

CORRESPONDENCE

Psychological response and survival in breast cancer

Sir—M Watson and colleagues' (Oct 16, p 1331)¹ report will no doubt be cited as showing a significant interaction between psychological attitude and outcome in early-stage breast cancer. However, the methodology has serious flaws which have not been addressed. Any practising clinician would have asked the question "What was the patient's knowledge of the extent of her disease at the time of answering the baseline questionnaire (which was administered 4–12 weeks after diagnosis)?"² Nowhere is this stated in the report.

Patients who attend clinics at this early stage of their illness and who have poor prognostic features (on the basis of tumour size, grade, lymph node involvement, and oestrogen-receptor status) have a totally different perception of their prognosis and long-term survival when compared with patients with small hormone-sensitive cancers with very good prospects of long-term survival. The only comment on this in the paper is a single line in the discussion where the investigators state: "The results for the HAD scale category of depression indicated increased risk of death by 5 years in women with high initial scores and, after adjustment for known clinical prognostic factors, this association was strengthened." None of the other data are discussed in this context. The psychological scores are described in isolation and are meaningless without being put in the obvious context of biological risk.

R C F Leonard

Department of Clinical Oncology, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK

- 1 Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. *Lancet* 1999; **354**: 1331–36.

Sir—M Watson and colleagues¹ have reduced the varied and incredibly complex human response to the diagnosis of a life-threatening illness to psychological traits measurable by a few selected tests. They focus on anxiety/depression, helplessness/hopelessness, and fighting spirit. The

impossibly imprecise descriptive nature of fighting spirit aside, the notion that these are the most important traits, or even deserving of study, suggests the simplistic reductionism of the hypothesis.

The human response to illness is as varied and complex as that of any other life challenge. To suggest that this response can be described in a handful of words is to misunderstand the nature of life. Why not choose to investigate other traits (also descriptive of emotional states, but without easily administered tests by which they can be quantified) for possible responses to illness? For instance, some people look for meaning in their illness, or see it as a challenge to grow in spirit, or welcome the opportunity to come to a place of silence and quiet and examine the purpose of their life. Some relate to their bodies as the messenger of their subconscious mind or their spirit and choose to look closely at the message they are being given in the form of their symptoms. Some learn to truly live with their illness, or in spite of it, or because of it. Still others speak of their illness as the greatest gift of their life, the one that taught them how to heal. Perhaps these are some of the responses relating to quality of life, or more accurately to healing in life-threatening illness that need to be nurtured as J B Tucker suggests in his commentary.²

An outcome measure is an essential component of any scientific study these days. But why have Watson and colleagues and so many other investigators chosen survival as a measure of success? Survival is one arbitrary, yet unequivocal and easily demonstrated outcome measure, that has little relevance as a measure of healing. How would the investigators quantify the healing that occurs in patients who die consciously, having healed relationships, forgiven themselves, and found comfort in connection to a higher power? Can this be measured in terms of survival? Does survival have anything to do with healing? Perhaps some of those women who died from their disease in the shortest time were the ones who died most healed. Perhaps the ones who

spend their remaining time on this planet in a desperate attempt not to die, to fight their illness with every ounce of their strength, are the ones who die the least healed, the angriest, the most defeated by their death.

When I see a scientific article that looks at healing rather than survival as an outcome measure, I will pay attention to the variables investigated.

Judith J Petry

Vermont Healing Tools Project, PO Box 172, Westminster, VT 05158, USA

- 1 Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. *Lancet* 1999; **354**: 1331–36.
- 2 Tucker JB. Modification of attitudes to influence survival from breast cancer. *Lancet* 1999; **354**: 1320.

Sir—In interpreting the results of their otherwise excellent study concerning the influence of psychological response on survival in breast cancer, M Watson and her colleagues¹ have improperly and unjustifiably rejected the potential contribution of a type C coping style, which they neither described correctly nor assessed.

Watson and co-workers assert that there is only flimsy evidence for the role of type C, but ignore the reports my colleagues and I have published on type C and cancer.^{2–5} Three of the studies that they cite as suggesting "the type C personality" never used this term or assessed the construct, whereas the single reference that actually mentions type C is not a study, but a one paragraph abstract that merely poses a question.

The investigators perpetuate an unfortunately common error in discussing type C as a "cancer-prone personality", when none of my studies has tested the hypothesis that a type C coping style (I have never used the word personality) leads to the development of cancer. Instead, like Watson and her colleagues, we have focused on type C responses, such as not expressing anger, after cancer diagnosis. Specifically, we have found the type C pattern significantly associated with thicker and more invasive malignant melanomas,² a

weaker lymphocyte response to the primary tumour, higher autonomic arousal in conjunction with lower self-report of perturbation, and greater disease progression when controlling for known prognostic indicators.^{3,4}

Perhaps the investigators' more grievous error, however, is their claim: "Although suppression of negative emotions has been suggested as a focal characteristic of the type C cancer-prone personality (*sic*), we could find no evidence that this tendency has any effect on survival in this group." The way in which the investigators assessed suppression of negative emotions was by asking participants to rate on a scale the way they generally react. This is not, however, how I have assessed type C in my studies. I have argued^{4,5} that type C cannot be assessed accurately by self-report questionnaires, which assume that people are fully aware of their emotions and how they handle them. This notion is contraindicated by my research that shows that the type C coping style involves a discrepancy between the conscious experience and self-report of emotion, and physiological evidence of emotion or stress.

Because Watson and colleagues did not assess the type C coping style, they have no basis to assert, as is apparently the case concerning their own concept of fighting spirit, that there is no evidence that type C coping influences cancer survival. All they can conclude legitimately is that emotional control, as assessed by their self-report measure, was not associated with cancer outcomes.

Lydia R Temoshok

Behavioral Medicine Program, Division of Clinical Research, Institute of Human Virology, University of Maryland at Baltimore, MD 21201, USA
(e-mail: temoshok@umbi.umd.edu)

- 1 Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. *Lancet* 1999; **354**: 1331-36.
- 2 Temoshok L, Sagebiel RW, Blois MS, et al. The relationship of psychosocial factors to prognostic indicators in cutaneous malignant melanoma. *J Psychosom Res* 1985; **29**: 139-53.
- 3 Temoshok L. Biopsychosocial studies on cutaneous malignant melanoma: psychosocial factors associated with progression, psychophysiology, and tumor-host response. *Soc Sci Med* 1985; **20**: 833-40.
- 4 Temoshok LR, Dreher H. The type C connection: the behavioral links to cancer and your health. New York: Random House, 1992.
- 5 Temoshok L. Complex coping patterns and their role in adaptation and neuroimmunomodulation: theory methodology and research. *Ann NY Acad Sci* (in press).

Authors' reply

Sir—R C F Leonard asserts that our report will be cited as showing an important interaction between psychological attitude and outcome in early-stage breast cancer. However, our paper is equally important in what it fails to prove—namely, that a fighting spirit improves survival. The other point Leonard raises is about knowledge of the extent of disease at the time of answering the baseline questionnaire, but this point is not relevant because the study was restricted to women with early-stage disease. However, patients might be aware of the factors linked to prognosis in early-stage disease. If this were so, one might expect baseline psychological response to be affected.

We analysed baseline psychological response in association with known clinical prognostic factors but showed that there was no significant association. Knowledge of clinical prognostic factors could not explain the association we discovered between psychological response and survival. Even if there were weak associations between baseline psychological response and the clinical factors, we have adjusted for these in the survival analysis.

Judith Petry raises a point about the limitations of a questionnaire methodology. We agree that "the human response to illness is as varied and complex as that of any other life challenge". We do not claim to measure all these varied responses and agree with her that it might be impossible to do so with a questionnaire. However, our study does show a modest effect on survival for a questionnaire measure of a helpless/hopeless attitude, and this merits further investigation.

Lydia Temoshok's comments suggest that she is under the misconception that we have tried to replicate some of her findings and she takes us to task for not using the correct methodology. Our aim was not to confirm her findings, but to test the notion that the putative type C cancer-prone personality, previously described by us,^{1,2} might be linked to breast cancer survival. We define type C behaviour differently, with emotional control being the central element.

Finally, it is vital that scientific truth is based on replication. We judge it entirely appropriate that others should now seek to replicate our results and encourage them to do so.

