Double jeopardy for women in cervical screening

The East Kent Health Authority in the UK has spent an estimated £500000 in a legal battle to deny compensation to three women who underwent hysterectomies because of misread cervical smears. The Authority lost the first round at the High Court which found that the laboratory (since closed) at the Kent and Canterbury Hospital had been to blame. While expressing “the deepest sympathy” for the women “in this difficult process”, the Authority, with the backing of the Department of Health, had taken its case to the Court of Appeal to protect the national cervical-screening programme from the suggestion from the lower court that the test must be 100% accurate.

The Department of Health itself sought clarification of the law about what would be expected from a reasonably competent practitioner, adding “we very much regret any distress this appeal may have caused to the three women”. Such justification is disingenuous, and led to misguided thinking by those whose job it is to provide a healthcare service. Compensation for the three women is yet to be set, but could reach £50000. The authorities lost their gamble and those responsible for the decision to fight these cases now need to account for themselves, professionally and morally.

The UK reintroduced cervical-smear screening in 1988, with “call and recall” for women registered with general practitioners. Coverage is high, up to 85% in some areas, most probably because general practitioners are paid on a fee-per-service basis. Since 1988, the incidence of invasive cervical cancer has fallen by 35%, and for 1997, an estimated 800 deaths from cervical cancer were prevented in women aged 25–54. However, the screening campaign is not without detractors, who point out that incidence and mortality were falling anyway, false-positive results lead to psychological morbidity, the discomfort and morbidity of colposcopy, biopsy, and unnecessary treatment, and the costs of screening.

The WHO has principles for screening. The disease being tested for should be an important health problem and its natural history should be well understood. There should be a recognisable early stage, in which treatment is more beneficial than at a later stage. There should be a suitable test that is acceptable to the population being screened and resources for diagnosis and treatment; and screening should be repeated with intervals suggested by the natural history of the disease. Benefit for those screened must outweigh the risk of physical or psychological harm, and the cost of screening should be balanced against the benefit.

It is around such principles that the debate about screening for cervical cancer hinges. For instance, the screening interval varies (by postcode) in the UK from 3 to 5 years. In the USA, a 1-year gap is usual. The cervical-smear campaign sometimes fails to reach the women most at risk (eg, those who are sexually active without a barrier contraceptive from a young age). And women can be embarrassed about the procedure, especially if done by a male doctor.

For high-grade lesions, the sensitivity of the smear test is about 75%. For low-grade lesions, the figure is about 60%. Such rates might come as a shock to many of those going for screening, which brings into question what women are actually told during the consent process before the smear is done (in practice, consent is usually implied). Research is needed into the consent process and what women would consider an acceptable and unavoidable error rate.

Opinion about compensation when screening fails is divided. If a screening programme with invitations, recalls, and financial incentives to primary-care givers constitutes, in effect, a contract, a woman who is let down for whatever reason should be entitled to compensation without litigation. However, even when a screening service is of high standard and when the woman is fully informed in appropriate language about the screening, there will be outcomes perceived as “mistakes”. Once both ideals are met, and there is a way to go yet, compensation will be unnecessary.

The Lancet
COMMENTSARY

Meta-style and expert review

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Systematic review, or meta-analysis, seeks to distil common results from a plethora of studies attempting to answer a similar question. The meta-analyst is one part scientist, one part mathematician, and eight parts auditor, and it is to this last role that the QUOROM (Quality of Reporting of Meta-analyses) recommendations should bring clarity. QUOROM is a vade-mecum for reporting the assessors' work, but the scientist's role in systematic review is what counts the most.

QUOROM's older sibling is CONSORT (Consolidation of Standards of Reporting Trials), which specified how randomised controlled trials should be reported.1 Like CONSORT, QUOROM was the result of a group process in which trialists, statisticians, meta-analysts, epidemiologists, and editors vetted one another's ideas against empirical research on the factors that affect the results of randomised trials. Where data were lacking, the writing panels relied on aesthetics and common sense. QUOROM and CONSORT contain checklists for the narrative of the report and flow diagrams for the numbers. Both set out to assure transparency rather than correctness.

Critics have dwelled on shortcomings and internal contradictions, but few question the impact of CONSORT.2 Some 70 journals have endorsed the document, which has been so widely translated and adopted that its creators worry that such strong early support might stunt the guideline's natural growth.3

Despite the family resemblance to CONSORT and a longer gestation, QUOROM is off to a sleepy start. Only five people commented on the e-print on The Lancet's website of the QUOROM statement published in today's issue,4 and a side-by-side comparison of QUOROM with CONSORT gives the sense that QUOROM will be helpful, but not nearly so ascendant as CONSORT. The reasons for the difference are worth exploring.

Tom Chalmers pointed out that systematic review, considered as retrospective observational research, shares many of the shortcomings of other historical techniques.4 Though the meta-analytical investigator may be able to assess data quality, he or she has no real control over it. There is no guarantee that all relevant observations are in hand. Crucial elements may be missing from otherwise useful records. The entry criteria chosen are finely balanced between the stringent and the permissive.5

Jesse Berlin and Graham Colditz have suggested that trials could be orchestrated in advance to facilitate analysis across research designs.6 The effort would make sense, since the current hodgepodge of RCTs is hardly efficient. As things stand, if meta-analysts combine the results of large, similar, well-conducted studies, the insight that emerges may relate to effects too small to worry about. If the trials are small, the statistician-meta-analyst estimates an overall effect, but the scientist-meta-analyst wonders whether the different trials have really measured the same phenomenon. If the results are mixed, the meta-analyst may call on subgrouping or meta-regression to disentangle effects but without the benefit of randomisation, masking, or balance, so this analysis is beset by the uncertainties of observational research. Meta-planning of randomised trials would strengthen the process, but such planning is so impracticable that the prospects are dim.6 Clinical trial registers will empower meta-analysts and energise the planning of new trials, but they will not guarantee either breadth or balance of trial designs.

No-one proposes that a digest of bad studies is somehow good research. Unfortunately, whether studies have "good" or "bad" features, they may be biased or unbiased quite independently of their apparent quality. Randomisation, masking, and follow-up all affect study outcome in randomised trials,7 but different quality-weighted meta-analyses of the same randomised trials can give contradictory results.8 Quality assessment is not easily codified, and transparency alone may not be enough to enlighten the reader.

The lucidity of a systematic review says more about the analyst than it does about the facts that the analyst has considered. Since the meta-analyst cannot pull up a single datum by its roots, the summary can be at once exhaustive and, paradoxically, superficial. By contrast, the CONSORT guidelines direct the trialist to present crucial determinants of data quality to the reader.

Emphasis on preplanned endpoints is proper in a single randomised trial, but may be shortsighted when the job is to blend the results of many trials. Adverse outcomes, for example, are unpredictably varied. They are not as well reported as is efficacy, and reports can differ according to the trialist's culture.4 Adverse effects may be noted in non-standard formats that are impossible to summarise. As a result, meta-analyses, by their emphasis on common elements, downplay safety in favour of efficacy.

Data taken out of context, malleable quality weights, complicity in the trialist's penchant for reporting benefit and for omitting human cost: is meta-analysis really needed? Yes. Because there is no serious alternative for taming medical publication, QUOROM will bring clarity to the process, and consistency may follow. QUOROM may yet grow into a robust, authoritative, even authoritarian arbiter of meta-style. But even if QUOROM becomes consensus, systematic review will remain difficult, messy, exploratory, and beholden to the informed judgment of the experts who do the work.

