Phantom-limb pain

Sir—It would be a shame if the impact of the randomised trial by Lone Nikolajsen and colleagues (Nov 8, p 1353) were to be diminished by Joel Katz's accompanying commentary.1 The trial showed no fall in the frequency of stump or phantom limb pain at 1 year if epidural local anaesthetic was given for a median of 18 h before amputation.

This result is important because an earlier influential, though non-randomised, trial1 did report a reduction in pain at 1 year: all of eight patients given lumbar epidural blockade were pain free, compared with eight of 11 (72%) in a control group not given the blockade. In the new (larger) randomised trial at 1 year only three of 12 (25%) patients with epidural blockade were pain free, compared with five of 16 (31%) in the control group.

The results of these two studies are quite different—not only in direction, but also fundamentally. In the Bach study, only three patients of 19 (16%) had pain at 1 year, whereas in the Nikolajsen study, 20 of 28 (72%) had pain at this time. Professionals involved with amputations must judge which is closest to their own experience. But we do not think they will be helped by Katz, who mixes up randomised studies with non-randomised reports, and counts the various positive and negative results. His commentary is unlikely to yield great insight and he does not explain why promising results from basic science fail in the clinic.

Underlying all this is the pressing issue of knowing when the dodo is extinct. Treatments reported in case series and non-randomised studies often show tantalisingly good efficacy. Only when studies of higher quality are done does a more realistic view emerge. How many times do we have to learn the law of initial results?

Commentators often ask how many positive studies do we need before accepting the utility of a treatment? The challenge is in creating rules about rejecting a treatment—defining the point at which lack of evidence of efficacy changes into evidence of lack of efficacy. Until then, enthusiasts will continue to use unproven treatments on the basis of their experience, and commentators will continue to press for more unnecessary, expensive, time-consuming, and perhaps unethical research to be done. We do not need more research to know that we must provide the best pain relief for our patients, before and after amputations.

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Author's reply

Sir—H J McQuay and colleagues compare the study by Bach et al with that of Lone Nikolajsen and colleagues.1 But these trials evaluated different hypotheses by use of different experimental designs, making it difficult to interpret the discrepant outcomes. As the figure in my commentary showed (see Department of Error, p 604 for correct figure), Nikolajsen's trial is the only one of its kind in design and outcome. The three other studies that evaluated preoperative epidural anaesthesia for patients undergoing amputation reported a reduced incidence of phantom limb pain relative to patients not given epidural anaesthesia1,3 or those given epidural anaesthesia during surgery.1 To declare the issue resolved on the basis of a single negative study is premature—notwithstanding the quality of Nikolajsen's study. In their haste to declare this "dodo" extinct and to abandon research in this area, McQuay and colleagues would deprive those individuals undergoing amputation of the possibility of a future with less pain. We must continue to investigate methods to reduce the frequency and intensity of this very real and difficult pain problem.

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had had general anaesthesia and 22 patients (63%) regional anaesthesia. Time between date of operation and date of answering the questionnaire was a mean of 4–3 years (range 0-5 10-3 years). 20 patients (57%) answered that they still felt phantom pain. Stump pain was recorded by nine patients (26%), phantom sensations by 20 (57%). There was no significant difference between the regional anaesthesia and the general anaesthesia group with respect to frequency and intensity of phantom pain, stump pain, or phantom sensation.

We have not investigated preemptive analgesia in the classic sense. However, there should be an observable difference between regional and general anaesthesia if central sensitisation processes have clinically measurable effects. Perhaps this effect is underestimated and is in reality only a pathophysiological observation of as yet unknown relevance.

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**Pregnancy outcome with ACE-inhibitor use in early pregnancy**

Sir—Angiotensin-converting enzyme (ACE) inhibitors are effective antihypertensive drugs that can be fetotoxic or teratogenic, causing long-term fetal hypotension, renal tubular dysplasia, anuria-oligo-hydramnios, growth retardation, hypocalcaemia, and death if used in the second and third trimesters of pregnancy. 1 This class of drugs is contraindicated in pregnancy, but women are often not aware of their pregnancy during the early weeks of gestation. It has, therefore, been suggested that ACE inhibitors should not be used at all in women of childbearing age. 2 However, very early exposure need not have harmful effects. Bar and colleagues' case series 3 of 18 women and Gregory Lip and co-workers' case series (Nov 15, p 1440) 4 of eight women exposed to ACE inhibitors in early pregnancy showed no indication of any adverse fetal effects. 5 We report the outcome of 21 pregnant women from North Jutland County, Denmark who had a prescription for ACE inhibitors during their first trimester between 1991 and 1996.

The tax-supported insurance programme of the Danish National Health Service covers all inhabitants and refunds 75% of the costs of ACE inhibitors prescribed by doctors. From the computerised accounting system maintained by Danish pharmacies, data on prescriptions were identified from Jan 1, 1991, and linked to the Danish birth registry by means of a unique personal identification number. The birth registry contains information on all births in Denmark from official reports filed by midwives. We also collected information on any recorded discharge diagnoses on congenital malformations or renal failure in the 21 children from their birth to Oct 1, 1997, by linkage to the regional hospital discharge registry. The indication for the drug exposure was recorded for 17 of the 21 pregnancies (11 cases of chronic hypertension and six of pre-eclampsia). The drug was prescribed at 5–15 gestational weeks (median 8 weeks).