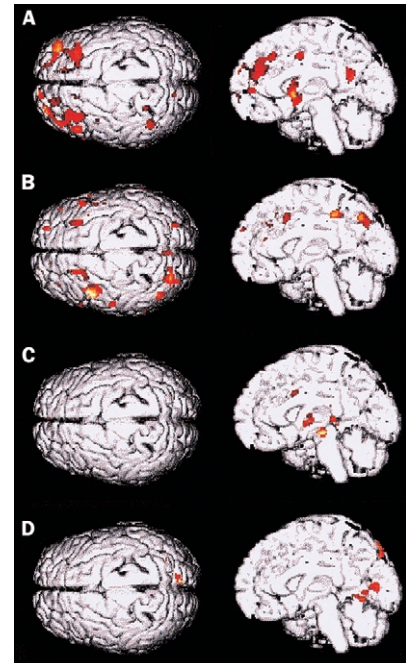
*M Watson, J Davidson, J Haviland

Psychological Medicine, Royal Marsden NHS Trust Hospital, Sutton, Surrey SM2 5PT, UK
(e-mail: maggie.watson@rmh.nthames.nhs.uk)

- 1 Pettingale KW, Watson M, Greer S. The validity of emotional control as a trait in breast cancer patients. *J Psychosoc Oncol* 1984; **2**: 21-30.
- 2 Greer S, Watson M. Towards a psychobiological model of cancer: psychological considerations. *Soc Sci Med* 1985; **20**: 773-77.

Sir—Because of advances in psychoneuroimmunology,¹ many investigators will not be satisfied by the simple study by M Watson and colleagues,² in which the association between psychological factors and disease outcome is assessed. It is now understood that psychological factors may determine immune function via abnormal functions of hypothalamic-pituitary-adrenal axis and autonomic nervous system. Interpretation of Watson and colleagues' results is not easy because there seems to be a missing link between the psychological (depression) and biological (survival) dimensions. The findings need to be reinterpreted in the context of an interaction between the mind, brain, and body.

In a preliminary study,³ we assessed influences of psychological factors on the regional cerebral glucose metabolism of patients with cancer by positron emission tomography (PET). PET with 18-fluorodeoxyglucose was done on 21 patients with cancer, but without brain metastases, and ten controls, and their brain images were compared. The 21 patients were



PET scan showing areas of metabolic reduction in brains of patients with cancer

Summary images of areas of metabolic reduction in brain of 21 cancer patients (A); in patients with high scores on depression scale (B); in patients with remaining tumours (C); and patients who had had chemotherapy (D).

subgrouped by median split with: high and low scores in Zung's self-rating depression scale; with and without existence of remaining tumours; and with and without chemotherapy. Statistical parametric mapping (SPM96) was used to test for brain changes.

Metabolic reduction was detected in several areas of the frontal and parietal cortices (figure, A). These areas are close to known lesions of major depression.⁴ Intra-group comparisons with high and low scores on the depression scale confirmed the psychological disturbance (figure, B). Comparison of patients with and without remaining tumours and patients who had had chemotherapy with those who had not showed no major regional differences in the cortex (figure, C and D).

Our results suggest that even patients with cancer who do not have brain metastases would show abnormalities in the regional cerebral metabolism and that the abnormalities in regional metabolism may be associated with their degree of emotional disturbance. Psychological changes in general population of people with cancer may be accompanied by biological changes in their brains. Analysis of brain activity should be included in future research on survival of patients with cancer to provide the missing link between mind, brain, and body.

*M Tashiro, F Juengling, M Reinhardt, E Moser, E Nitzsche

[†]Division of Nuclear Medicine, Albert-Ludwigs University Freiburg, Freiburg, D-79106, Germany; and Division of Nuclear Medicine, Cyclotron and Radioisotope Center, Tohoku University, Japan (e-mail: tashiro@ukl.uni-freiburg.de)

- 1 Psychoneuroimmunology: interactions between the nervous system and the immune system. *Lancet* 1995; **345**: 99–103.
- 2 Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. *Lancet* 1999; **354**: 1331–36.
- 3 Tashiro M, Kubota K, Itoh M, et al. Hypometabolism in the limbic system of cancer patients observed by positron emission tomography. *Psycho-oncology* 1999; **8**: 283–86.
- 4 Doris A, Ebmeier K, Shajahan P. Depressive illness. *Lancet* 1999; **354**: 1369–75.

Sir—It is a paradox that fighting spirit, the opposite of being helpless/hopeless, showed no association with an increase in survival from breast cancer in M Watson and colleagues' study.¹ The researchers state that fighting spirit is characterised by a determination to fight the illness and adopt an

optimistic attitude. The tables in the article show that a significant number of women adopt the fighting spirit response. It can also be derived that although this response, contrary to popular belief, did not result in improved survival, neither was a significant reduction in survival seen. So, if a woman fights her illness we can conclude that such behaviour should not be discouraged because it may be an important coping strategy for her. However, family and friends could be discouraged from placing undue and unfounded moral pressure on their loved one to fight the illness.

Watson and colleagues mention that the coping response may affect other behaviours, which could alter survival. Patients who are helpless and passive may differ from those who fight their illness in several ways—such as the amount of financial and social support they seek and their ability to make use of resources, such as specialist nurses.

The findings that women who are helpless/hopeless in response to a breast cancer diagnosis may have a reduced overall survival are important for all professionals who work in this area. That a diagnosis of breast cancer can be associated with psychological morbidity is well documented. 20–30% of such patients have anxiety, depression, and low self-esteem at any one time in the year after diagnosis.² This morbidity can continue long after the diagnosis is known and treatment is completed.

In his commentary, J B Tucker,³ suggests that at the very least, screening for distress in oncology patients is needed, and that paper and pencil self-report methods can be used. Although this is a practical suggestion, professionals who carry out the screening would need some education in the methods being used. Breast-cancer nurse specialists such as myself, who have been consistently shown to reduce psychological morbidity⁴ in their patients, are ideally placed to carry out such screening tests and follow up the patients. The timing of such screening tests is particularly important. For instance, a huge array of responses may fall within the bracket of natural and normal reactions to such a diagnosis in the first few days to weeks of receiving the news.

Watson and colleagues state that the helplessness/hopelessness response can be improved by the use of cognitive-behavioural therapy, a technique which more breast-cancer nurse specialists could be trained in. This study certainly adds to the ammunition needed to convince health authorities

of the need to develop psycho-oncology teams and services.

One concern is now that the study codes are broken, will women be informed as to the results? The investigators had stated that to avoid bias the women who took part were unaware of the hypothesis being investigated. Informing patients of the results could lead to feelings of guilt and regret at the coping response adopted and probably is unnecessary.

Siobhan Carroll

Department of Surgery, Cork University Hospital, Wilton, Cork, Ireland

- 1 Watson M, Haviland JS, Greer S, Davidson J, Bliss JM. Influence of psychological response on survival in breast cancer: a population-based cohort study. *Lancet* 1999; **354**: 1331–36.
- 2 Ramirez AJ, Richard A, Jarrett SR, et al. Can mood disorder in women with breast cancer be identified preoperatively? *Br J Cancer* 1995; **72**: 1509–72.
- 3 Tucker JB. Modification of attitudes to influence survival from breast cancer. *Lancet* 1999; **354**: 1320.
- 4 McArdle JMC, David George W, McArdle CS, et al. Psychological support for patients undergoing breast cancer surgery: a randomised study. *BMJ* 1996; **312**: 813–17.

Prophylactic antidepressant treatment before patients are admitted

Sir—Admission to hospital is commonly associated with acute physical and psychological distress due not only to the illness that precipitated the admission, but also to the mere fact of going to hospital. The environment is strange, and sometimes frightening; the patient has to cope with the feelings of anxiety, fear and powerlessness associated with being ill and unsure about what the future has in store.¹ These stresses can cause anxiety and in some cases clinical depression.² Anxiety and depression can affect not only quality of life, but also morbidity, and perhaps even mortality. There is a link between stress and immune symptoms and poor health status.³ Moreover, there are data showing a bidirectional connection between myocardial infarction and depression.⁴

In many hospitals, prophylaxis against gastrointestinal disturbance and deep-vein thrombosis is routine. The brain is subjected to unusual stresses too. I propose that routine prophylactic treatment of depression and anxiety in hospital inpatients might be beneficial. Such treatment could include both pharmacological and other approaches,²

and could be continued for a while after discharge, until complete resolution of symptoms. Clinical trials are planned to assess the prophylactic use of selective serotonin-reuptake inhibitors (SSRIs) in cardiac patients. Trials for hospital inpatients with other illnesses should be attempted. Obviously, drug interactions and side-effect profiles need to be carefully taken into account, and not all patients would be good candidates (for example, people with a history of mania would be excluded).

