation, Healthcare Productions Limited, to develop suitable training materials for NHS Direct nurses to enable them to advise this group appropriately. Neither organisation is in the NHS, and the funding comes from a pharmaceutical company (SmithKline Beecham). Fine words about primary care training are not quite enough.

Elizabeth Armstrong *executive director*
Depression Care Training Centre, University College, Northampton NN2 7AL

The training centre is endorsed by the RCGP Unit for Mental Health Education in Primary Care.

Competing interests: The company of which Ms Armstrong is executive director is a company limited by guarantee and receives payments and fees for services from a variety of organisations.

1 Tyrer P. The national service framework: a scaffold for mental health. *BMJ* 1999;319:1017-8. (16 October.)

Time to switch from whole cell to acellular pertussis vaccines?

EDITOR—In a letter to all doctors last December the chief medical and nursing officers and pharmacist announced that triple vaccines against diphtheria, tetanus, and pertussis containing acellular pertussis would, for the first time, but only temporarily, enter routine use for infants in the United Kingdom.[1] Difficulties in obtaining supplies of triple vaccine containing whole cell pertussis during 1999 seem to have precipitated this decision.

We found a much lower rate of febrile reactions in infants in the United Kingdom given triple vaccine combined with vaccine against *Haemophilus influenzae* type b when the pertussis vaccine was acellular rather than whole cell; both groups were given injections at 2, 3, and 4 months.[2] In November last year new data from Canada showed a noticeable reduction in more serious reactions to pertussis vaccine in infants after switching from whole cell to acellular vaccine.[3] New combined formulations including vaccine against meningococcus group C and hepatitis B, pneumococcal conjugate vaccine, and inactivated poliovirus will certainly be based on or tested alongside triple vaccine containing acellular pertussis. As in its use of oral polio vaccine,[4] the United Kingdom is becoming increasingly isolated among its European neighbours in its routine use of whole cell pertussis vaccine. Health professionals and the public may also become confused and uncertain about the comparative merits of the whole cell and acellular preparations currently being used alongside one another.

We believe that the time has come in the United Kingdom to use acellular pertussis vaccines as the basis of the complex infant immunisation schedule of the future.

Adam Finn *director*
sivs@shef.ac.uk

Frank Bell *research fellow*
Sheffield Institute for Vaccine Studies, Children's Hospital, Sheffield S10 2TH

Competing interests: This group has received research funding from vaccine manufacturers including Pasteur-Merieux and SmithKline Beecham, which manufacture the acellular triple vaccines currently in use. Dr Finn has received reimbursement for attending symposiums, fees for speaking, and funds for research. He has done consultancy work for SmithKline Beecham.

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4 Finn A, Bell F. Polio vaccine—is it time for a change? *Arch Dis Child* 1998;78:571-3.

The other Dr Finlay is commemorated in Cuban stamps

EDITOR—Mortimer's interesting filler describes the lack of recognition of Carlos Juan Finlay for his work on yellow fever[1]; but Finlay and his work on yellow fever have been remembered and commemorated frequently by the Cuban postal authorities. His portrait appears on stamp issues of 1934 (two values), 1951 (one value), 1954 (two values) 1965 (one of seven values), 1981 (one value), and 1993 (one value).

In 1981 the centenary of his proposal that the *Aedes aegypti* mosquito was the vector in the transmission of yellow fever was commemorated by the issue of a stamp depicting the mosquito, a statement of his thesis, and his portrait.

On 20 August 1965, to commemorate the 50th anniversary of Finlay's death, a set of seven stamps was issued, which depict

Cuban stamp commemorating 50th anniversary of Finlay's death. From left to right: Dr Carlos J Finlay; Dr Antonio Dias Albertini; Dr Walter Reed, US army; Dr James Carroll, US army; Dr Jesse W Lazear, US army; unknown

Finlay's portrait, his microscope, his statue, his autograph, and his Cuban coworker, Dr Claudio Delgado. The figure shows the last in the set, which is a mirror image of Esteban Valderrama's now lost mural *The Triumph of Finlay*, depicting the Yellow Fever Commission in Havana, Cuba, in 1900. As part of the work of the commission, Carroll and Lazear, two of the doctors from the US army depicted in the stamp, along with Clara Maas, a US army nurse, allowed themselves to be bitten by infected mosquitos. They all developed yellow fever; Lazear and Maas died in 1900, and Carroll sustained damage to his heart, from which he died in 1907. Maas has been commemorated in Cuban and US stamps also. Would that the British postal authorities were as assiduous in commemorating the plethora of outstanding British medical workers.

S W S Menzies *editor, Meditheme (quarterly journal of the Medical Philately Study Group)*
Tynemouth, Tyne and Wear NE30 2RP
smenzies@epulse.net

1 Mortimer PP. The other Dr Finlay. *BMJ* 1999;319:618. (4 September.)

Correction

Prediction of survival for preterm births

An editorial error occurred in the letter by Emma L Ferriman and others, the second in the cluster (4 March, pp 647-8). The colours of the lines in the key to the figure were transposed. Thus the top line, survival, should have been red [not blue] and the bottom line, serious morbidity, should have been blue [not red].