None of the 21 babies were stillborn. One preterm infant (delivered at 27 gestational weeks; birthweight 725 g) of a diabetic mother died at 1 week old. There was no neonatal renal failure and the necropsy examination showed no congenital malformations. The mean gestational age for the remaining 20 neonates was 38 6 weeks (range 36–41) and the mean birthweight was 3703 g (2570–5390). One case of congestive cardiomypathy without structural cardiac malformations was diagnosed 3 weeks after birth. Apart from this case, there were no reports of congenital malformations, skull ossification abnormalities, fetal or neonatal renal failure in these infants in the medical birth registry or the hospital discharge registry.

The cardiomyopathy could be due to the underlying disease rather than treatment, but we need more observations to make proper risk assessment for the use of ACE inhibitors in early pregnancy. We did not have information on spontaneous abortions which is the most likely effect of early treatment. So far the results are not alarming and it seems unreasonable to deny women of childbearing age these effective drugs, especially in countries where most pregnancies are planned and contraceptive methods make it possible to stop treatment when a pregnancy is planned.

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**Endocrine-cell allotransplantation**

Sir—C Hasse and colleagues (Nov 1, p 1296) 6 describe the correction of post-thyroidectomy hypoparathyroidism within 5 weeks after allotransplantation of hyperplastic parathyroid tissue. The tissue was harvested from HLA-mismatched donors, cultured for 2 days, immunoprotected in semi-permeable membranes, and implanted in the brachioradial muscle. In their opinion, the results show the clinical relevance of microencapsulation.

Transplantation without immunosuppression of encapsulated heterologous cells has been proposed for nearly two decades as a potential cure for various endocrine diseases. Much studied in rodents, the success of this notion has been confirmed in primates with insulin-dependent diabetes mellitus. 7 Hasse and colleagues' findings may represent the first successful transplantation of non-autologous encapsulated cells in immunocompetent human beings. Nevertheless, we feel that three points should be more convincingly clarified before Hasse and colleagues' conclusion can be accepted: the stable and irreversible endocrine deficiency of the recipients; the presence of viable endocrine tissue at the implantation site; and the source of the observed hormonal secretion.

Hypocalcaemia after thyroidectomy is frequently caused by the inadvertent devascularisation of parathyroid glands.
parathyroid tissue in Hasse's two patients will undoubtedly confirm the clinical effectiveness of cell culture and microencapsulatation to prevent rejection in immunocompetent recipients. Although hypoparathyroidism is a rare and often iatrogenic disease, this successful transplantation of encapsulated non-autologous cells would represent a major milestone towards the clinical application of endocrine-cell transplantation in more common disorders such as diabetes mellitus.

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Sir—C. Hasse and colleagues report the successful cure of postoperative hypoparathyroidism in two patients with allografted parathyroid tissue. Plasma intact PTH values rose within 4 weeks from undetectable to the low normal range in both their patients. However, the patients required continuous vitamin-D replacement therapy thereafter, although at a lower dosage than before allograft implantation.

The successful transplantation of HLA-mismatched parathyroid tissue of human origin with the encapsulation technique is a novel, promising procedure in the treatment of surgically induced hypoparathyroidism. However, we would like to caution against some potential pitfalls with such a strategy. Before considering this invasive treatment, one must ascertain that the hypoparathyroid state is permanent. This clearly is not so in most patients with postoperative hypoparathyroidism. In our experience and that of others, plasma intact PTH generally increases again, often only several months or even a year after surgery. It is therefore unfortunate that Hasse and co-workers did not mention the time they waited before undertaking allograft transplantation in their patients.

Hasse and colleagues say that the usual treatment with oral calcium and vitamin-D supplements may not be sufficient. Although we agree that the ideal treatment would be PTH replacement therapy, the administration of oral calcium and active vitamin-D derivatives (not parent vitamin D, as stated) is generally satisfactory in this condition.

Finally, we would like to caution against the use of parathyroid tissue sampled from patients who are potential carriers of various infectious agents, such as hepatitis B and C viruses and retroviral agents—as is more often the case in uraemic patients who receive intermittent haemodialysis than in the general population. Can the microencapsulated Hasse et al use be regarded as protective against the transmission of viral DNA or RNA? Another issue of potential concern is that in such patients parathyroid tissue hyperplasia frequently evolves to a monoclonal, benign tumoral growth pattern.

For these reasons, and because of the risk of a late adverse immune response in case of HLA-incompatible allografts despite microencapsulatation we would rather opt, in the case of persistent hypoparathyroidism, for a PTH-gene-transfer approach with the recipient's own cells, as has been proposed for erythropoietin-deficient anaemia.

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Mortality from non-cardiovascular disease and diabetes mellitus

Sir—In their report on mortality from non-cardiovascular disease and diabetes mellitus, Beverley Balkan and colleagues (Dec 6, p 1680) found that 35% of diabetic men who died in the Paris Prospective study died because of neoplasms compared with 8% in the Helsinki study and 19% in the Whitehall study.