Until definitive studies are done, I suggest that hospital clinicians look out for signs of depression and anxiety in their patients, and have a low threshold for consulting a psychiatrist and starting a trial of low-dose SSRI early in the hospital stay.

Alexander B Niculescu *III*

Department of Psychiatry, University of California, San Diego, School of Medicine
0603-R, 9500 Gilman Drive, La Jolla,
CA 92093-0603R, USA
(e-mail: aniculescu@ucsd.edu)

- 1 Morris PL, Robinson RG, Raphael B, Bishop D. The relationship between the perception of social support and post-stroke depression in hospitalized patients. *Psychiatry* 1999; **54**: 306–16.
- 2 Twillman RK, Manetto C. Concurrent psychotherapy and pharmacotherapy in the treatment of depression and anxiety in cancer patients. *Psychooncology* 1998; **7**: 285–90.
- 3 Judd LL, Paulus MP, Wells BK, Rapaport MH. Socioeconomic burden of subsyndromal depressive symptoms and major depression in a sample of the general population. *Am J Psychiatry* 1996; **153**: 1411–17.
- 4 Seiner SJ, Mallya G. Treating depression in patients with cardiovascular disease. *Harv Rev Psychiatry* 1999; **7**: 85–93.

Hyperemesis gravidarum and sex of child

Sir—Johan Askling and colleagues (Dec 11, p 2053)¹ report that hyperemesis gravidarum is associated with a sex ratio of offspring that differs from the general population: 44.3% males when hyperemesis occurs in the first trimester, versus 51.4% males in the Swedish population in 1987–95. The investigators suggest that raised concentration of human chorionic gonadotropin (hCG) is associated with hyperemesis gravidarum,¹ because in normal pregnancies female fetuses are associated with higher hCG concentrations at birth than male fetuses.

We studied the sex ratio in a population-based follow-up study from 1991 to 1998, in North Jutland County, Denmark, which has about 500 000 inhabitants (9% of the Danish population). We used the North

Jutland County Prescription Database, Pregnancy Outcome Section,² the purpose of which is to study the birth outcomes in women exposed to drugs during pregnancy. This database contains information from the Danish Birth Registry, to which data are sent by midwives and doctors, the National Health Service, and the Regional Hospital Discharge Registry, which transfers data to the Nationwide Registry, in which 99.4% of all discharges from Danish hospitals are recorded. Information in the registry includes dates of admission and up to 20 discharge diagnoses, classified according to the Danish version of the International Classification of Diseases (eighth and tenth revision).

We identified 47 931 singleton deliveries, and 650 (1.4%) women had been admitted to hospital for hyperemesis gravidarum. The ratio of males to females was 0.87 (95% CI 0.83–0.90), compared with 1.05 for all singleton births ($p=0.018$).

Since hospital admission for hyperemesis may be confounded by social factors, we stratified the cohort according to marital status. We found that the risk of hospital admission for hyperemesis was increased in women living alone (relative risk 1.39 [95% CI 1.14–1.69]), and the sex ratio among newborn infants was 0.68 (0.56–0.78), whereas the sex ratio among those living with a husband was 0.93 (0.90–0.96). Thus, sex ratio also seems to be associated with marital status.

*Henrik Toft Sørensen,
Ane Marie Thulstrup, Jens T Mortensen,
Helle Larsen, Lars Pedersen

*Department of Clinical Epidemiology, Aarhus and Aalborg University Hospitals, 8000 Aarhus C, Denmark; Danish Epidemiology Science Centre, Institute of Epidemiology and Social Medicine, Aarhus University, Aarhus; and Department of Obstetrics and Gynaecology, Aalborg Hospital, Aalborg.

- 1 Askling A, Erlandson G, Kaijser M, Akre O, Ekbohm A. Sickness in pregnancy and sex of child. *Lancet* 1999; **354**: 2053.
- 2 Sørensen HT, Nielsen GL, Christensen K, Tage-Jensen U, Ekbohm A, Baron J. Birth outcome following maternal use of metoclopramide. *Br J Clin Pharmacol* (in press).

Sir—Johan Askling and colleagues¹ report that women who suffer nausea and vomiting in pregnancy are more likely to bear daughters than sons. They cite evidence that in normal pregnancies, female fetuses are associated with higher concentrations of human chorionic gonadotropin (hCG) at birth than are male fetuses, “although concentrations in early pregnancy are unknown”.

In this context, births after hormonal induction of ovulation (ie, with hCG) show a significant excess of females.² This effect is not simply because subfertile couples are more likely to produce daughters. Artificial insemination in general is associated with a slight excess of sons, but artificial insemination preceded by hormonal induction of ovulation is associated with a significant excess of daughters.³ These data provide strong evidence that the sexes of mammalian (including human) offspring are partially controlled by parental hormone concentrations at the time of conception.⁴

I suggest that a (maternal) hormone profile that predisposes a woman to the bearing of daughters has features in common with a hormone profile that causes hyperemesis gravidarum. High gonadotropin concentrations would seem likely to comprise at least part of this common component.

William H James

Galton Laboratory, Department of Biology, University College London, London NW1 2HE, UK

- 1 Askling J, Erlandsson G, Kaijser M, Akre O, Ekbohm A. Sickness in pregnancy and sex of child. *Lancet* 1999; **354**: 2053.
- 2 James WH. The sex ratio of infants born after hormonal induction of ovulation. *Br J Obstet Gynaecol* 1985; **92**: 299–301.
- 3 James WH. The sex ratio of infants born after hormonal induction of ovulation. *Br J Obstet Gynaecol* 1985; **92**: 993–96.
- 4 James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. *J Theor Biol* 1996; **180**: 271–86.

Xenotransplantation debate

Sir—I disagree with your Nov 13 editorial view¹ that discussion and research on xenotransplantation “has been conducted openly” and with little input from special interests.

The US Public Health Service, UK Xenotransplant Interim Regulatory Authority, and WHO acknowledge that xenotransplantation poses unique public-health risks because it could spread potentially deadly zoonotic viruses. Public money has been used to develop the technology yet there have been few public meetings to discuss the public-health, economic, legal, ethical, animal welfare, societal, and religious issues. The recently announced committee set up to advise the US Secretary of Health and Human Services on

policy is unlikely to convene until early in 2000. The US Centers for Disease Control (CDC) and Prevention (given \$11 million by Congress to study xenogeneic viruses, and working closely with industry to do so), and the National Institutes of Health, which dispenses grants to researchers developing xenotransplants, will be represented on this committee. Indeed, most experts participating in policy discussions are xenotransplant researchers, transplant surgeons, or consultants to industry.

WHO's "electronic discussion" on xenotransplantation has left a lot to be desired. Questions have focused on how xenotransplantation can be implemented, not whether it should be, and "comments" have bordered on personal attacks, important questions have gone unanswered, and animal-welfare concerns have been censored.

Money buys power, in politics and in science.² The public-relations budgets in biotech companies developing xenotransplantation dwarf those of most non-governmental organisations. Regulations governing xenotransplantation are virtually non-existent—not surprisingly since optimistic forecasts, fed regularly to the media, appear unchallenged in newspapers and critics are unfairly dismissed as "unhelpful" and "extreme" in scientific journals.

Fears about the possible transmission of animal pathogens have not receded. Dominic Borie and colleagues have thoroughly described the dangers of porcine xenotransplants.² Porcine endogenous retroviruses (PERVs) are by no means the only public-health concern. Let us not forget the novel Malaysian Nipah viral encephalitis virus, which jumped from pigs to man, infecting 269 people (102 fatally and dozens left brain-damaged) and led to the mass slaughter of a million pigs.