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Importance of position in which patients are nursed in intensive-care units

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A Europe-wide study has shown a high prevalence of infections acquired in intensive-care units (ICU). 4501 patients (44.8%) had one or more infections on the study day, and 3039 (30.3%) of these had been acquired either in hospital or on the intensive-care unit itself. More than half of the infections were of the respiratory tract. This high prevalence of infections contributes significantly to the ICU mortality rate, and several studies specifically examining risk factors for nosocomial infections have shown an increased mortality among those patients with nosocomial pneumonia.2–4

The US Centers for Disease Control and Prevention (CDC) have recommended that patients on ICU be nursed in a semirecumbent position to minimise the likelihood of nosocomial infections. In a study reported in today's Lancet, Mitra Drakulovic and colleagues randomly allocated intubated and mechanically ventilated ICU patients to be nursed in either the semirecumbent or the supine position. The likelihood of clinically suspected (on the basis of CDC criteria) and microbiologically confirmed nosocomial pneumonia was assessed, and other known risk factors for pneumonia were also analysed. The findings were so clear that the study was terminated at a scheduled interim analysis after only 86 patients had been recruited.

Clinically suspected pneumonia developed in significantly fewer patients nursed in the semirecumbent position (three of 39 [8%]) than in those nursed supine (16 of 47 [34%]; p=0.003), and this difference was also true for microbiologically confirmed nosocomial pneumonia (two of 39 [5%] vs 11 of 47 [23%]; p=0.018).

Supine body position, enteral nutrition, mechanical ventilation for 7 days or longer, sedation score of 4 or more, and Glasgow coma score on admission of less than 9 were significant risk factors for nosocomial pneumonia. There was a tendency to increased incidence of pneumonia among patients who were receiving sucralfate, a finding that is contrary to previous reports. Mortality did not differ between the two groups, nor was it higher among those with confirmed pneumonia.

How might the risk factors identified affect the occurrence of pneumonia? Aspiration of colonised or infected oropharyngeal or gastrointestinal contents is the main cause of ventilator-associated pneumonia. Several non-antibiotic measures for preventing aspiration have been proposed—eg, drainage of subglottic secretions, adoption of the semirecumbent position, prevention of gastric microbial overgrowth by stress-ulcer prophylaxis with sucralfate (which, unlike antacids or antagonists of the histamine-2 [H2] receptor, maintains normal gastric acidity), or early institution of enteral feeding.4 Nursing in the semirecumbent position reduced the likelihood of aspiration as assessed after placement of radiolabelled sulphur colloid in the stomach.6 Other studies have shown that the presence and size of the nasogastric tube also influence the frequency of aspiration, presumably by compromising the action of the lower oesophageal sphincter. The introduction of enteral feeding early in the ICU stay has been widely advocated, although there is limited evidence that it prevents ventilator-associated pneumonia. In fact, many studies have shown increased rates of nosocomial pneumonia associated with enteral nutrition.8,9

A review and meta-analysis of different techniques for stress-ulcer prophylaxis10 showed that H2-receptor antagonists were more likely than placebo to be associated with the development of pneumonia (odds ratio 1.25 [95% CI 1.078–2.00]). The use of sucralfate was associated with a lower frequency of nosocomial pneumonia when compared with antacids (0.80 [0.56–1.15]) and H2-receptor antagonists (0.77 [0.60–1.01]).

A study of factors associated with ventilator-associated pneumonia in 277 patients showed that mortality was higher among those with than among those without nosocomial pneumonia (37.2% vs 8.5%; p<0.001). In that study, supine head position during the first 24 h of ventilation was associated with a significant increase in the occurrence of pneumonia (odds ratio 3.1; p=0.016), which in turn resulted in a significant increase in mortality (30.2% vs 8.9% in the semirecumbent group; p<0.001).

The study by Drakulovic and colleagues highlights another interesting and often forgotten point in the pathogenesis of nosocomial pneumonia. Duration and depth of sedation were associated with a significantly increased frequency of infection. There is now much evidence of the immunosuppressive effects of many of the sedative agents commonly used in ICU.11

In Drakulovic and colleagues' study, the patients allocated to nursing in the supine position were more likely than those in the other group to have received ranitidine, to have a large-bore nasogastric tube in place, and to have an ultimately fatal disease status and a higher APACHE II score. Although for each of these variables the differences between the groups did not reach statistical significance, all the p values were less than 0.08. Combination of all these factors may have led to an inadvertent bias in the patients assigned to the supine group. However, on the basis of the data given, only six patients need be treated in a semirecumbent position to prevent one pneumonia. Kolle's data suggest even greater efficacy for the semirecumbent position; since the number needed to be placed in that position to prevent one death from nosocomial pneumonia is five.

There seems to be no evidence of harm attributable to the semirecumbent position. There is proof that aspiration of gastric contents and associated nosocomial pneumonia are less likely when patients are nursed in the semirecumbent position. There is also some evidence of a significant reduction in mortality rate when this position is...
Safety of outpatient dental anaesthesia for children

See page 1864

Every year in the UK, about one in 250,000 people undergoing dental anaesthesia die in the dentist’s chair. Most of those who die are young adults or children, and the deaths are attributed to respiratory difficulties or sudden cardiovascular collapse. Over the past decade in the USA, the annual incidence of death during anaesthesia for dental procedures was about one in 670,000 to one in 1,000,000. Although anaesthetic deaths may have occurred in healthy young people in the USA since 1994, in that year there were no deaths with the 69,795 general anaesthetics administered in Massachusetts. Only 12 of 317,673 patients receiving anaesthesia in dental offices in Massachusetts in 1994 were transferred to hospital. Arrhythmias requiring treatment were reported only in older adults.

Is there a difference between the mortality rate during anaesthesia for dental procedures in the USA and the UK? Perhaps reporting is incomplete in the USA. Whether or not there is a difference, most clinicians would agree that even one preventable death is too many, and that further information is needed about the safety of outpatient dental anaesthesia.

In today’s Lancet, Michael Blayney and colleagues report the results of a randomised trial of two anaesthetic agents given via nasal masks to children undergoing dental extraction. The investigators found a higher frequency of ventricular arrhythmias in children who received halothane than in those who received sevoflurane, and conclude that sevoflurane is a safer anaesthetic than halothane for paediatric dentistry. Bigeminy and short episodes of ventricular tachycardia occurred only in children who received halothane. These cardiac events were independent of the transient episodes of hypoxaemia that were common during sevoflurane as during halothane anaesthesia. This study and others1-4 clearly show that sevoflurane has fewer cardiac side-effects than halothane. However, in the USA halothane is commonly given to children for complete oral check-ups and treatment, and cardiac side-effects are rarely reported. When the patient is under halothane anaesthesia in hospital, ventilation is controlled through an endotracheal tube and anticholinergic medication is commonly part of the general anaesthetic plan. Spontaneous ventilation during halothane anaesthesia may result in hypercapnia and precipitate ventricular tachycardia.1-4

General anaesthetics, sedatives, and narcotics all depress respiratory drive and lead to hypercapnia and hypoxaemia. These potentially life-threatening physiological abnormalities are easily treated or prevented by controlled ventilation. However, routine practice in dentists’ offices in the UK and the USA is not to place endotracheal tubes or to control ventilation. When the choice is made not to use skilled personnel to deliver general anaesthesia with controlled ventilation, the safety of the patient depends on his or her physiological state, the monitoring procedures used, the preparedness of the practitioner giving the anaesthetics, and the choice of drugs and doses given. In Blayney and colleagues’ study, inhalational anaesthetics were administered through a Goldman nasal mask: carbon dioxide concentrations in expired air were not monitored, and no anticholinergics or analgesics were given. Breathing during induction of and emergence from anaesthesia and partial airway obstruction were the causes of hypoxaemia, but repositioning of the oral pack was the only manoeuvre needed to improve oxygenation—clearly these were skilled practitioners of dental anaesthesia. But it is very probable that hypercapnia was present in their patients.