The high rate of cancer deaths in the French study may reflect the more frequent use of clofibrate in France than elsewhere to treat hyperlipidaemia in diabetic men. Clofibrate was available in France at the start of the French study in 1968-73, so some of the policemen in the French study who were under medical supervision were probably treated with clofibrate.

The WHO clofibrate trial for treating hypercholesterolaemia in men found that clofibrate was associated with a significant 75% increase of non-cardiac mortality (age-standardised death rate per 1000 and per year for the period of the trial, 4·15 in the clofibrate group vs 2·36 in the placebo high-cholesterol group) and with a significant 68% increase in cancer mortality (age-standardised death rate per 1000 and per year, 1·95 in clofibrate group vs 1·18 in placebo high-cholesterol group).

Clofibrate ranks second of the 80 possible human carcinogenic compounds, based on its rodent carcinogenic potency in rodents. Hypolipaemic agents have been used extensively in France (in 1990, they were used 15 times more than in the UK). The use of clofibrate decreased after the first publication of the WHO results in 1978, but was still more commonly used in France than in the UK. Sale records in France indicate that clofibrate was used by 20000 people in 1985 (unpublished observation), twice the number estimated from prescriptions in the UK.

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Authors' reply

Sir—François Pattou, Tilmann Driêüe, and their colleagues make the valuable point that the success of allotransplantation of endocrine tissue can only be assumed if irreversibility of the endocrine deficiency syndrome as well as the source of hormonal secretion after transplantation are established beyond doubt. Indeed, transient hypoparathyroidism may be encountered with a frequency of up to 15% after subtotal thyroid resections. Its incidence is not related to a particular operative strategy.1 Within 6 months, almost all cases resolve spontaneously. If not, the parathyroid deficiency is permanent and irreversible.

In our transplant recipients serum PTH, measured with radio immunoassays for intact PTH, became undetectable at 27 and 2 years, respectively, before transplantation, and have remained so. Clinically both patients depended on massive substitution of calcium and calcitriol, to maintain acceptable, albeit subnormal serum concentration of calcium, clearly indicating irreversible and total parathyroid-hormone deficiency.

The increase of serum PTH in our patients from undetectable to normal occurred within 12 weeks. The only intervention that took place during this period was allotransplantation of parathyroid tissue. Moreover, during a Casanova test2 done in both patients 3 months after allotransplantation, maximum values of intact PTH obtained from the graft-bearing forearm were 234 and 33 pg/mL, versus a minimum of 4 and 5 pg/mL, respectively, from the contralateral arm (as measured by an independent laboratory). Thus, the graft was the source of hormonal secretion in our two patients.

Although oral calcium and vitamin D might be beneficial for patients with mild hypoparathyroidism (ie, some residual PTH-secretion) it is certainly not true for severe disease (ie, no PTH secretion at all). A milder symptomatology is most commonly encountered in patients with postoperative hypoparathyroidism, representing by far the majority of those with persistent hypoparathyroidism. Long-term therapy of patients in which the disease takes a moderate course with only minor symptoms is challenging. Non-specific conditions such as bone pain, loss of energy, exhaustion, depressive mood, and latent convulsion are often unrecognised until irreversible consequences arise.3 Stringent implementation and life-long control of the many such patients is important.

Even with rigorous symptomatic long-term treatment, sequelae may still arise. Chronic parathyroid hormone deficiency invariably causes a reduction of bone metabolism, resulting in osteoporosis and bone pain.4 On the other hand, calcitriol lacks the full renal calcium-retaining ability of parathyroid hormone. Patients given vitamin D inadvertently develop hypercalcaemia, although their serum calcium may be normal. These patients face an increased risk of nephrolithiasis, nephrocalcinosis, and subsequent impairment of renal function. Moreover, they often develop calcium depositions in soft tissues, as well as accelerated arteriosclerosis.

In allotransplantation of parathyroid tissue the regulatory authorities require screening of potential donors for viral infectious diseases, with which we have strictly complied. Whether or not microencapsulation would provide additional protection against the transmission of viral RNA or DNA, however, is unclear.

Finally we do not share the concern that a multicentric, benign growth pattern, occasionally observed in parathyroid hyperplasia, holds significant risks for the recipients of HLA-mismatched parathyroid tissue. As we have shown in numerous experimental studies, transplant rejection and death of allografted cells is complete and inevitable as soon as the integrity of the capsule is impaired.

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Diagnosis of chronic pancreatitis

Sir,—Klaus Mergener and John Baille (Nov 8, p 1379) give an almost complete picture of chronic pancreatitis. Some points, nonetheless, warrant discussion.