Alleged "safety" studies do not take into account latent or unknown viruses. "The greatest danger would come from something causing disease with a very long latency period."³ HIV-1 was transmitted silently until it was recognised as a cause of AIDS.

A retrospective Novartis/CDC study⁴ raises more questions than it answers. 30 patients who had received "splenic perfusions" in Russia tested positive for PERV DNA; 23 had pig cells circulating 8.5 years after treatment; and four patients injected with pig cells produced antibodies to

PERV, suggesting active infection. None of the patients had been exposed to tissue or organs from transgenic pigs. These data are hardly relevant to whole-organ xenotransplants. 14 patients were injected with porcine pancreatic islet cells but important information about exposure times and health and immunological status is missing.

Transplantation of pig organs into non-human primates or pig neuronal cells into rats, as several biotech companies are doing, cannot tell us how pig organs and tissues will perform in man. These experiments also raise animal-welfare concerns.

The Campaign for Responsible Transplantation (CRT) challenges the notion that "uncertainties regarding the advancement of xenotransplantation will only be answered in clinical trials". Such trials will pose enormous medical and legal problems for hospitals and public-health authorities, especially if patients become infected with viruses, refuse to cooperate with infection monitoring, or are sacrificed as guinea pigs. Some technologies pose too great a risk and should simply not be pursued, no matter how much energy and effort has been spent developing them.

CRT believes that safer and more cost-effective means to solve the perceived human organ and tissue shortage do exist.⁵ Given the risks and costs inherent in xenotransplantation, the public has the right to scrutinise the technology; and to decide whether the alleged benefits of xenotransplantation outweigh the risks. Censoring of critics, or purposely excluding them from policy debates, will only heighten public mistrust of the technology and its proponents.

Alix Fano

Campaign for Responsible Transplantation,
PO Box 2751, New York, NY 10163, USA
(e-mail: alixfano@mindspring.com)

- 1 Editorial. Xenotransplantation: time to leave the laboratory. *Lancet* 1999; **354**: 1657.
- 2 Borie D, Cramer DV, Phan-Tham L, et al. Microbiological hazards related to xenotransplantation of porcine organs into man. *Infect Control Hosp Epidemiol* 1998; **19**: 355–65.
- 3 Stoye JP, Le Tissier P, Takeuchi Y, Patience C, Weiss RA. Endogenous retroviruses: a potential problem for xenotransplantation. *Ann N Y Acad Sci* 1998; **862**: 73.
- 4 Paradis K, Langford G, Long Z, et al. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. *Science* 1999; **285**: 1236–41.

- 5 Fano A, Cohen MJ, Cramer M, Greek R, Kaufman SR. Of pigs, primates and plagues: a layperson's guide to the problems with animal-to-human organ transplants. New York City: Medical Research Modernization Committee, 1997.

Sir—Your editorial on xenotransplantation¹ states "WHO has, for once, led imaginatively with an Electronic Discussion Group on ... xenotransplantation ... with precisely defined questions and objectives on concerns ranging from animal welfare to risk assessment".

The British Union for the Abolition of Vivisection (BUAV) is an animal protection organisation, which campaigns against xenotransplantation. I subscribed as its representative to the WHO discussion group in the hope and expectation that I would have the opportunity to raise and share the serious animal-welfare issues that xenotransplantation involves. I read the comments on the discussion site made by a representative of Imutran about the conditions in which pigs, bred as potential source animals, were allegedly kept. I attempted to respond since I judged these comments highly misleading. My response was based entirely on evidence obtained during an undercover investigation into an establishment that maintained pigs for Imutran, apparently intended for use as breeding stock for xenotransplantation. I pointed out that, among other things, the conditions under which these pigs were kept breached UK government guidelines on overcrowding; the animals fought and scratched each other, and some had been removed from their mothers and transported to the establishment when apparently only 3 days old. The establishment in question is currently under serious investigation by the government, and we have submitted a report and video evidence. However, the WHO Moderators refused to post my comments.

The BUAV therefore believes that far from providing an objective forum in which animal welfare concerns can be discussed, the WHO discussion group shows evidence of a pro-industry bias, and that serious criticism of industry's animal-welfare practices is not welcome. This attitude seems to us completely inconsistent with the aims of a discussion site.

Christine Orr

British Union for the Abolition of Vivisection,
16a Crane Grove, London N7 8NN, UK

- 1 Editorial. Xenotransplantation: time to leave the laboratory. *Lancet* 1999; **354**: 1657.

Autism and measles, mumps, and rubella vaccine

Sir—The paper by Brent Taylor and colleagues¹ will reassure the general public that there is no substantial association between measles, mumps, and rubella (MMR) vaccination and autism. However, I would like to know a little more detail about the first two analyses in the study.

For their first analysis, Taylor and colleagues state in the Summary that “there was a steady increase in cases by year of birth with no sudden ‘step-up’ or change in the trend line after the introduction of MMR vaccination”. The visual support for this statement is given in their figure 1, which apparently shows cases increasing before the introduction of the vaccine to the 1987 birth cohorts, the “first birth cohorts eligible for MMR vaccine in the second year of life”; and the statement is supported statistically by a non-significant test for a “step-up” at this time point. The persuasiveness of the graph and the choice of this time point rest presumably on the idea that cases born before 1987 either would not have been vaccinated or would have been vaccinated after they were diagnosed as having autism. But children born before 1987 were also eligible for MMR vaccination, albeit after their second year of life. I have not been able to deduce from the numbers presented how many of the 109 study children born before 1987 received MMR vaccine. Could Taylor and colleagues supply the relevant details of this group of 109 (in particular the number vaccinated before diagnosis)? They could also helpfully give some idea of the proportion of the population vaccinated by year of birth, starting at the 1983 birth cohort, the earliest which in principle could have been vaccinated before a diagnosis under age 60 months. Readers could then assess whether a single “step-up” or a more gradual increase should be expected if there were a causal association.

As regards the second analysis, there are two issues on which further clarification is desirable. Taylor and colleagues found that age at diagnosis did not differ between the three groups (children vaccinated before 18 months, at or after 18 months, or never vaccinated). However, this finding is useful only if age at diagnosis is closely related to the true age of onset of symptoms. There is some evidence that this may not be the case. Research by the National Autistic Society found that 40% of parents wait more than 3

years for a diagnosis.² Indeed, Taylor and colleagues allude to delays in diagnosis. There is therefore some need for caution in interpretation here. Although the variable age at parental concern is heavily prone to bias, use of age at diagnosis in this context may introduce an important bias in the opposite direction (ie, towards obtaining a negative finding).

An equivalent analysis with age at parental concern, which showed no evidence of a difference between the three groups, would be particularly reassuring, because it would be despite a bias working towards a positive finding.

Secondly, because Taylor and colleagues presented evidence for an absence of association, regression coefficients and CIs would be helpful, rather than just the p value (0.41) for what I guess is the *F* test for the null hypothesis of no difference in the (geometric) means of the three groups. In the absence of explicit power calculations, I would like to know that any differences in means were small as well as non-significant.

I am surprised that so much of the burden of public reassurance is made to fall on attempts to show that there is no association between autism and MMR vaccination. I have been persuaded to have my own child vaccinated mainly by the fundamental idea that the risks from not vaccinating are substantially higher than those from vaccinating. What I would find helpful is a calculation of how many cases of autism would have to be caused by MMR—if there were a causal association—for the risks of vaccinating to outweigh the risks of not vaccinating.

Dan Altmann

London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK

- 1 Taylor B, Miller E, Farrington CP, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet* 1999; 353: 2026–29.
- 2 Stirling A, Prior A. Opening the door. London: National Autistic Society, 1999.

Authors' reply

Sir—Dan Altmann is correct in noting that some children born before 1987 received MMR vaccine. This issue was raised by Wakefield.¹ We responded² by identifying the 36 children in our cohort born before 1987 who received MMR vaccine. Age at parental concern was recorded in 29 of these; in all cases this was before MMR vaccination was given. Thus the “catch-up” programme could have had no effect on our

findings. Nor do these findings support Wakefield's assertion¹ that the apparent rise in the prevalence of autism up to 1992 can be linked to the introduction of MMR vaccine.