Pulse oximetry and monitoring of carbon dioxide concentrations can provide objective evidence of adequate ventilation.4 Use of a stethoscope, particularly a precordial stethoscope continuously connected to the anaesthetist’s ear, provides the earliest sign of altered respiratory function. Practice guidelines for the administration of sedatives and anaesthetics outside of the operating room were widely discussed in the 1980s, and professionals developed protocols suitable for the environment in their practices.11 One requirement in the guidelines is that practitioners giving sedation must be competent in basic life-support skills, such as maintenance of ventilation with a mask. But practice guidelines and monitoring standards will not in themselves ensure safety of patients. Those guidelines must be followed. The practitioner must also exercise judgment, both in the choice of drugs and in the timing of interventions to improve respiratory function. When guidelines developed by professional associations are not followed, the occurrence of serious adverse events may provoke tightening of legal restrictions on practice—at least in the USA.

*Barbara W Brandom, Andrew Herlich


2. D’Eramo EM. Mortality and morbidity with outpatient anesthesia: the
Is simple clinical assessment adequate for cardiac risk stratification before elective non-cardiac surgery?

With surgical outcomes being the subject of increasing medical and non-medical scrutiny, there is pressure to identify patients at high risk of perioperative cardiac events, most importantly fatal and non-fatal myocardial infarction. T homas Le e and colleagues have shown that a simple clinical assessment is the only risk-stratifying measure required for most patients being considered for major non-cardiac surgery. T heir revised Cardiac Risk Index, based on the type of surgery and risk factors related to the individual (panel) is derived from multiple-regression analysis of a large cohort of patients (2893 in the derivation set, 1422 in the validation set) and represents a helpful simplification and improvement of their original scoring system developed in the 1970s. Patients with fewer than two risk factors, who made up 75% of the population, had a risk of a major cardiac event of less than 1%. Patients with two or more factors had a 6% risk. It is these symptom-free but high-risk patients who are nevertheless at high risk (5% or more) of a perioperative cardiac event after subsequent non-cardiac surgery for patients with multivessel coronary disease on angiography, which leads to a perioperative cardiac event rate for patients with angina, the investigations and any treatment should be completed before the date of the operation.

The most difficult group of patients to assess and manage are those without symptoms of coronary disease who are nevertheless at high risk (5% or more) of a perioperative cardiac event on clinical grounds (revised index 2 or more). M any patients being considered for non-cardiac vascular surgery are in this category, since 40% of those without any cardiac symptoms have obstructive coronary disease on angiography, which leads to a perioperative cardiac event rate for all vascular operations of about 8%. T hus, if elective non-cardiac surgery is planned for patients with angina, the investigations and any treatment should be completed before the date of the operation.

The choice of test depends primarily on local expertise, and the overall strategy of which it forms a part is of far greater importance than the exact investigation chosen.

Symptom-free but high-risk patients, whether identified on clinical grounds alone or following non-invasive testing, are conventionally assessed with coronary angiography for revascularisation. T his strategy provides reassurance for the clinician, although there is little hard evidence to support it. Coronary bypass surgery in symptom-free patients has never been shown to reduce the risk of subsequent non-cardiac surgery, whatever the pattern of coronary disease. Percutaneous intervention is unlikely to improve prognosis because it cannot protect against plaque rupture over most of the length of the coronary artery. Current approaches cannot identify specific risk factors with non-invasive tests and, when indicated, coronary angiography, whether or not non-cardiac surgery is planned. According to the revised index, the risk of a perioperative cardiac event for patients with angina undergoing major surgery (abdominal or thoracic) is greater than 5%. However, the CASS data suggest that, after successful coronary bypass surgery, the risk of a cardiac event after subsequent non-cardiac surgery for patients with multivessel coronary disease falls from 6% to 2.5%.

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<tr>
<th>Risk factor</th>
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<tr>
<td>High-risk surgery</td>
<td>AAA repair, thoracic, abdominal</td>
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<tr>
<td>Ischaemic heart disease</td>
<td>Mi, Q, angina, nitrates, EST+</td>
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<tr>
<td>Congestive heart failure</td>
<td>History, examination, CXR</td>
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<td>Cerebrovascular disease</td>
<td>Stroke, TIA</td>
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<td>Insulin-treated diabetes</td>
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* Myocardial infarction, pulmonary oedema, ventricular fibrillation or primary cardiac arrest; complete heart block.

Abbreviations: AAA=abdominal aortic aneurysm; M=history of myocardial infarction; Q=Q-waves; EST=history of positive exercise electrocardiogram; CXR=chest radiograph; TIA=transient ischaemic attack.


individuals who will definitely experience a perioperative cardiac event, and revascularisation inevitably means treatment of many patients in an attempt to prevent a few adverse outcomes. In any event, the modest survival benefit is unlikely to exceed the additional risk of a bypass operation that would not ordinarily have been done. These risk/benefit considerations apply particularly to patients with peripheral vascular disease, in whom coronary bypass surgery carries an especially high risk.

The cause of perioperative myocardial infarction probably differs from that of spontaneous myocardial infarction, with important management implications. Although infarction might be expected to occur during the stress of the operation itself, it is commonest on the second and third postoperative days, and is strongly predicted by episodes of ischaemia on postoperative Holter monitoring. The peak burden of electrocardiographic ischaemia on postoperative days 2 and 3 is itself preceded by a peak in the amount of tachycardia on days 1 and 2. A hypothesis proposed is that the stress response to surgery (eg, high circulating concentrations of catecholamines, prothrombotic tendency) results in increased myocardial oxygen demand and increased shear stresses on atherosclerotic plaques, leading to secondary plaque rupture.

The emphasis in the perioperative management of patients at high cardiac risk should therefore be directed away from mechanical revascularisation towards improved control of myocardial oxygen demand and protection of vulnerable atherosclerotic plaques. Aggressive modification of coronary risk factors with anti-smoking advice, cholesterol lowering, and control of hypertension are essential. Perioperative haemodynamic monitoring, meticulous pain control, and the careful use of β-blockers are also crucial. Mangano and colleagues showed that atenolol given intravenously at induction of anaesthesia and continued during the hospital stay reduced overall mortality by 55% over the subsequent 2 years. This result was due mainly to improved survival over the first 8 months, possibly as a result of a reduction in shear stresses on vulnerable atherosclerotic plaques postoperatively.

Despite advances in perioperative management, there continues to be pressure for patients at high cardiac risk to be identified preoperatively. The data obtained by Lee and colleagues emphasise that for most patients cardiac risk-stratification before elective non-cardiac surgery requires only a knowledge of the risk associated with the procedure and a simple clinical assessment. Resources should be directed away from the unnecessary investigation of low-risk individuals, towards improved perioperative management for those at high risk.

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Albumin infusion for spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is a common complication of ascites and cause of death of patients with cirrhosis. The survival of a patient with spontaneous bacterial peritonitis depends on an aggressive approach to diagnosis and treatment (see figure). This strategy has been shown to reduce infection-related mortality to 5% or less. However, about 40% of patients do not survive the admission to hospital during which the infection is detected, and renal failure and gastrointestinal bleeding are the commonest causes of death. This infection may lead to a deterioration in renal function by increasing the peripheral vasodilatation and renal vasoconstriction that are present in patients with advanced cirrhosis.

A recent randomised controlled trial lends support to an association between circulatory dysfunction and bacterial peritonitis in patients with cirrhosis. The study showed that renal impairment can be prevented by intravenous albumin infusion—1.5 g per kg bodyweight within 6 h of detecting the infection and 1 g per kg on day three. The infusion of albumin was associated with a stable plasma renin concentration. Patients who did not receive albumin experienced a significant increase in plasma renin concentrations. In-hospital mortality was 29% in the antibiotic-only group compared with 10% in the antibiotic-plus-albumin group. The latter rate is the lowest reported for patients with spontaneous bacterial peritonitis and the difference in survival rates was still statistically significant at 3 months. The study was not blinded or placebo controlled, but observational studies have been very well done and provides some of the much needed evidence for making "evidence-based" decisions for these patients.