Unfortunately, pain in chronic pancreatitis does not diminish as the disease progresses. Even at the end of a 10-year follow-up study, 202 (65%) of 311 patients with chronic pancreatitis still had pain.1 Pain and exocrine pancreatic insufficiency were not significantly correlated. Many (60 of 141, 43%) patients with severe exocrine pancreatic insufficiency (so-called burnt-out gland) continued to have pain attacks.2

The urine pancreolauryl test is similar to the bentiomide test. Testing of serum has been developed as a more practical alternative to urine tests, but the pancreolauryl test has been shown to be better than those in serum.1

Most importantly, diagnostic dependence on pancreatic imaging such as endoscopic retrograde cholangiopancreatography (ERCP) to the exclusion of dynamic tests has drawbacks. Pancreatic-duct abnormalities are known to persist after recovery from acute pancreatitis, whereas exocrine pancreatic function returns to normal.3 Although secretin-pancreozymin test (SPT) and ERCP results correlated in 202 patients with suspected chronic pancreatitis (Wilcoxon’s rank sum test p=0.001; see figure), divergence between the two tests proved greater than might be expected. In 30 (15%) patients, SPT and ERCP results differed. Remarkably, 19 (83%) of 23 patients with abnormal ERCP but only one (14%) of seven with normal ERCP and abnormal SPT results had a history of acute pancreatitis (Fisher’s exact test p=0.005).1 On later follow-up, for all patients with normal ERCP and abnormal SPT results, but for only two (9%) (both alcoholics) of the 23 patients with normal SPT and abnormal ERCP results, the diagnosis was chronic pancreatitis.1

We strongly recommend both dynamic function tests and pancreatic imaging for diagnosis of chronic pancreatitis and its complications. The gold standard for exocrine pancreatic function remains the SPT plus faecal-fat estimation. Indirect pancreatic function tests may suffice for outside referral hospitals, but mild exocrine pancreatic insufficiency in some patients would then probably go undetected. Ultrasound examination and, if this is inconclusive, computed tomography would be indicated in suspected chronic pancreatitis. An ERCP should be done only in patients with relapsing pain attacks.

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Authors’ reply

Sir—Several of Paul Lankisch’s comments merit a response. Although several major textbooks continue to propagate the belief that the pain of chronic pancreatitis diminishes with time, this is a contentious issue. At least three studies1–3 support this view, whereas that of Lankisch and colleagues4 does not. Patients in these series were followed for up to 20 years, but the data were all retrospective, which introduces potential biases. No study of which we are aware has continuously evaluated pain in chronic pancreatitis either prospectively or in a quantitative manner (ie, with a pain rating scale). Simply reporting the presence or absence of pain at 5, 10, or 20 years does not answer the question of pain or loss of pain diminishes with time. A well designed, prospective study to address this important issue would be welcome.

Regarding the utility of pancreatic function tests, we tried to convey the widely held impression that although these provide unique information and may help to evaluate selected patients with chronic pancreatitis, they do not influence management in most cases. The secretin-pancreozymin test (SPT) may be the gold standard for assessing pancreatic exocrine function but, as has been pointed out by Lankisch himself, it is invasive, time-consuming, and expensive. Comparisons of SPT and ERCP that detect a “divergence between the two tests in 15% of patients” are interesting but rarely influence clinical practice. Less invasive (and less sensitive) indirect tests of pancreatic exocrine function such as the bentiomide test and pancreolauryl test are of limited value; bentiomide is not available in many European countries and is currently off formulary in the USA. The fact that direct and indirect testing of pancreatic exocrine function have been largely abandoned by gastroenterologists in the USA suggests that they have not proved helpful in managing patients with chronic pancreatitis.

We disagree with Lankisch’s opinion that “ERCP should be done only in patients with relapsing pain attacks”. He offers no supporting data. A patient with chronic pancreatitis who develops weight loss and jaundice is likely to come to ERCP to assess and manage his common bile-duct stenosis. Patients with progressively worsening constant pain may have pancreatic ductal pathology that merits diagnostic and sometimes therapeutic ERCP. Increasingly, surgeons who operate on the pancreas request preoperative ERCP to provide a map for their interventions. The indications for ERCP and adjunctive imaging studies such as endoscopic ultrasound and magnetic resonance cholangiopancreatography continue to expand.

Despite our institution’s reputation as...
a major centre for diagnostic and therapeutic gastrointestinal endoscopy, we would be the first to insist that ERCP be used judiciously. However, there is no justification for limiting its use in chronic pancreatitis to the assessment of relapsing pain alone.

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5 Lankisch PG, Seidensticker F, Otto J, et al. Secretin-pancreozymin test (SPT) and endoscopic retrograde cholangiopancreatography (ERCP); both are necessary for diagnosing or excluding chronic pancreatitis. Pancreas 1996; 12: 149–52.

Post-exposure prophylaxis after accidental prion inoculation

Sir—Adriano Aguzzi and John Collinge’s report (Nov 22, p 1519) shows how prevention of infection is difficult, and hence it may be impossible to convince the patient at risk of the advantages of these methods. We must not forget the work carried out with scrapie in mice and hamsters showing that specific polysulphonated polyglycosides were able to decrease the apparent size of the inoculum given, and to prevent infection taking place. As a result, single doses of dextran sulphate (molecular weight 500 Kd, 400 mg/kg intramuscularly, toxicity unknown) or oral doses of pentosan polysulphate (Norton Healthcare Ltd, Harlow, UK) as 400 mg thrice daily for 3 months (the human life expectancy equivalent of 72 h in the mouse) after transmissible spongiform encephalopathy inoculation should be considered in man.