We agree with Altmann that there may be delay in the diagnosis of autism. He suggests that such delays might have affected the power of our analyses on age at diagnosis by vaccine group. We presented that analysis in our paper, with parameter estimates and CIs as well as p values. We have undertaken a further analysis, as Altmann suggests, of age at parental concern by vaccine group; this presented some difficulties because parental concern predated vaccination in many more cases than did age at diagnosis. We restricted the analysis to the 244 cases with age at parental concern between 15 months and 48 months (excluding two unvaccinated outliers with first parental concern at 84 months and 132 months). We found no significant difference in mean log age at parental concern between children receiving MMR vaccine before the age of 15 months (n=108), those receiving vaccine at 15 months or later (n=88), and those not receiving MMR vaccine (n=48). The p value for the *F* test was 0.61 and the parameter estimates, expressed as fold-differences in geometric mean ages, were: vaccinated before 15 months over unvaccinated 0.96 (95% CI 0.86–1.09); vaccinated after 15 months over unvaccinated 0.94 (0.84–1.06). Similar results were obtained (p=0.35) for the 229 cases with age at parental concern at 18 months or later, with vaccine recipients categorised into those receiving MMR vaccine before or after age 18 months.

We agree with Altmann that the benefits of vaccination outweigh the risks. The purpose of our study was to address a specific hypothesis on a possible association between MMR vaccination and autism raised by Wakefield and colleagues.³ These investigators were careful to emphasise that they had not proved such an association. The three senior paediatricians involved subsequently emphatically endorsed current vaccination policy.⁴ The negative findings of our study reinforce these messages.

*Brent Taylor, Elizabeth Miller, Paddy Farrington

*Community Child Health, Royal Free and University College Medical School, Royal Free Campus, London NW3 2PT; Immunisation Division, Public Health Laboratory Service, Colindale, London; and Department of Statistics, Open University, Milton Keynes, UK

- 1 Wakefield AJ. MMR vaccination and autism. *Lancet* 1999; 354: 350.

- 2 Taylor B, Miller E, Farrington P. MMR vaccination and autism. *Lancet* 1999; **354**: 350.
- 3 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; **351**: 637–41.
- 4 Murch S, Thomson M, Walker-Smith J. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; **351**: 908.

Cervical screening

Sir—Your Nov 27 editorial¹ describes the real predicament of informed consent and what women might want from cervical screening, and the difficulty in reaching women at high-risk. These are particular problems in inner east London, which has the highest deprivation index and the highest proportion of people of non-white ethnic origin in the country as well as an extremely mobile population, including many refugees. Cultural, language, knowledge, and socioeconomic barriers impede awareness and use of cervical screening services. The best efforts of health promotion, primary care, and community services to provide services to women who want them are hindered by lack of resources, despite imaginative initiatives from school age upwards. Improvements are needed in: advocacy and practitioner time (particularly nurse and female doctor); training on communication, informed consent, and smear taking; and community outreach.

Unfortunately, you are wrong to state that achievement of 85% in some areas can be attributed to general practitioners being paid a fee for service. It is 9 years since this was abolished in the 1990 general practitioners' contract, only 2 years after national recall was introduced, and since then payment has been tied to achieving target levels of 50% and 80% adequate smears in women aged 25–64 years. Only the higher level attracts a payment that is commensurate with effort. Targets are a perverse incentive if 80% is not achievable, in the light of the cost per smear in nursing or medical and administrative time, and if factors beyond the influence of local health services are involved.

In 1992, 17.8% of the registered patients in our practice, which had a 35% turnover, were untraceable, despite letters, telephone calls, and visits to their registered address, and only a further 5.6% had moved away, although almost half of these had been seen in the last year of the study (A Warren, A Livingstone, J Gray, J Gosling, unpublished).

Cervical cytology is another example of the inverse care law.² Locally sensitive general practice targets for uptake, and better resourcing of cytology service support is needed.

Anna Eleri Livingstone

The Limehouse Practice, Gill Street Health Centre, London E14 8HQ, UK
(e-mail: A.E.Livingstone@qmw.ac.uk)

- 1 Editorial. Double jeopardy for women in cervical screening. *Lancet* 1999; **354**: 1833.
- 2 Hart JT. The inverse care law. *Lancet* 1971; **i**: 405–12.

Sir—With respect to your editorial¹ about the judgment on the Kent and Canterbury appeal, the dust needs to settle before we can assess the extent of the damage caused to the screening programme by that whole debacle. You also make some comments without references that could be misleading. Women are therefore placed in double jeopardy by the idea on one hand that screening may be unnecessary and on the other that it is rather ineffective. Neither is true.

The rate of cervical cancer may have been falling when screening was first introduced in the 1960s, but the risk has increased for women born since about 1940. In the 1980s it was recognised that disorganised screening was failing to control an increased rate of invasive cervical cancer in young women, who may have been at maximum risk of disease now if screening had not improved.² Before the introduction of screening, the peak incidence of cervical cancer in England was in women in their late 40s.³ Resources were put into improving coverage and quality control, as a result of which incidence has fallen by 42% between 1990 and 1996.⁴ The fall is more impressive when set against a predicted rise.

An individual cervical smear test may have an overall sensitivity as low as 70%, for reasons of sampling more than accuracy of screening. However, regular screening achieves a high level of sensitivity and was the only method of detecting the consistent 18 000 or so cases of cervical intraepithelial neoplasia grade 3 (CIN3) that have been registered each year since 1988 by the Office for National Statistics (<http://www.ons.gov.uk> assessed Dec 30, 1999). A similar number of cases of CIN2 have been treated each year, and detected in the same way, but the cases are not registered nationally. How much more high-grade CIN is there to be found?

Now that invasive cervical cancer is an uncommon disease, affecting nine women per 100 000, it is likely that only a third of those cancers are clinical cases arising in previously screened women. A study in Southampton showed a shift

from high-stage symptomatic cancers to occult screen-detected cancers as the overall rate fell.⁴ In 1994–96 in Southampton, when the rate was the same as in England and Wales, 40% of cancers were occult screen-detected cancers and half of these were stage IA cancers with prognosis and treatment similar to CIN3. 35% of cancers were in women who had never been screened (unpublished personal observations). If those percentages are similar in the country as a whole, there are now only about 600 clinical cancers each year in previously screened women. There are many reasons for screening not preventing cervical cancer, of which misreading a smear is only one.

Cervical screening was not introduced as a cost-saving measure. However, the increased costs and availability of chemotherapy mean that we might have needed the £132 million spent each year on screening if all high-grade CIN had remained undetected.

Amanda Herbert

Histopathology Department, St Thomas' Hospital, London SE1 7EH, UK
(e-mail: amanda.herbert@kcl.ac.uk)

- 1 Editorial. Double jeopardy for women in cervical screening. *Lancet* 1999; **354**: 1833.
- 2 Draper GJ, Cook GA. Changing patterns of cervical cancer rates. *BMJ* 1986; **287**: 510–12.
- 3 Gustafsson L, Ponten J, Bergstrom R, Adami H-O. International incidence rates of invasive cervical cancer before cytological screening. *Int J Cancer* 1997; **71**: 159–65.
- 4 Herbert A, Bryant TN, Campbell MJ, Smith J. Investigation of the effect of occult invasive cancer on progress towards successful cervical screening. *J Med Screen* 1998; **5**: 92–98.

Sir—I am the solicitor who represents the three women with court proceedings against the East Kent Health Authority (EKH) and many others affected by screening errors made at the Kent and Canterbury Hospital and elsewhere. I am also a member of the Juliet Trust—a campaign group set up in the aftermath of the Kent and Canterbury situation to improve standards and awareness of cervical screening.

Although the EKH now tries to justify the enormous public expense of disputing these cases to appeal on the basis that the initial judgment implied a 100% effective test and threatened the viability of the programme, this begs the question why they were not settled out of court in the first place. These were never going to be costly cases to settle and no precedents would have been set because they arose from a deeply discredited screening laboratory. Also, the errors were made many years ago, and since then standards and knowledge have improved. When first negotiating compensation on behalf of the three

women, I wrote on two occasions to the Department of Health to indicate that to make test cases out of any of the Kent and Canterbury cases was potentially disastrous, not just in terms of costs but in terms of further reducing confidence in the screening process. The EKH was even considering a further appeal to the House of Lords, but I am pleased to say that this avenue will not be pursued, and at last the EKH has accepted negligence in these cases.