The use of intravenous infusions of albumin in clinical practice is controversial. The Cochrane meta-analysis, which reviewed the use of albumin in many disorders, concluded that albumin may increase mortality. This conclusion led to a very heated debate in the medical and lay press. However, rather than drawing one conclusion about the value and safety of albumin from 30 distinctly different randomised studies, a more useful approach may be to focus on each specific setting in which albumin is used. The randomised trial of albumin infusion carried out by Pau Sort and colleagues to prevent renal failure and death in patients with spontaneous bacterial peritonitis is very encouraging. The recommended initial dose of albumin is more than 100 g for an average man, and 50–100 g for the day 3 infusion. Although this regimen is very expensive, it would be justified if further trials confirm the impressive survival advantage. As the
sensitive ascites are most appropriately treated with a spontaneous bacterial peritonitis, can maximise survival of patients with this common complication of cirrhosis. The plasma renin concentration has been associated with an increase in mortality. However, no randomised trial has shown a direct association between paracentesis without albumin replacement and an increase in mortality; the association is an indirect one. The studies that do propose an association have been criticised for including patients who had diuretic-sensitive ascites. Patients with diuretic-sensitive ascites are most appropriately treated with a sodium-restricted diet and oral diuretics. Large-volume paracentesis should be used only for initial treatment of tense ascites (with removal of 2–4 L) or for treatment of diuretic-resistant ascites (removal of nearly all ascitic fluid every 2 weeks). Too frequently, large-volume paracentesis is repeated in diuretic-sensitive patients who seem refractory to diuretics, but in fact are simply not eating a sodium-restricted diet. The sodium concentration in a 24 h urine sample can indicate non-compliance with the diet. M any patients make little effort to comply with the diet or do not realise that foods such as dill pickles, soy sauce, or buttermilk are extremely high in sodium. Diet education by a dietician can lead to successful diuretic treatment and prevent the need for therapeutic paracentesis and the debate associated with it.

Immediate infusion of albumin, in addition to broad-spectrum antibiotic treatment at the time of detection of spontaneous bacterial peritonitis, can maximise survival of patients with this common complication of cirrhosis. The benefits of albumin infusion for other disorders must be weighed against the cost and potential hazards before its use can be recommended or opposed.

Whether albumin infusion after each sequential therapeutic paracentesis improves the survival of patients with truly diuretic-resistant ascites remains to be proved.

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New treatments for pulmonary fibrosis?

Idiopathic pulmonary fibrosis (IPF) is a life-threatening syndrome. Various factors, such as aspiration and exposure to wood dust or metal dust, may lead to a common clinical and histological expression of lung disease. After initial epithelial-cell injury and inflammation, the lung is reorganised by a destructive fibroproliferative response. In 65% of IPF patients, histological evaluation reveals usual interstitial pneumonia (UIP). At low magnification, UIP shows between-field variability in features such as honeycomb lung, interstitial fibrosis, and normal lung. UIP reduces the surface area of the lung and obliterates pulmonary vessels, which results in ventilation-perfusion mismatch, hypoxaemia, and breathlessness. Patients with an UIP pattern of IPF have a mean age of 65 years, do not respond to steroids, and have a median survival of only 2–8 years. A minority of patients present with the clinical syndrome of IPF, but histological examination reveals either the more recently described non-specific interstitial pneumonia (NSIP) or desquamative interstitial pneumonia (DIP). NSIP is a diagnosis of exclusion, characterised by the absence of the typical pattern of UIP and the presence of uniform fibrosis with cellular infiltration of the alveolar walls. DIP is characterised by excess numbers of macrophages in the alveolar spaces. Patients with NSIP and DIP are significantly younger than those with UIP. Their mean age is 57 years, and they tend to respond to oral corticosteroids and have a median survival of more than 10 years. An appreciation of potential histological subgroups (not all patients are fit for lung biopsy), demographics, and survival patterns are important in the evaluation of outcomes of treatment.
The treatment of the UIP pattern of IPF is a major therapeutic challenge. Standard treatment is no treatment or immunosuppression with corticosteroids and azathioprine or cyclophosphamide. However, a different approach has been taken in two recent studies, in which the aim was to augment concentrations of interferon gamma-1b or prostaglandin E1 (PGE1).

R Ziesche and colleagues have reported a pilot study in which interferon gamma-1b was associated with a statistically significant 9% improvement in total lung capacity over 1 year. Interferon gamma, whose production is impaired in IPF, inhibits the proliferation of fibroblasts and downregulates transforming growth factor β (TGF-β) gene, so it was chosen as a therapeutic agent to counterbalance the fibrogenic process. Nine IPF patients received interferon gamma 200 mg three times per week with 7.5 mg of oral corticosteroids per day, and nine controls received a symptom-driven schedule of oral corticosteroids. The IPF patients were selected on the basis of two criteria—failure to respond to steroids over 1 year and histological evidence of UIP from tissue acquired by nebuliser. H Olschewski and colleagues aimed was to augment concentrations of interferon gamma-1b or prostaglandin E1 (PGE1).

The IPF patients were selected on the basis of two criteria—failure to respond to steroids over 1 year and histological evidence of UIP from tissue acquired by nebuliser. H Olschewski and colleagues aimed was to augment concentrations of interferon gamma-1b or prostaglandin E1 (PGE1).

IPF to be compared with either placebo or no treatment. Moreove, in the control group, which received oral corticosteroids (25–50 mg), there was a trend towards worsening lung function. This trend may be due to the promotion of Epstein Barr virus replication within the pulmonary tissue or to the increase in body-mass index with corticosteroids. The deterioration in patients receiving corticosteroids alone statistically conferred an advantage on the group receiving interferon gamma, which highlights the necessity for novel therapies for UIP-pattern IPF to be compared with either placebo or no treatment.

A recognised but under-emphasised feature of clinical progression of IPF is the vascular and haemodynamic consequences of lung fibrosis. IPF patients show striking hypoxaemia and exercise-induced hypoxia, unlike patients with systemic sclerosis who have pulmonary fibrosis of similar severity as assessed by high-resolution computed tomography. Structural vascular changes and an imbalance of vasomotor tone are important factors in the development of secondary pulmonary hypertension in IPF. Endothelial-cell production of the vasodilators prostacyclin and nitric oxide (NO) is thought to be impaired in patients with secondary pulmonary hypertension. Correction of these deficiencies might thus be a therapeutic measure for IPF. In 1994, Channick and colleagues reported that the inhalation of NO by an IPF patient with secondary pulmonary hypertension led to a significant fall in pulmonary-artery pressure, but its therapeutic application is limited by the lack of availability of suitable delivery systems for outpatients. Furthermore, the abrupt cessation of supply may result in rebound pulmonary hypertension.

PGI2, or its synthetic analogue, iloprost, are alternative vasodilators which may be given intravenously or by nebuliser. H Olschewski and colleagues have reported the haemodynamic consequences of an acute challenge of intravenous PGI2, inhaled NO, and of nebulised PGI2, in a heterogeneous group of patients with pulmonary fibrosis and secondary pulmonary hypertension. Both NO (40 ppm) and nebulised PGI2 (54–68 μg), in combination with oxygen (0–4 L/min), resulted in a significant fall in mean pulmonary-artery pressure (about 10 mm Hg). The augmentation, by nebulised PGI2, of blood flow to ventilated areas prevented the development of a clinically significant intrapulmonary shunt, which was observed with intravenous PGI2. Nebulised PGI2 also had a partial systemic vasodilator effect, which suggested that some of the PGI2 was absorbed by the lung and reached the systemic circulation. Systemic vasodilatation in the absence of a shunt may be advantageous because left-ventricular impairment may occur in patients with pulmonary hypertension, as a consequence of septal-wall dysfunction due to right-ventricular hypertrophy. This effect raises the question of whether chronic administration of nebulised PGI2 will attenuate disease progression by protecting against the haemodynamic consequences of pulmonary fibrosis, potentially providing bridging therapy to lung transplantation?