About 3% of pentosan is absorbed from the gut, it is partly desulphated by liver and splenic enzymes, and then excreted largely in the urine over 24 h. Pentosan has 8% of the activity of heparin and the single dose of 100 mg/kg shown to be effective against scrapie in mice would greatly reduce blood clotting. Pentosan given within 72 h of the scrapie inoculum was effective, but it is unclear whether separating the dose over such a long period in man because of its acute toxicity would seem reasonable from work in animals, but has not been demonstrated in them. The activity of pentosan polysulphate has been shown in animals, so, since it is potentially available for use in nephropathy and has been used widely in France, it could be given on a compassionate-prescription basis.

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Sir—Adriano Aguzzi and John Collinge’s letter about post-exposure prophylaxis after accidental prion inoculation will undoubtedly cause raised eyebrows in the people who are identified as risk groups for occupational exposure to prion material. Accidental exposure (be it surface exposure or needlestick injury) is most likely to occur on hands.

Most professionals (eg, neurosurgeons) rely on their hands to perform their craft. They will be probably (reluctantly) willing to subject their hands to 1 mol/L NaOH or 20% Chloros treatment, but most will strongly object to surgical excision of the site of exposure. Although it is conceivable that sufficiently concentrated NaOH or Chloros can inactivate PrP*, there are at present insufficient data on the prevention of prion spreading (and hence neuroinvasion) by surgically excising the contaminated site. There definitely exists some risk of iatrogenic transmission when handling potentially infectious prion material, but it is at present impossible to make an informed risk assessment. Although draconian measures have always been advocated for mysterious afflictions, it would seem that prions have recently become less mysterious (although still fascinating)—not through wild speculation but through systematic research. It would be wise to apply the same scientific diligence to prion treatment and prophylaxis. Save the knife for the steak.

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New variant Creutzfeldt-Jakob disease and treatment of haemophilia

Sir—Christopher Ludlam, on behalf of the executive committee of the United Kingdom Haemophilia Centre Directors’ Organisation (UKHDCO), expresses concern (Dec 6, p 1704), about the possibility that blood products might transmit the agent responsible for new variant Creutzfeldt-Jakob disease (nvCJD). The UKHDCO have used this concern to strengthen the recommendation they made in 1996 that recombinant factor VIII (rFVIII) should be used for all people with haemophilia A in place of plasma-derived products. Additionally they have recommended that patients should be treated, as soon as possible, with rFVIII manufactured without the use of bovine proteins or human albumin.

Recombinant gene technology and viral inactivation processes used in the production of factor VIII have reduced the known risks of viral transmission through the infusion of blood products to a low level. Recombinant gene technology uses mammalian cell expression systems to produce rFVIII, and in the UK the final product is stabilised with human albumin (personal communication, G Leighton, Bayer Plc and I Thomas, Baxter Healthcare Ltd). The abnormal prion-related protein (PrP) associated with nvCJD has proved resistant to viral inactivation processes and may be present in human albumin. Recommending that patients are switched from plasma-derived factor VIII (pdFVIII) to rFVIII at this time offers no absolute protection against PrP transmission and would be very costly.

There is no published evidence of any direct outcome benefit from rFVIII compared with pdFVIII. However, viral transmission through the transfusion of infected blood products did occur in the 1980s. The chance, although slight, that nvCJD could also be transmitted in this way has created real anxiety for people with haemophilia. We believe that the focus of debate about this issue
should be whether society values the peace of mind conferred to patients by recombinant technology, rather than the theoretical risk of very rare conditions. Valuing peace of mind in this situation is even more difficult when at least some of the reassurance provided by rVIII is based on a misapprehension that is has no potential to transmit vCJD, when its human albumin content implies that it does.

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**Bartonella-like organisms**

Sir—Stefano Taratolo and colleagues (Nov 29, p 1602) were unable to culture any microorganism, demethylate antibody to *Bartonella* antigens, or replicate *Bartonella* DNA by PCR in their five patients with thrombotic thrombocytopenic purpura. I am not surprised: the structure appearing in the photomicrograph accompanying their letter looks like a Howell-Jolly body, which is an expected finding in severe haemolytic or megaloblastic anaemias. In fact, Howell-Jolly bodies circulate in the blood of patients without haematological disease, although at levels rarely detected until splenectomy unmasks their presence.

These structures correspond to chromosomes that have become detached from spindle fibres during mitosis of erythroid precursors in the marrow. Because of their DNA content, they stain brilliantly with acridine orange. Their detection in the peripheral blood of patients with an intact spleen signals marrow stress and nothing more.

This is not the first time that the detritus of erythrocyte maturation has been misconstrued as an infectious pathogen. Several years ago, American investigators, also misled by the use of acridine orange stain, nominated as the aetiological agent of lupus erythematosus, bacilliform bodies, which, on the basis of their tinctorial characteristics, were probably of polyribosomal origin—i.e., the basophilic stippling often encountered in Romanovsky-stained preparations.

2 Discombe G. L'Origine des corps de Howell-Jolly et des anneaux de Cabot. La Sang 1948; 29: 262–64.

Authors' reply

Sir—We initially considered Howell-Jolly bodies and other red-cell inclusions as a possible explanation for the unusual rod-shaped structures found in our patients with thrombotic thrombocytopenic purpura (TTP). Although pathologists and haematologists at several institutions concluded that the rods were morphologically inconsistent with red-cell inclusions, we pursued additional studies to rule out the possibility. Electron and confocal microscopy showed that the rods were external to red-cell membranes. Further, Howell-Jolly bodies cannot be washed off the surface of red blood cells, as were the structures in our cases. An alternative explanation for the absence of antibodies to *Bartonella* spp is that the suspected organism is not *Bartonella* but an unrecognised organism.