The other issues you raise¹ need to be discussed further. The Juliet Trust believes that women should have more information about the limitations of the smear test. Many of my clients were let down not just by screening mistakes, but by their own lack of knowledge, and that of their general practitioners, who disregarded symptoms and relied on smear results. Many of my clients were led to believe that a smear every 3 or 5 years was all that was needed to avoid cervical cancer, and have suffered the consequences of that message. Julietta Patnick of the National Screening Programme now tells us that all the protection we can expect from the test is the equivalent to that provided by a seat belt. If this is true then women are entitled to argue for more frequent tests to increase their chances of early detection. The cost may be prohibitive under the National Health Service but we are entitled to honesty.

On many occasions since the Kent and Canterbury errors came to light, attempts have been made to hush up any debate about efficacy and frequency in the screening process for fear of discouraging women to have smear tests. The Juliet Trust supports the smear test and indeed advocates women, especially younger women, to have tests more frequently than is permitted at present. At the very least, every woman having a test should be provided with clear information about its limitations as well as its benefits. This is still not happening and needs to be urgently addressed.

Sarah Harman

16 Station Road West, Canterbury, CT2 8BP, UK

1 Editorial. Double jeopardy for women in cervical screening. *Lancet* 1999; **354**: 1833.

Sir—I found inaccuracies in your editorial¹ on cervical screening, in particular the third paragraph in which you state that general practitioners (GPs) are paid on a fee-per-service basis for cervical screening. The new contract in 1990 for general practice in the UK brought with it a complete change in how GPs were remunerated for cervical screening, with the introduction of targets. The way in which these targets

are calculated adds a further twist to your story, in that those women who refuse to take part in cervical screening are still included in the target population. Thus the GP who gains informed consent to take a cervical smear risks not only losing one item of service payment but the thousands of pounds involved in not reaching targets in the current system. The disincentive to gaining informed consent is even more powerful than you thought.

Noreen Powell

The Burn Brae Medical Group, Burn Brae, Hencotes, Hexham NE46 2ED, UK

1 Editorial. Double jeopardy for women in cervical screening. *Lancet* 1999; **354**: 1883.

Polycystic ovarian disease: a misleading label?

Sir—Polycystic ovarian disease (PCO) was first described by Stein and Leventhal.¹ The characteristics of the condition are obesity, infertility, hirsutism, and raised concentrations of luteinising hormone (LH). After the advent of ultrasonography, the appearances of the polycystic ovary were redefined by Adams and colleagues.² The classic picture is a string of small follicles (2–8 mm in diameter) arranged like a necklace completely encircling the cortical surface of the ovary. Women with PCO are generally referred to gynaecology clinics complaining of infertility, or oligomenorrhoea or hirsutism, or both. The diagnosis is usually confirmed by ultrasound and raised concentrations of serum LH in the early proliferative phase of the menstrual cycle.

When women are informed of the diagnosis of polycystic ovaries, they often have a feeling of distress and concern; this is especially the case in infertile couples. From the time women are first given the diagnosis, during an ultrasound examination or clinic visit, they might assume they have a number of abnormal cysts within their ovaries. The word cyst represents an abnormal enlargement of any tissue. In polycystic ovaries there are multiple follicles arrested at prophase of their development.

We decided to assess patients' perception of PCO. 450 women who were attending the Reproductive Medicine Unit at Liverpool Women's Hospital, Liverpool, UK, and the Fertility Centre at the University of Aberdeen, Aberdeen, completed a questionnaire. 319 (71%) women had heard of PCO and 128 (28%) were

actually diagnosed as having the disorder. All women who were diagnosed to have PCO initially thought it to be a condition in which large cysts were formed within the ovaries. They explained their feelings as "seriously worried" and "shocked".

After the diagnosis, 123 (96%) of the 128 women with a diagnosis of PCO thought that the finding meant they were no longer fertile. 83 (65%) of 128 women assumed they would need urgent surgery, and 74 (58%) believed it was a diagnosis that had been previously missed. The findings suggestive of PCO were first explained by an ultrasonographer during a diagnostic ultrasound scan examination to 102 (80%) women who had to wait until the next available appointment for a detailed explanation from a gynaecologist. 108 (84%) women were not entirely satisfied with the explanations given by the first doctor they had seen and 72 (56%) women were still not satisfied after their second consultation. 55 (43%) women persisted in the perception that they had large cysts in their ovaries.

PCO remains an enigma. Its aetiology, pathophysiology, and cure are not clearly identified. Although diagnosis of the condition can be based on a wide range of variables that may not be always reliable, doctors should at least make an effort not to inflict undue distress on women. In most cases fears subside after adequate, often repeated, counselling and explanation. However, we see no reason to continue the use of an erroneous and unrepresentative term, such as polycystic ovaries.

Some workers have suggested that women with PCO are more susceptible to environmental stresses of daily life,³ whereas others have reported that women with PCO show significantly higher depression and anxiety scores than controls.⁴ We suggest that the more representative and less distressing term polyfollicular ovarian appearance be used instead of the currently used terminology, which is misleading and distressing.

*M Rafet Gazvani, Mark Hamilton, Charles R Kingsland, A Templeton

*Department of Obstetrics and Gynaecology, University of Aberdeen, Aberdeen Maternity Hospital, Foresterhill, Aberdeen, AB25 2ZD, UK; Grampian University Hospitals Trust, Foresterhill, Aberdeen; and Liverpool Women's Hospital, Reproductive Medicine Unit, Liverpool (e-mail: m.r.gazvani@abdn.ac.uk)

1 Stein IF, Leventhal ML. Amenorrhoea associated with bilateral polycystic ovaries. *Am J Obs Gyn* 1935; **29**: 181–91.

2 Adams J, Polson DW, Abdulwahid N, et al. Multifollicular ovaries: clinical and

endocrine features and response to pulsatile gonadotropin releasing hormone. *Lancet* 1985; *ii*: 1375–78.

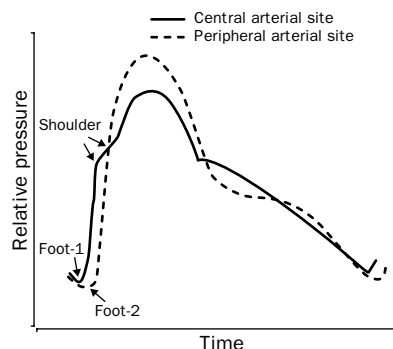
- 3 Beard R, Reginald P, Pearce S. Psychological and somatic factors in women with pain due to pelvic congestion. *Adv Exp Med Biol* 1988; **245**: 413–21.
- 4 Rocco A, Falaschi P, Perrone G, Pancheri P, Rosa M, Zichella L. Psychoneuroendocrine aspects of polycystic ovary syndrome. *J Psychosom Obstet Gynecol* 1991; **12**: 169–79.

Aortic pulse-wave velocity versus pulse pressure and pulse-wave analysis

Sir—Ian Wilkinson and colleagues (Dec 4, p 1996)¹ raise various points that they think I should have discussed in my commentary² on the clinical value of aortic pulse-wave velocity (PWV) measurements. I disagree with them on three points.

They highlight pulse pressure as a surrogate index of arterial stiffness, and state that “the key question remains as to whether PWV or assessment of the arterial waveforms adds to information obtained from measurement of peripheral (brachial) pulse pressure”. The report I cited by Blacher and colleagues showed quite clearly that PWV was the strongest predictor of both all-cause and cardiovascular mortality, independent of other variables, including peripheral (brachial) pulse pressure. Other studies cited² also suggest PWV to be such a predictor. Therefore, why concentrate on a surrogate (pulse pressure) when it is possible to measure the real thing?