The absence of appropriately powered randomised studies limit the application of exciting developments in therapy, such as interferon gamma, nebulised PGI2, and the antifibrotic pirfenidone. However steps are being undertaken to provide the infrastructure to address this problem, by the development of collaborative groups and specialist multidisciplinary clinics for IPF patients.

Jim J Egan
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8 Stewart JP, Gaj J, Hasleton PS, Lok S, N ash AA, Woodcock AA. The detection of EBV DNA in lung biopsy specimens from patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1999; 159: 1336–41.
Myocarditis and cardiomyopathy associated with clozapine

Jens G Kilian, Kristin Kerr, Christopher Lawrence, David S Celermajer

Summary

Background Clozapine is effective for resistant schizophrenia. After two sudden deaths in physically well young men soon after starting clozapine, we investigated the cardiovascular complications for this drug.

Methods From January, 1993, to March, 1999, 8000 patients started clozapine treatment in Australia, and were registered with a mandatory monitoring service. We identified cases of myocarditis and cardiomyopathy from voluntary reports to the Australian Adverse Drug Reaction Committee and sought details of the relevant diagnostic studies, necropsies that had been done in suspicious cases, or both.

Findings 23 cases (20 men, three women, mean age 36 years [SD 9]) were identified: 15 of myocarditis and eight of cardiomyopathy associated with clozapine treatment. Six patients died. All cases of myocarditis (five deaths) occurred within 3 weeks of starting clozapine. Cardiomyopathy (one death) was diagnosed up to 36 months after clozapine was started. Necropsy results showed mainly eosinophilic infiltrates with myocytolysis, consistent with an acute drug reaction.

Interpretation Clozapine therapy may be associated with potentially fatal myocarditis and cardiomyopathy in physically healthy young adults with schizophrenia.

Lancet 1999; 354: 1841-45

Introduction

Clozapine is a dibenzodiazepine antipsychotic, distinguished from traditional antipsychotic agents by its weak D2-dopaminergic activity, strong affinity for D4-receptors, potent serotonin and noradrenergic antagonism, and few extrapyramidal symptoms.1 The drug is generally valuable in the 30% of patients with schizophrenia who do not respond to conventional therapy or who cannot tolerate other agents.2 Clozapine has been prescribed for more than 1 million patient-years in more than 60 countries worldwide.

Clozapine-associated agranulocytosis occurs in about 1% of patients in the first year of treatment3 and has received widespread attention. Many countries, including Australia, have therefore introduced mandatory schemes for registering and monitoring patients started on clozapine. Such early monitoring has led to a decrease in the number of deaths from neutropenia or agranulocytosis.4 No such deaths were recorded in the first 8000 patients on the Australian registry.

Other less troublesome side-effects have been noted. Orthostatic hypotension and tachycardia are well-recognised cardiovascular effects, occurring in up to 9% and 25% of cases, respectively,5 but are rarely clinically important. Two cases of sudden cardiac death and acute myocarditis with an eosinophilic infiltrate at necropsy occurred at our institution soon after the patients had started taking clozapine. These deaths prompted us to investigate the possible relation between clozapine therapy and more serious cardiac complications.

Methods

Data collection

We requested from the Adverse Drug Reactions Advisory Committee (ADRAC) of Australia all accumulated data on previous reports of sudden death, myocarditis, or cardiac disease noted in connection with clozapine treatment, from January, 1993, to March, 1999, inclusive (during which time the first 8000 patients were registered in the monitoring system). We identified an additional case at our own institution. Because of the voluntary and confidential nature of the ADRAC reporting system, only limited original clinical data could be obtained for cases not from our own institution, and individual patients could not be contacted directly.

We obtained further information on cases by contacting the manufacturers of clozapine (Novartis, North Ryde, Australia), who gave us data collected by them on cases of myocarditis and cardiomyopathy (cross-referenced by the ADRAC case number). Data were clinical assessments, chest radiographs, electrocardiograms, echocardiograms, cardiac-enzyme measurements, nuclear scans, angiograms, endomyocardial biopsy samples, and necropsy results, as well as details of diagnoses made by consulting physicians or cardiologists (tables 1 and 2). The central registry of clozapine recipients supplied details of the number of patients who had received treatment since 1993 and information about the frequency of agranulocytosis and duration.
of therapy. Records contain the initials, date of birth, and sex of each new patient started on clozapine therapy, and assign each patient an identification number (to avoid dual entry of patients receiving intermittent courses). All new patients are enrolled through registered sites across Australia with an estimated 99% compliance. Blood-test results (total white-cell and neutrophil counts) were recorded as per protocol.

We reviewed 32 cases in which a formal adverse drug reaction associated with clozapine had been suspected that included the complications of myocarditis or cardiomyopathy. The additional case identified at our institution was diagnosed during the investigation. Of these 33 cases, the diagnosis of myocarditis in 15 and cardiomyopathy in eight associated with clozapine was supported by objective findings, including necropsy (in six deaths), clinical findings of unequivocal heart failure (eg, raised jugular venous pressure and lung crepitations in the absence of concomitant disorders), abnormal electrocardiograms consistent with cardiitis (ST-segment changes or T-wave inversion), echocardiographic or nuclear-scan evidence of ventricular dysfunction, raised creatinine kinase, with or without MB fraction, cardiac catheterisation findings, endomyocardial biopsy results, or a combination of these. Ten other cases were only possibly associated with clozapine, since the reported diagnosis of myocarditis (nine) or cardiomyopathy (one) was not supported by objective clinical and investigational findings. We did not include these cases in this report.

Data analysis
Since acute drug-related inflammatory myocarditis is most likely to present within 1 month of starting clozapine, we calculated the incidence of myocarditis in the first month of clozapine treatment and compared it with the monthly incidence reported in the general population. For cardiomyopathy, which may present at any stage after the start of treatment, annual background risk was derived from available data and we calculated the incidence in the study population from the number of documented cases and the number of patient-years of treatment.

In late 1998, a man aged 46 years was admitted as a voluntary patient to the psychiatric unit of the Royal Prince Alfred Hospital, Camperdown, Australia. He had a history of treatment-resistant chronic schizophrenia. He had no history of alcoholism or known heart disease, and was physically well. The admission had been arranged to discontinue his current antipsychotic medications (chlorpromazine, benzatropine, fluphenazine) and to start therapy with clozapine. The other drugs were discontinued within 5 days of starting clozapine. The patient was taking no other medications. Routine electrocardiography and baseline blood tests were unremarkable. Resting heart rate was 76 beats per min.

Clozapine was started at 12.5 mg twice daily and gradually increased to 300 mg daily over the next 2 weeks, as per protocol. The patient’s psychotic symptoms improved strikingly. His vital signs remained stable throughout, except for a mild tachycardia (90–100 beats/min), which developed on day 10. He did not complain of any physical symptoms.

On the morning of his planned discharge, 18 days after starting clozapine, the patient was found dead in his bed. Necropsy showed a florid acute myocarditis with a prominent eosinophilic infiltrate and associated myocytolysis (figure). Coronary arteries were patent. There was mild inflammation in the portal tracts of the liver associated with eosinophilic infiltrates. No other organs showed inflammatory changes on microscopy. Toxicological screening showed only therapeutic concentrations of clozapine in the blood. The forensic pathologist concluded that clozapine-induced myocarditis was the most likely cause of death.

A man aged 27 years with chronic schizophrenia was admitted to hospital to start clozapine in late 1998. He had been physically well but had not responded to haloperidol, risperidone (a long time previously) and olanzapine (recently) for his psychotic symptoms. Except for mild sedation, no adverse events were noted during his 7-day admission. Olanzapine was gradually tapered and treatment with incremental doses of clozapine was started. 11 days after discharge (while taking clozapine 200 mg/day) the patient was found dead in his bedroom by a community nurse. Resuscitation was unsuccessful.