The lessons of the past decade indicate that a continued search for answers to complex clinical entities such as TTP often lead to important discoveries. Indeed, the 1980 paper by John Dooley suggests that multiple undefined haemotrophic bacteria exist. Although haemotrophic organisms are uncommon in man, they are frequently encountered in animals. New associations are continually being made between established clinical conditions and infectious agents. *Cycomegalovirus* and *Chlamydia pneumonae* are associated with coronary artery disease, *Helicobacter pylori* with peptic ulcer disease, *Campylobacter jejuni* with Guillain-Barré syndrome, and bacillary angiomatosis-peliosis with *B. quintana* and *B. henselae* infections. The discovery of *B. henselae* as one of the causative agents for peptic ulcer disease, has revised the treatment paradigm with the recognition that antimicrobial agents can cure ulcers related to the organism by eradication and prevent recurrence. Empirical antibiotics have improved the outcome for patients with Wegener's granulomatosis and rheumatoid arthritis without the identification of a specific micro-organism.

The essential question is whether researchers should communicate promising therapies before an organism can be recovered from affected patients. Considering that 100 years passed from when Whipple's disease was first thought to have an infectious cause until *Tropheryma whipplei* was cultured, we believed that the reporting of a successful outcome with a non-toxic therapy was important. In the future, molecular approaches may reduce the amount of time needed to recover suspected organisms. Our findings indicate further investigation into a potential infectious cause of TTP is warranted and that empirical antibiotics should be considered in the treatment plan.

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**Vancomycin-resistant Staphylococcus aureus**

Sir—Keichi Hiramatsu and colleagues (Dec 6, p 1670) report of vancomycin-resistant *Staphylococcus aureus* in Japan was followed by two further reported cases in Michigan and New Jersey in the USA. Will the next isolate be in the UK or Europe? We agree with Tabaschali's Dec 6 commentary on vancomycin-intermediate-resistance *S. aureus* (VRSA; minimum inhibitory concentration 8–16 mg/L). The management of invasive *S. aureus* infection, already a serious and costly disease, will become nigh impossible if resistance to the glycopeptide antibiotics, including vancomycin, becomes widespread. We report UK data from a study in our unit, based on recommendations from the Centers for Disease Control and Prevention (CDC) (Atlanta, USA) made in August, 1997, that routine disk antibiotic susceptibility testing may not detect many of these isolates and that quantitative susceptibility testing should be used routinely.

Between March, 1994, and March, 1997, we conducted a

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Sir—We report a strain of *Staphylococcus aureus* in the UK similar to the heterogeneously vancomycin-resistant isolates described by Keichi Hiramatsu and colleagues.

An 82-year-old man with chronic renal failure secondary to retroperitoneal fibrosis was admitted with pyrexia and rigors having been supported by haemodialysis via a central venous catheter for 4 weeks. The diagnosis of line-associated septicemia was confirmed when blood cultures taken peripherally and via the line and the line tip after removal grew *S. aureus*. The strain was resistant to meticillin but sensitive to vancomycin on testing by the modified Stokes method; plasmic typing suggested it was epidemic meticillin-resistant *S. aureus*—15 (EMRSA-15). The patient began therapy with vancomycin and remained stable, but blood cultures taken via a new line on days 12 and 19 of therapy continued to grow EMRSA-15. Serum concentrations of vancomycin concentrations (ten blood samples) remained above 9·4 mg/L throughout treatment. On day 21 of therapy, the patient became clinically septic and died the next day. Peripheral and line blood cultures once again grew EMRSA-15.

We used the screening procedure for heterogeneously vancomycin-resistant *Staphylococcus aureus* (VRSA) suggested by Hiramatsu,1 to test the blood-culture isolates. An overnight Tryptone soya broth was adjusted to a turbidity equal to MacFarland 0·5, and 10 μL of this suspension was inoculated onto brain heart infusion (BHI) agar that contained 4 mg/L vancomycin. After 48 h of incubation, scant colonies of *S. aureus* grew from the initial isolate (9/642) and an isolate from day 21 (10/323). These colonies were picked and numbered: small colony type 9/642(2); large colony type 9/642(3); and mixed small and large 9/642(26) and 10/323(25).

We repeated the screening process on four further occasions with our original strains, picked strains, 20 MRSA strains representing EMRSA-15, EMRSA-16, and stored isolates from 1985–1990. Our original strains did not grow on BHI agar containing 4 mg/L vancomycin on all four occasions. However, 9/642(2) and 9/642(26) consistently yielded 10–50 colonies (mixed large and small) at 48 h on BHI agar plus 4 mg/L vancomycin. Strain Mu3 (Hiramatsu’s hetero-VRSA) also yielded mixed colonial types on agar containing 4 mg/L vancomycin. Strains 9/642(2), 9/642(26), and Mu3 also grew when subcultured onto BHI agar containing 8 mg/L vancomycin. We measured the minimum inhibitory concentration (MIC) of vancomycin by the National Committee for Clinical Laboratory Standards broth microdilution method with cultures taken directly from blood agar and also from BHI agar containing 8 mg/L vancomycin (table). Strains 9/642(2) and 9/642(26) gave similar results to Mu3 on screening and MIC testing, thereby fulfilling the criteria for hetero-VRSA.