The investigators include “assessment of the arterial waveforms” along with PWV as though the two are interchangeable and equally reliable measures. They are not. PWV measurements are generally undertaken with a foot-to-foot method to determine the transit time for the pulse wave to travel a given distance along the vasculature. This method requires the identification of the systolic upstroke, or foot of the waveform signal (figure), which needs to be done accurately for the measurements to be reliable. Even with a large feature such as the foot to be identified, undertaking these measurements is not without its difficulties,³ being quite dependent on the actual foot-detection algorithm used.⁴ Nevertheless, the method has been refined and developed over the years, since Bramwell and Hill’s pioneering work in the 1920s, which I highlighted in my commentary. In this respect the method has stood the test of time, and PWV is now well accepted as a useful index of arterial stiffness which can be measured both accurately and reproducibly.³



Blood pressure pulse waveform data from central and peripheral arterial sites

By contrast, pulse-wave analysis requires the identification of much less substantial characteristics of the pressure waveform signal—eg, the first point of inflection, or shoulder (figure)—and therefore can be quite difficult to undertake, especially if the measurements are attempted in real-time. Furthermore, these waveform analyses need to be done on central arterial waveform signals. Determining the central waveform shape non-invasively is fraught with difficulties when tried in the aorta.^{3,5}

Wilkinson and colleagues suggest that “measurement of central pressure may further refine assessment of cardiovascular risk”. It is clearly of interest to know the blood pressure as close as possible to the heart and coronary vessels, and rather important if one wishes to undertake pulse-wave analysis on aortic-pressure waveform signals. However, at this time, there are no accurate or well validated methods for measuring blood pressure non-invasively in vivo in the aorta.^{3,5}

Therefore, I avoided discussing these issues in my commentary because PWV offers a much more reliable way of assessing arterial stiffness non-invasively in vivo. Furthermore, much more methodological work is needed together with many more validation studies before researchers can claim to be able to accurately measure central aortic blood pressure or waveform parameters non-invasively in individual patients.^{3,5}

Eldon D Lehmann

*Academic Department of Radiology, St Bartholomew’s Hospital, London EC1A 7BE, UK; and Department of Imaging, National Heart and Lung Institute, Imperial College, London (e-mail: aida@globalnet.co.uk)

- 1 Wilkinson IB, Webb DJ, Cockcroft JR. Aortic pulse-wave velocity. *Lancet* 1999; **354**: 1996–97.
- 2 Lehmann ED. Clinical value of aortic pulse-wave velocity measurement. *Lancet* 1999; **354**: 528–29.
- 3 Lehmann ED. Non-invasive measurements of aortic stiffness: methodological considerations. *Path Biol* 1999; **47**: 716–30.

- 4 Chiu Y, Arand PW, Shroff SG, Feldman T, Carroll JD. Determination of pulse wave velocities with computerized algorithms. *Am Heart J* 1991; **121**: 1460–70.
- 5 Lehmann ED. Regarding the accuracy of generalized transfer functions for estimating central aortic blood pressure. *J Hypertens* 1999; **17**: 1225–26.

General anaesthesia in dental treatment

Sir—M R Blayney and colleagues report (Nov 27, p 1864)¹ on cardiac arrhythmias in children undergoing general anaesthesia for dental treatment supports evidence that the incidence of ventricular arrhythmias is associated with halothane.² We have found similar results in 291 patients who had dental anaesthesia in their dental surgery. 33 (17%) of 184 patients who were given halothane developed ventricular arrhythmias as opposed to none of the 107 who were given sevoflurane.

Despite known dangers of halothane, A Breckenridge, the Chairman of the Committee on the Safety of Medicines, in the UK, suggests in his bulletin on the safety of halothane³ that halothane should continue to be used in the hospital setting for paediatric dental anaesthesia, but should not be used in community settings. The study by Blaney and colleagues shows this approach to be illogical. The study was hospital based and showed arrhythmias that most doctors would consider life threatening no matter what the setting. Also, there is no evidence that these arrhythmias are more successfully treated in hospital than in a properly equipped and staffed community setting. Guidelines for community dental clinics⁴ state that anaesthetists who provide anaesthesia in the community should be on the specialist register; there are no such recommendations for children anaesthetised in hospital.

*T J Dexter, K L Scott

Department of Anaesthetics, Wycombe General Hospital, High Wycombe HP11 2TT, UK

- 1 Blayney MR, Malins AF, Cooper GM. Cardiac arrhythmias in children during outpatient general anaesthesia for dentistry. *Lancet* 1999; **354**: 1864–66.
- 2 Paris ST, Cafferkey M, Tarling M, Hancock P, Yate PM, Flynn PJ. Comparison of sevoflurane and halothane for outpatient dental anaesthesia in children. *B J Anaesth* 1997; **79**: 280–84.
- 3 Breckenridge A. Safety of halothane in dental anaesthesia in children use to be restricted to hospitals only. London: Public Health Link, 1999.
- 4 Royal college of anaesthetists. Standards and guidelines for general anaesthesia for dentistry. London: Royal College of Anaesthetists, 1999.

Bias against publication of surgical papers

Sir—As readers of the leading non-specialist medical journals—such as *The Lancet*, *British Medical Journal*, *New England Journal of Medicine*, and *Journal of the American Medical Association*—it has become apparent to us that few of the leading research articles relate to surgical specialities.

We looked at all the major studies published in the four journals during the first 6 months of 1999. On the basis of the topic and speciality of the investigators, we coded the subject matter according to the National Library of Medicine classification system,¹ with studies involving different specialities, the speciality most relevant to the topic was chosen. We further subcoded each report as surgical or non-surgical; for a report to be labelled as surgical, the main emphasis had to involve surgical technique or the outcome of surgical intervention.

Overall, the area of public health accounted for over 21% of all publishers. The table summaries results of our analysis with respect to non-surgical and surgical reports.

We found that on average only one in 15 of the main research reports published in these journals were surgical. At least during the time period under review, the *New England Journal of Medicine* seemed more sympathetic to surgical manuscripts than the others, particularly the *British Medical Journal* (χ^2 test, $p=0.0189$).

This disparity between surgical and non-surgical publications does not relate to hospital practice. For instance, in our own hospital in the financial year 1998/99, 165 177 (53%) of the outpatient consultations were surgical and 148 316 (47%) medical, while 33 496 (40%) of finished consultant episodes were surgical and 51 191 (60%) were medical. The work pattern is similar nationally: in the data year 1997–98, there were 5 187 865 finished consultant episodes in England for medical specialities, and 5 033 390 for surgical specialities (unpublished data). During the same period, there

were more surgically-based hospital admissions than medical ones (4 827 879 versus 4 498 693).

Why is there such a discrepancy between the subject matter of studies published in these leading general journals when, at least in hospital practice, treatment is as likely to involve a surgeon as a physician? We have no knowledge about the readership of these journals, but we suspect that the proportion of surgeons is not inconsiderable and likely to exceed the proportion of surgical reports published. Neither do we have data on the number of surgical and non-surgical submissions these journals receive. Although physicians may be more likely to send a manuscript to a general medical journal than surgeons, is this because surgeons have learnt long ago that their efforts are more likely to be rejected? Whatever the reason, many surgeons are denied publication of their work in journals with some of the highest impact factors.

In its instructions for authors, *The Lancet* states that it “. . . will consider any contribution that advances or illuminates medical science or practice or that educates or entertains the journal's readers . . .”. Surely, the surgical specialities deserve the same representation as physicians? Or are surgically-based studies going the way of those with negative results and the ones in non-English language journals?²⁻⁴ We hope not.

*Adam Magos, Athanasios Cumbis, Christopher Katsetos

Minimally Invasive Therapy Unit and Endoscopy Training Centre, University Department of Obstetrics and Gynaecology, Royal Free Hospital, London NW3 2QG, UK
(e-mail: amagos@endoscopy.org.uk)

- 1 National Library of Medicine Classification, 5th edn. Washington DC: US Department of Health and Human Services, 1994.
- 2 Egger M, Smith GD. Bias in location and selection of studies. *BMJ* 1998; **316**: 61–66.
- 3 Begg CB, Berlin JA. Publication bias: a problem of interpreting medical data. *J R Stat Soc A* 1998; **151**: 419–63.
- 4 Nieminen P, Isohanni M. Bias European journals in medical publication databases. *Lancet* 1999; **353**: 1592.

Probiotics strain for credibility

Sir—Marilynn Larkin's feature (Nov 27, p 1884)¹ seems to concentrate only on the negative aspects of probiotics. This focus seems retrograde at a time when the public is turning more and more to natural remedies, and the medical profession is being urged to be more open-minded and receptive to such practices.