At necropsy, the lungs were congested, with evidence of frank pulmonary oedema. Examination of the heart showed acute myocarditis with an eosinophilic infiltrate. Coronary arteries were patent. There was no inflammation of other organs on microscopy or signs of vasculitis. Blood screening showed non-toxic concentrations of clozapine. Clozapine-induced hypersensitivity myocarditis was recorded as the cause of death by the forensic pathologist.

Results
From January, 1993, to March, 1999, 8000 patients started clozapine in Australia (15 520 patient-years of exposure). Of these, 23 patients (20 men, three women, mean age 36 years [SD 9]) had objective evidence of myocarditis or cardiomyopathy (absolute risk 0·29%); six patients died. The clozapine doses at the time of diagnosis of a cardiovascular complication ranged from 100 mg to 725 mg daily.

All 15 cases of myocarditis (table 1) occurred early after the start of clozapine (median 15 days [range 3–21]). The cases were not clustered geographically or by time. Peripheral-blood eosinophilia was documented in six cases and five patients had complained of influenza-like symptoms. Five of these 15 patients died (three sudden deaths, two from rapidly progressive heart failure). All five deaths occurred 14–18 days after the start of clozapine treatment and all had features consistent with florid inflammatory myocarditis at
Cases of clozapine-associated myocarditis

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Time to onset of symptoms (days)</th>
<th>Symptoms at presentation</th>
<th>Evidence for cardiovascular involvement</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>18</td>
<td>Sudden death in hospital</td>
<td>Eosinophilic myocarditis on necropsy</td>
<td>Death</td>
</tr>
<tr>
<td>27</td>
<td>15</td>
<td>Found dead at home</td>
<td>Eosinophilic myocarditis on necropsy</td>
<td>Death</td>
</tr>
<tr>
<td>29</td>
<td>16</td>
<td>Sudden death in hospital</td>
<td>Eosinophilic myocarditis on necropsy</td>
<td>Death</td>
</tr>
<tr>
<td>43</td>
<td>16</td>
<td>Collapse, acute cardiac failure, need for intensive care</td>
<td>Lymphocytic myocarditis on necropsy</td>
<td>Death</td>
</tr>
<tr>
<td>39</td>
<td>14</td>
<td>Influenza-like symptoms, fever, delirium, tachycardia</td>
<td>Myocarditis, mixed cellular infiltrate on necropsy</td>
<td>Death</td>
</tr>
<tr>
<td>27</td>
<td>5</td>
<td>Muscle pain, malaise, fatigue</td>
<td>Widespread T-wave inversion on echo, resolved 1 week after drugs were stopped</td>
<td>Unknown*</td>
</tr>
<tr>
<td>34</td>
<td>8</td>
<td>Influenza-like illness, palpitations, dyspnea, fever, collapse</td>
<td>Global hypokinesia, dilated left and right ventricles, functional mitral regurgitation on echo; cardiologist diagnosed myocarditis</td>
<td>Recovered</td>
</tr>
<tr>
<td>28</td>
<td>11</td>
<td>Influenza-like symptoms, chest pain, dyspnea</td>
<td>Clinical signs of heart failure, CXR, pulmonary oedema; cardiologist diagnosed myocarditis</td>
<td>Recovered</td>
</tr>
<tr>
<td>27</td>
<td>11</td>
<td>Chest pain, sweating, dizziness</td>
<td>Raised creatine kinase, mild global hypokinesia of right and left ventricles on ECG</td>
<td>Recovered</td>
</tr>
<tr>
<td>39</td>
<td>12</td>
<td>Fever, malaise, influenza-like symptoms, pleuritic chest pain, syncope</td>
<td>Abnormal ECG, raised creatine kinase/creatinine kinase MB, GBPS, biventricular failure, small pericardial effusion on echo</td>
<td>Recovered</td>
</tr>
<tr>
<td>39</td>
<td>13</td>
<td>Palpitations, fever, dyspnea</td>
<td>Clinical signs of heart failure, CXR, pulmonary oedema, raised creatine kinase, reduced left ventricular systolic function on echo</td>
<td>Recovered</td>
</tr>
<tr>
<td>37</td>
<td>15</td>
<td>Fever, chest pain</td>
<td>Raised creatine kinase/creatinine kinase MB, progressive widespread T-wave inversion on ECG, pericardial effusion on echo, normal coronary angiography, clinical diagnosis of myocarditis</td>
<td>Recovered</td>
</tr>
<tr>
<td>17</td>
<td>18</td>
<td>2-3 weeks of chest pain</td>
<td>Signs of myocarditis on ECG and echo</td>
<td>Unknown*</td>
</tr>
<tr>
<td>36</td>
<td>19</td>
<td>Dyspnea followed by stroke after 4 days</td>
<td>Lateral T-wave inversion on ECG, raised creatine kinase, abnormal inferobasal segment on echo, apical thrombus, normal coronary angiography</td>
<td>Unknown*</td>
</tr>
<tr>
<td>45</td>
<td>21</td>
<td>Fever, lethargy, dyspnea</td>
<td>Clinical signs of cardiac failure, CXR, interstitial oedema; physician diagnosed myocarditis</td>
<td>Unknown*</td>
</tr>
</tbody>
</table>

Table 1: Cases of clozapine-associated myocarditis

Discussion

Clozapine is highly effective in the treatment of schizophrenia. The existence of a registry in Australia has permitted assessment of the minimum incidence of clozapine-related cardiac complications, since reporting of adverse events is voluntary, despite user registration being compulsory. Because voluntary reporting schemes such as ADRA C may miss a proportion of adverse events, our results may underestimate the true incidence of these complications.

We found an high incidence of fatal and non-fatal myocarditis in the first month of treatment of about one in 500 young adult patients with schizophrenia treated with clozapine. The median time to onset of symptoms of 15 days was consistent with acute hypersensitivity myocarditis. Eosinophilic infiltrates in several cases were consistent with an acute drug reaction.

Symptomatic myocarditis is uncommon in physically healthy young people and is due mainly to viral illness leading to lymphocytotic infiltration, and leads only rarely to death.11 In 1990, the incidence of fatal myocarditis worldwide was calculated as four per 105 people, or about 3-3 in 105 people per month. Estimates

Table 2: Cases of clozapine-associated cardiomyopathy

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Time to onset of symptoms (months)</th>
<th>Symptoms at presentation</th>
<th>Evidence for cardiovascular involvement</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>2</td>
<td>Gradually increasing dyspnea</td>
<td>Dilated cardiomyopathy on echo, LVEDD 77 mm, LVEF 40%</td>
<td>Death after 2 years*</td>
</tr>
<tr>
<td>37</td>
<td>2</td>
<td>Dyspnea, cough, fatigue, anorexia</td>
<td>Severe dilated cardiomyopathy on echo, endomyocardial biopsy, mild anisocytosis and myocytoysis, mild focal interstitial fibrosis</td>
<td>Unknown*</td>
</tr>
<tr>
<td>22</td>
<td>5</td>
<td>Tachycardia, tachycardia, eosinophilia</td>
<td>Clinical signs of heart failure, CXR, cardiomegaly, abnormal ECG, severe dilated cardiomyopathy on echo, no inflammation on endomyocardial biopsy</td>
<td>Unknown*</td>
</tr>
<tr>
<td>46</td>
<td>5</td>
<td>Atrial fibrillation, rapid ventricular rate</td>
<td>Dilated cardiomyopathy on echo</td>
<td>Improvement on serial echo</td>
</tr>
<tr>
<td>36</td>
<td>6</td>
<td>Clinical symptoms and signs of acute heart failure</td>
<td>Ejection fraction 10% on echo</td>
<td>Transferred to acute-care hospital</td>
</tr>
<tr>
<td>37</td>
<td>30</td>
<td>Dyspnea, orthopaedia</td>
<td>Clinical and radiographic signs of heart failure, diagnosed as dilated cardiomyopathy</td>
<td>Unknown*</td>
</tr>
<tr>
<td>52</td>
<td>36</td>
<td>Collapse</td>
<td>Dilated cardiomyopathy on echo</td>
<td>Unknown*</td>
</tr>
<tr>
<td>49</td>
<td>36</td>
<td>Palpitations</td>
<td>Dilated cardiomyopathy on echo, LVEDD 63 mm, LVEF 35%</td>
<td>Stable on anti-failure treatment*</td>
</tr>
</tbody>
</table>