It should be noted that the screening procedure of Hiramatsu is similar to that of Daum and colleagues used to select for VRSA; hence the procedure could have selected for the resistance in vitro rather than having screened for it. In addition, BHI is not a standard sensitivity testing medium and similar media have been shown to yield raised MICs (4·16 mg/L) of vancomycin for *S. aureus*. Finally, when MICs are measured by standard methods with inocula from non-antibiotic-containing media, the results for Mu3 and our hetero-resistance strains show them to be sensitive to vancomycin (MIC <4 mg/L).

Whether hetero-VRSA, as defined in Hiramatsu’s report, account for the therapeutic failure of vancomycin remains to be proved in a clinical setting.

*Robin A Howe, Karen E Bowker, Timothy R Walsh, Terry G Feest, Alasdair P MacGowan*

4 Piter D, Waldvogel FA. To control or not to control colonisation with MRSA... that’s the question. *Q J Med* 1997; 90: 239–41.
Tumour necrosis factor and septic shock

Sir—An advertisement by Bayer in your (non-UK, non-USA) issue of Oct 25 edition (p 1234) thanks the investigators in the North American Sepsis Trial (Norasept) II study (antibodies to tumour necrosis factor [TNF] to septic shock patients) and comments that "The excellence of the trial's design and execution gives us confidence that we can rule out a useful role for this agent (TNF-α Mab) in septic shock".

Let us recall the development since TNF was cloned in 1985. Basic work and animal studies showed that TNF could induce pathophysiological and histopathological changes characteristic of septic shock. Furthermore, TNF antibodies protected against shock induced by endotoxin or gram-negative bacteria.1 About the same time, we reported that high serum concentrations of TNF were strongly associated with fatal outcome of meningococcal septicaemia.2 In the following years, similar observations were repeatedly made. The evidence for a causual relation between TNF and development of septic shock was strong. So why not start trials with antibodies to TNF?

Science was now carried further by the pharmaceutical industry; the chance of success was reasonably good and the potential market was enormous. Starting in 1990, several clinical studies were designed, but only a few of them have been completed. In a study of an antibody to TNF in 82 patients run by Knoll, no overall effect was found, but a subgroup analysis showed an effect in the patients with the highest concentrations of interleukin (IL)-6. A study on patients with high concentrations of IL-6 was started, but was stopped because no effect was shown in an interim analysis. The Intersept Trial (European South African Sepsis Trial, Bayer) showed no improvement in survival and the study was interrupted. The Norasept I study of 900 patients did not have sufficient power to support the efficacy of the TNF antibody.3 The results formed the basis for an optimum design of the Norasept II study of 1900 patients. The results have recently been presented: there was no improvement of survival in septic shock.

Other approaches in the antimediator strategy have been investigated. The soluble TNF receptor of subtype p55 and p75 bind to TNF and compete with receptor binding on the cell surface. Theoretically and in animal experiments, the receptors antagonise the development of septic shock. However, a p75 construct tested in a phase II study increased mortality.4 Furthermore, the investigation of interleukin-1 receptor antagonists has a parallel profile—a sound antiinflammatory principle, good effect in animal studies, but no effect in phase III clinical studies. Within this concept framework, one should mention the most logical approach of all: antagonism to endotoxin. Even this strategy has been without success.

Is the concept wrong? Do cytokines play the part we think they do in septic shock? The experimental evidence is still overwhelming, and the cytokine cascade is certainly a basic reaction in this setting. However, there is gap between well-defined experimental conditions and septic shock in human beings. Many of the patients have preexisting events such as surgery, trauma, and underlying diseases, which could modulate the cytokine response. The infection may develop gradually and the onset is not similar to the sudden reaction after injection of a bolus of endotoxin in experimental animals. Perhaps the animal models do not accurately reflect models for human septic shock as it appears in infection and intensive-care units. The cytokines are there, but we are not able to modulate the cascade in our favour.

The conclusion should not be restricted to TNF. The fact is that a broad strategy based on antimediator treatment has been extensively tested in septic shock for 10 years and has failed. Science has given us a well-founded conclusion although we do not like the answer.

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Pallestinian health care

Sir—As occupying power, Israel is required by the Fourth Geneva Convention to ensure the healthcare needs of the Palestine population are met. Rachelle Fishman's Nov 22 news item (p 1527)1 dismisses evidence that the draconian Israeli closures policy imposed on the West Bank, East Jerusalem, and Gaza compromise medical care. Two member groups of the International Federation of Health and Human Rights Organisation, having completed an assessment of health-care delivery in the Occupied Territories, reached a different conclusion—that the closures violate medical neutrality and transgress international law.