The general concept that the use of probiotics to modulate intestinal flora may produce various beneficial effects has been proven beyond reasonable doubt.^{2,3} The methodical, scientific application of this concept to human health and disease, although still in its infancy, has already given some solid positive results. The interest in probiotic use among the medical and scientific communities is shown by the fact that at least eight reviews have appeared in 1999 alone, in prestigious, peer-reviewed journals devoted to microbiology, medicine, or nutrition (*Environmental and Applied Microbiology*, *Antonie van Leeuwenhoek*, *International Journal of Antimicrobial Agents*, and *Clinical Microbiology and Infection*, and *Digestive Diseases and Sciences*, *British Medical Journal*, *Annals of Medicine*, *Critical Reviews in Food Science & Nutrition*). Each of these reviews, having examined the evidence for and against, draws a generally optimistic conclusion.

Although I agree with the tenor of Gerald Tannock's quoted remarks that knowledge of how probiotics work is desirable, surely at this stage what is more important is to discover which probiotics are most effective, and for what disorders? Fortunately for patients, Domagk and Florey did not wait to use sulphonamides and penicillin until the modes of action were understood.

It was difficult to visualise a clinical trial scenario that could find out whether probiotics improve or maintain the health of healthy people; on the other hand, there is no evidence against this idea. By encouraging the public to make a considered decision to consume probiotics as part of a healthy lifestyle (many components of which are not scientifically proven), the medical profession would be taking to heart the Hippocratic exhortation “*Primum non nocere*”. Perhaps probiotics should be made available in combination with a measured daily intake of multivitamins, since each needs to be taken daily for maximum benefit, and a single tablet makes for convenience and aids compliance.

I fully agree that there is a serious problem, that must be addressed, as regards the quality assurance of many

	Non-surgical	Surgical
<i>The Lancet</i>	117 (93.6%)	8 (6.4%)
<i>British Medical Journal</i>	112 (98.2%)	2 (1.8%)
<i>New England Journal of Medicine</i>	91 (87.5%)	13 (12.5%)
<i>Journal of the American Medical Association</i>	91 (92.9%)	7 (7.1%)
Overall	411 (93.2%)	30 (6.8%)

Proportion of non-surgical versus surgical papers published in the leading non-specialist journals

probiotic preparations.⁴ For this reason, I have publicly urged⁵ that all such products are subject to external independent assay. I understand that such a service will shortly become available in the UK, and I hope that all suppliers will take advantage of it. The quality of information available to the general public about some specific probiotic products also leaves much to be desired. However, several brands of probiotics that I have tested are of high quality and correct quantity and they contain bacteria with scientifically proven desirable properties. Furthermore, information available with these products is reasonable and clear.

There are undoubtedly some probiotic products of dubious value on the market, and some claims that are exaggerated, but these should not be allowed to detract from further serious investigation of this approach.

I act as a consultant for a company that markets probiotic products.

Jeremy Hamilton-Miller

Department of Medical Microbiology, Royal Free and University College Medical School, Royal Free Campus, London NW3 2PF, UK

- 1 Larkin M. Probiotics strain for credibility. *Lancet* 1999; **354**: 1884.
- 2 Fuller R, ed. Probiotics: the scientific basis. London: Chapman and Hall, 1992.
- 3 Tannock GW, ed. Probiotics: a critical review. Wymondham: Horizon Scientific, 1999.
- 4 Hamilton-Miller JMT, Shah S, Winkler JT. Public health issues arising from microbiological and labelling quality of foods and supplements containing probiotic microorganisms. *Public Health Nutr* 1999; **2**: 223-29.
- 5 Hamilton-Miller JMT. Probiotics used in trials should be independently checked microbiologically. *BMJ* 1999; **319**: 189-90.

Do genetically modified foods affect human health?

Sir—The controversy over genetically modified (GM) foods was a deciding factor in the proposal for a European Food Agency. In the UK, a report on the health implications of GM foods (www.doh.gov.uk/gmfood.htm) concludes that “there is no current evidence that GM technologies used to produce food are inherently harmful”; this is true, but one cannot conclude that all applications will be harmless.

The insecticide *criendotoxin* is not harmful when used judiciously as a spray. Much larger quantities would be consumed from plants making the toxin after the incorporation of the bacterial gene, *Bt*. Another potential problem is that the promoter used to switch on any gene after it has been

transferred might also switch on one of the many silent genes that form part of the normal DNA. A third uncertainty is the importance of the finding that foreign DNA ingested by mice may reach peripheral leucocytes, spleen, and liver via the intestinal-wall mucosa.¹ A gene that has been transferred may be incorporated in an unpredictable place in the genome.

People in some countries, particularly the USA, already eat a lot of GM foods. People in the UK do not. If GM foods are bad to eat, a robust study relating consumption to health records should show the adverse effects. Such studies would entail comparisons between regions and groups as well as between countries. There would be problems of comparability and of controls. In September, 1999, I advocated such a study to a subgroup of the UK's Advisory Committee on Novel Foods and Processes (ACNFP) and to a group advising the Research Directorate General of the European Commission on GM organisms research.

ACNFP is considering a feasibility study proposed by Paul Elliott (<http://maffweb/inf/newsrel/acnfp/acnfp1499.htm>) for linking the domestic health records, broken down by census ward level, to data on household purchasing patterns. This study would focus on all novel foods. However, since GM foods are scarcely being consumed in the UK or the EU, such a study in Europe would be unlikely to detect any effects of GM foods.

The health data of the National Center for Health Statistics in the USA are not so geographically specific, being mainly collated at the state level. Data on health could be recorded to allow comparison with the UK.

People on the two sides of the Atlantic have so far tended to take very different views on GM foods. However, the new Transatlantic Consumer Dialogue finds that the Americans are now becoming more worried about GM foods. The US agriculture secretary has spoken on the need for unbiased research on the safety of GM crops.² The US Food and Drug Administration has just held the first public forum on GM foods. The Consumers' Union demands that these foods be labelled. With such labelling, a prospective epidemiological study would become possible, along the lines envisaged by the ACNFP.

Collaboration between the EU and the USA would give a rational basis for the protection that the citizens of both need and might avert a trade war over GM foods. It would be a basis for

including health in the agenda for the new round of the World Trade Organisation.

John Godfrey

41 Lawford Road, London, NW5 2LG, UK

- 1 Schubert R, Renze D, Schmitz B, Doerfler W. Foreign (M13) DNA ingested by mice reaches peripheral leucocytes, spleen, and liver via the intestinal wall mucosa and can be covalently linked to mouse DNA. *Proc Natl Acad Sci USA* 1997; **94**: 961-66.
- 2 Reichardt T. US sends mixed message in GM debate. *Nature* 1999; **400**: 298.

Trap-door medicine

Sir—Larry Greenbaum's (Oct 9, p 1312)¹ piece on sibling rivalry catapulted me back to my student days in the early 1950s.

As students in Switzerland, we were permitted one semestre elsewhere. Most of us opted to spend this semestre in Paris at the Hôpitaux de Paris. I attended the Department of Dermatology as part of my rotation there.

As students, we stood at the back of the outpatient consulting hall. In the middle of the hall sat the professor at his desk; to right and left his assistants. Opposite us was a bank of six doors. The assistant pressed the first of six buttons; and door number 1 sprang open to reveal the first patient, nude. The diagnosis was established and treatment prescribed; the patient was ushered back into the cubicle. The next door was opened to reveal the next patient, and so on.

On one occasion, a lady emerged partly dressed. She was returned to the cubicle and had to wait the entire cycle of six doors before she reappeared nude.

This experience was indeed one of the most formative impressions I have encountered in the span of my professional life and into my retirement.

Therefore the prototype of the conveyor belt existed quite a few decades ago.

Michael Katzenstein

24 Hahagana Road, Raanana 43423, Israel

- 1 Greenbaum L. Sibling rivalry. *Lancet* 1999; **354**: 1312.

DEPARTMENT OF ERROR

Efficacy of cervical-smear collection devices: a systematic review and meta-analysis—In this Article by P Martin-Hirsch and colleagues (Nov 20, p 1763), reference 45 was omitted from the list of references. The missing reference is: Fokke HE, Salvatore CM, Schipper MEI, Bleker OP. A randomised trial of three methods of obtaining papanicolaou smears. *Eur J Obstet Gynecol Reprod Biol* 1993; **48**: 103-06.