LVEDD=left-ventricular end diastolic diameter; LVEF=left ventricular ejection fraction. *These two patients elected to remain on clozapine, despite cardiac dysfunction, because of otherwise intolerable psychotic symptoms. No further details available after initial diagnostic admission.
of the monthly frequency of fatal myocarditis among healthy young adults in Finland (1·8 in 10^7) and in the USA (0·5–0·6 in 10^7) is similar. By contrast, at least five of 8000 patients died with myocarditis in the first month of clozapine therapy in our series; this represents a relative risk of about 1000–2000-fold at the start of clozapine treatment. The relative risk of clozapine-associated non-fatal myocarditis in our series, compared with the 1990 community data, would be about 2000-fold. Patients with schizophrenia do, however, have an increased frequency of comorbidity and all-cause mortality (by up to two-fold) compared with the general population, and sudden death may be especially common in adults with schizophrenia.

The mechanism of cardiac disease in the cases we identified is uncertain. The timing in relation to start of clozapine (clinical presentation or death 10–21 days after first dose) suggests IgE-mediated hypersensitivity (type 1 allergic reaction). A type 3 allergic reaction (serum sickness) is also possible with this timing, but selective cardiac end-organ damage would be unusual. Other possibilities include a direct toxic effect on the heart that attracts an inflammatory infiltrate. A reported case of clozapine-induced acute interstitial nephritis, however, suggests that other internal organs may be involved in reactions to this drug.

Whereas drug-related hepatitis and nephritis are commonly reported adverse effects, drug-related myocarditis has been noted only rarely, especially as an acute reaction. One of the largest reported pathology series described 24 cases of drug-related cardiitis; the most common causes being α-methyl-dopa (eight cases) sulphonamides (five cases), and penicillins (four cases).

These drugs or have been commonly prescribed, and the frequency of this complication may, therefore, be low. Reports of specific drug-associated myocarditis have generally involved fewer than ten cases.

Many anecdotal case reports have associated other agents (including clozapine) with acute drug-related myocarditis. Four case reports and one small series of three cases reporting on suspected clozapine-related myocarditis have been published. Death occurred in four of the cases described. The evidence provided, however, included objective data for the diagnosis of myocarditis in only three of seven cases. Two of the deaths were related to deliberate overdoses of clozapine.

Walker and colleagues documented the causes of 859 deaths in a cohort of 67 072 current and former clozapine users in a retrospective study. In this North American series, current clozapine users aged 10–54 years were no more likely than formerly treated patients to have died from cardiovascular disease (as ascertained by death-certificate data). Myocarditis was not reported in either group of patients. Since necropsy findings were not available, however, the diagnosis of myocarditis may have been under-reported. It seems unlikely (although not impossible) that a particular genetic susceptibility or case clustering might account for a higher incidence of clozapine-associated myocarditis in Australia than in other countries.

Eight cases of dilated cardiomyopathy were also identified. This finding may represent acute myocarditis that was unrecognised in the early stages, or a more chronic form of illness. One previous case report shows an association between clozapine and cardiomyopathy. The incidence of dilated cardiomyopathy in the general population is 7·5–10·0 per 100 000 population. Our calculated incidence of 51·5 per 100 000 patient-years of clozapine treatment therefore suggests that patients receiving clozapine may be at least five times more likely to develop dilated cardiomyopathy than the general population.

Dilated cardiomyopathy may have been due to the accumulated effects of other antipsychotic agents, some of which have α-adrenoceptor blocking properties, used over several years in treatment-resistant cases. Such an effect seems unlikely, however, given the absence of reports linking other widely used antischizophrenia drugs to cardiomyopathy. The improvement of symptoms in one patient, however, suggests that the disorder might be reversible.

Except for the six deaths that had necropsy data and the non-fatal case from our own institution, we were unable to review clinical and diagnostic information directly. Our conclusions were, therefore, based on the clinical judgement and diagnostic interpretation of the reporting physicians, although corroborative objective evidence (clinical and diagnostic) was provided in all cases. Many of these cases may have been identified because of the attention clozapine patients receive as part of mandatory monitoring requirements. Confounding factors, such as alcohol or other substance abuse in some cases, may have been unreported. Furthermore, in the absence of a case-control study, a definitive assessment of the relative risk of cardiac complications in young patients receiving clozapine cannot be ascertained.

Clozapine is well tolerated by most patients with schizophrenia who take it, and has clinical benefit for many disabled young people. Nevertheless, potentially fatal cardiac complications may be associated with its use. Prospective studies may identify plasma or electrocardiographic markers of cardiac damage in at-risk patients, which may be useful in screening for these important adverse outcomes.

Contributors
Jens K Lilan gathered the data, researched the background information, and wrote the first draft. Kris K err first raised the possibility of this association, provided psychiatry input, and reviewed the paper critically. Chris Lawrence provided the figure, all pathology input, and reviewed the paper critically. David Celermajer conceived the idea, supervised and coordinated data collection, and wrote subsequent drafts.

Acknowledgment
We thank Novartis Pharmaceuticals for providing case information and constructive comments, and ADRAc for their assistance.

References
Pregnancy and risk of early breast cancer in carriers of BRCA1 and BRCA2

H Jernström, C Lerman, P Ghadirian, H T Lynch, J-J Garber, M Daly, O I Olopade, W D Foulkes, E Warner, J-S Brunet, S A Narod

Summary

Background Early age at first full-term pregnancy and increasing parity are associated with a reduced risk of breast cancer. However, whether pregnancy decreases the risk of early-onset hereditary breast cancer is unknown. There is concern that pregnancy may increase breast-cancer risk in carriers of BRCA1 and BRCA2 germline mutations. We aimed to establish whether pregnancy is a risk factor for hereditary breast cancer.

Methods We did a matched case-control study of breast cancer in women who carry deleterious BRCA1 or BRCA2 mutations. Cases were carriers who developed breast cancer by age 40 years, and controls were carriers of the same age without breast cancer, or who were diagnosed with breast cancer after age 40 years. Women who had undergone preventive mastectomy, hysterectomy, or oophorectomy, or who were diagnosed with ovarian cancer before the age at which breast cancer was diagnosed in the matched case were excluded. Information about pregnancies and pregnancy outcome was derived from a questionnaire completed by women in the course of genetic counselling.

Findings A higher proportion of cases than controls had had a full term pregnancy (173/236 vs 146/236; odds ratio 1·71 [95% CI 1·13–2·62], p=0·01). The mean number of births was also greater for cases than for controls (1·62 vs 1·38, p=0·04). The risk increased with the number of births and did not diminish with time since last pregnancy. There were no significant differences in age at first birth or age at last birth between cases and controls.

Findings

Each pregnancy is associated with an increased cancer risk. Among 35 BRCA1 carriers and 12 BRCA2 carriers, compared with other women with early breast cancer (carrier status unknown or negative), the expected number was 2·7 (odds ratio 4·46 [95% CI 1·95–10·2], p=0·002). We aimed to find out whether pregnancy affects the risk of early-onset breast cancer in carriers of BRCA1 and BRCA2 mutations.