In 1993, the Israeli government imposed a permanent blockade between Gaza and the West Bank, and East Jerusalem, which prevented free access of Palestinian patients to their own national tertiary-referral hospitals. Further, in the past 2 years, Israel have responded to terrorist attacks by imposing intermittent "internal closures", of disputed security value, on the whole Palestinian population. Sometimes known as sieges, super-closures imprison residents from six major West Bank towns within town limits and prohibit citizens from the environs and from the remainder of the West Bank from entering, for weeks at a time. Patients who live outside town cannot access hospitals without permission from checkpoint soldiers who lack medical knowledge, and many health employees cannot reach work. A survey in March, 1996, found that 38% of the health workers were unable to reach work and five of ten hospitals had a 50% or greater reduction in emergency patients. We interviewed doctors who had smuggled themselves into the village of Asira, after it had been under total closure over 2 weeks, so that they could treat patients, including children, whose medical conditions had deteriorated because they were denied access to appropriate services in nearby Nablus.

Tertiary health-care services for citizens of Gaza are, of necessity, Israeli because after 26 years of Israeli control no accessible tertiary Palestinian service exists, and must be relayed through a referral doctor acceptable to...
the Palestinian Authority and to Israel. The bureaucracy can hinder good medical practice, to the extent thatPhysicians for Human Rights (Israel) has frequently had to intervene to ensure Gazans receive appropriate medical care. Medical training and education is also disrupted—every Gaza doctor has to return to Gaza during a closure on pain of severe penalty. We had to repeatedly fax Erez checkup before a permit was issued to allow a West Bank doctor to present her paper on learning disability to an international conference in Gaza and another Palestinian physician, of international standing, was refused a permit.

Repeated obstructionsto the coordinated functioning of a national—health service promotes premature deaths, increase morbidity, and damage the medical infrastructure. The Israeli authorities' disregard for Palestinian health care, evident during their stewardship of the health system during 1967–94, continues to influence their security policy and will, ultimately, have been responsible for an incalculable number of deaths.

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2 Health care under siege: the February 1996 closure of the occupied territories. Health and development information project. hdp@hdp.org. 1996.


**Human bile for animals**

Sir—Consumption of animal bile to give strength to human beings is believed to have entered the Chinese pharmacopoeia 3000 years ago. Bear bile was, and is, the most prized. According to traditional Chinese medicine, bear bile is useful for combating fever and reducing inflammation, and was used predominantly for illnesses of the liver, gallbladder, spleen, and stomach. Its use spread to Korea, Japan, the Indian subcontinent, and Indo-China as early as the 6th century. In Japan, in 1927, ursodeoxycholic acid was isolated from yatan, a traditional medicine prepared from the bile of the Asiatic black bear (Ursus thibetanus). Modern use of synthetic ursodeoxycholic acid for gallstones and primary biliary cirrhosis originates from yatan.

The converse use of human bile to give strength to animals is less well-known. In 1296, Chou-Ta-Kouan travelled to Angkor, capital of the Khmer Empire, with the Chinese ambassador from the Emperor Temur. Chou wrote extensively on the customs of Cambodia and its crouserly neigbour Champa, and described the practice of collecting human bile:

"Harvesting the Gall—In times gone by, during the eighth Chinese moon, collection of gall took place; the king of Champa annually exacted (from the Khmers) a large jar filled with thousands of human gallbladders. In dead of night, men were stationed here and there in the more frequented parts of cities and villages. When they met people walking by night they threw over their heads a hood gathered together by a cord and with a small knife removed the gallbladder low down in the right side. When the necessary number had been obtained, they were offered to the King of Champa. No gall was taken from the Chinese, however, for one year the bladder had been removed from a Chinese and placed with the others, whereupon all the gallbladders in the jar putrefied and could not be used. Only recently has this practice of gathering gall been abandoned and the mandarins and their subordinates who were charged with it were segregated within the city near the North gate".1

Despite being forbidden since the end of the 13th century, this practice continued secretly in Laos and Cambodia up to the 19th century.4

The liver was thought to be the seat of courage and it was a widespread custom amongst warriors to eat the liver of the dead or wounded. Human bile, as a secretion of the liver, blended with alcohol was thought to be especially powerful, bestowing strength and courage to man and beast; it was rubbed into the heads of fighting elephants to make them more powerful and terrifying.1

Robert Phlipot's has described how the timing of the collection of gallbladders reflected the influence of traditional Chinese medical theory:

"The gallbladder was one of 12 'channels' in the body through which 'qi', a valuable liquid essential to good health, passed. 'Qi' was supposed to be in the gallbladder around midnight and so this would have been the reason why that part of the anatomy was targeted then".2

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**DEPARTMENT OF ERROR**

**Phantom-limb pain**—In this Commentary by Joel Katz (Nov 8, 1997, p 1338) the figure (with correct reference numbers for trials) should be as shown below:

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<tr>
<th>Trials for limb amputation</th>
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<td>Positive trials</td>
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Indicates the treatment combinations compared within a trial, with arrow pointing to combination associated with significantly reduced prevalence of phantom limb pain 6 or 12 months after amputation for positive trials. Negative trials show no difference between treatment combinations in prevalence of long-term phantom limb pain.

Numbers = study listed in reference list.

N = Nikolajsen study.

+ = Given | - = Withheld