Methods

Study population Eligible women were chosen from a registry of carriers of deleterious mutations in BRCA1 or BRCA2. These women were assessed for genetic risk at one of 14 genetic counselling centres in north America. All women received counselling and provided written informed consent for genetic testing. The study was approved by the ethics committees of all participating centres. In most cases, testing was initially offered to women who were affected by breast or ovarian cancer. When a mutation in BRCA1 or BRCA2 was found in a proband or in her relative, testing was offered to other at-risk women in her family. Mutations were sought with a range of techniques, but all nucleotide sequences were confirmed with direct sequencing of DNA. A woman was deemed eligible for the study when the molecular analysis.
Established that she was a carrier of the mutation. Most (>95%) of the mutations identified in the women included in this study were non-sense mutations, deletions, insertions, or small frameshifts.

We identified 248 women who had been diagnosed with breast cancer at age 40 or younger: age 40 was chosen as a cut-off since few women become pregnant after this age. Of the 248 women, 236 had not undergone previous preventive mastectomy, hysterectomy, or oophorectomy, and had not been diagnosed with ovarian cancer before their breast-cancer diagnosis. For each case we identified an eligible control carrier who met the same criteria but who had not developed breast cancer (n=194) or who had breast cancer diagnosed after age 40 (n=42). The median age at diagnosis for the affected controls was 45 years (range 41–68 years). Controls were matched for year of birth (controls were born within 2 years of the birth of the case) and mutation status (BRCA1 or BRCA2). Matching was done without knowledge of parity and reproductive history. There were 189 BRCA1 case-control pairs and 47 BRCA2 case-control pairs.

The year when breast cancer was diagnosed and the year of all pregnancies were recorded but we could not establish the sequence of breast cancer and pregnancy if both occurred during the same calendar year. 16 women gave birth for the first time during the year of diagnosis of the case and were classified as nulliparous. Only pregnancies that occurred in the controls before the age of diagnosis of the case were included in the matched-pair analysis. A pregnancy was classified as full term if it resulted in a liveborn child or a stillbirth. Induced abortions and miscarriages were excluded from the main analysis and were analysed separately.

Data analysis

Pregnancy histories of cases were compared with those of controls. For univariate matched comparisons, odds ratios were calculated by comparing the ratio of concordant and discordant pairs, and McNemar’s test was used to assess statistical significance. The paired t test was used to compare continuous variables in the matched analysis, including age at menarche and number of full-term pregnancies. Conditional logistic regression was used for the multivariate matched analyses.

Results

Cases and controls were similar with respect to year of birth and smoking history, but differed in ethnicity (table 1). There were no differences between cases and controls for age at menarche, age at first birth, or age at last birth (table 2). Significantly more of the cases than of the controls had had a full-term pregnancy (odds ratio 1.71 [95% CI 1.13–2.62], p=0.01). A previous full-term pregnancy was a risk factor for BRCA1 carriers (1.61 [0.99–2.63], p=0.05) and for BRCA2 carriers (2.13 [0.86–5.56], p=0.11). In each ethnic group the cases had more children than the controls. There were no significant differences in parity between French-Canadian controls (mean 1.31), Jewish controls (1.28), non-white controls (1.60), and other white controls (1.50). The p values were 0.48, 0.28, and 0.88 respectively for comparisons with other white women. After adjustment for ethnicity, parous women remained at significantly higher risk of breast cancer than nulliparous women (1.81 [1.19–2.75], p=0.006). Seven cases and nine controls had their first pregnancy the same year as diagnosis of the case. Inclusion of these women as parous in the analyses did not alter the results.

We used unaffected controls and controls who were diagnosed with breast cancer after age 40. The proportion of nulliparous women was similar among control women without breast cancer and those who were diagnosed with breast cancer after age 40 years (39 vs 36%). Furthermore, the adjusted odds ratio associated with parity was similar for the cases matched to controls without cancer (1.87 [1.16–3.02], p=0.01) and for the cases matched to controls who developed cancer after age 40 (1.66 [1.05–2.64], p=0.03). The mean number of births that occurred during the 10-year period before diagnosis was significantly higher for cases than for controls (table 2). The lifetime number of full-term pregnancies was also higher for cases than for controls (table 2). The odds ratio increased with each full-term pregnancy for cases than for controls (table 2).

### Table 1: Characteristics of cases and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=236)</th>
<th>Controls (n=236)</th>
<th>Univariate odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Term pregnancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of parous women</td>
<td>173</td>
<td>146</td>
<td>1.71 (1.13–2.62)</td>
<td>0.01</td>
</tr>
<tr>
<td>Parity</td>
<td>1.6 (0.5)</td>
<td>1.4 (0.8)</td>
<td>0.99 (0.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Births 1–10 years before diagnosis</td>
<td>1.1 (0.4)</td>
<td>0.8 (0.5)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Age at first birth (years)</td>
<td>25.0 (17–38)</td>
<td>24.8 (16–37)</td>
<td>0.81 (0.12–5.4)</td>
<td></td>
</tr>
<tr>
<td>Age at last birth (years)</td>
<td>28.5 (17–38)</td>
<td>28.5 (18–38)</td>
<td>0.98 (0.04–2.7)</td>
<td></td>
</tr>
<tr>
<td>Years from first to diagnosis</td>
<td>9.8 (1–23)</td>
<td>10.0 (1–22)</td>
<td>0.81 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Years from last birth to diagnosis</td>
<td>6.3 (1–22)</td>
<td>6.3 (1–20)</td>
<td>0.99 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Number with nonterm pregnancies</td>
<td>37</td>
<td>30</td>
<td>1.00 (0.54–1.87)</td>
<td>0.88 (0.4)</td>
</tr>
</tbody>
</table>

Data are mean (range) unless otherwise stated.

### Table 2: Univariate comparisons of reproductive histories of cases and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n=236)</th>
<th>Controls (n=236)</th>
<th>Univariate odds ratio (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at first birth (years)</td>
<td>10.7 (10–17)</td>
<td>12.7 (9–17)</td>
<td></td>
<td>0.57</td>
</tr>
</tbody>
</table>
term pregnancy up to three (p for trend in odds ratio 0-0065, table 3). The increased risk did not decline with time since last pregnancy in parous women, and all pregnancies during the period before diagnosis conferred a similar increase in risk (table 4). In a multivariate logistic regression model with adjustment for ethnicity, each pregnancy up to three conferred an additional 24% increase in risk (odds ratio 1·24 [95% CI 1·04–1·47], p=0.02).

<table>
<thead>
<tr>
<th>Time before diagnosis</th>
<th>Cases (n=236)</th>
<th>Controls (n=236)</th>
<th>Odds ratio (95% CI)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>63</td>
<td>90</td>
<td>1·00</td>
<td>.</td>
</tr>
<tr>
<td>1 year</td>
<td>20</td>
<td>14</td>
<td>2·04 (0·96–4·34)</td>
<td>0·06</td>
</tr>
<tr>
<td>2 years</td>
<td>26</td>
<td>23</td>
<td>1·62 (0·85–3·08)</td>
<td>0·14</td>
</tr>
<tr>
<td>3 years</td>
<td>28</td>
<td>24</td>
<td>1·67 (0·89–3·14)</td>
<td>0·11</td>
</tr>
<tr>
<td>4 years</td>
<td>22</td>
<td>19</td>
<td>1·65 (0·83–3·31)</td>
<td>0·15</td>
</tr>
<tr>
<td>5 years</td>
<td>31</td>
<td>17</td>
<td>2·61 (1·33–5·11)</td>
<td>0·005</td>
</tr>
<tr>
<td>6 years</td>
<td>26</td>
<td>18</td>
<td>2·06 (1·04–4·08)</td>
<td>0·03</td>
</tr>
<tr>
<td>7 years</td>
<td>29</td>
<td>16</td>
<td>2·59 (1·30–5·16)</td>
<td>0·006</td>
</tr>
<tr>
<td>8 years</td>
<td>30</td>
<td>22</td>
<td>1·95 (1·03–3·69)</td>
<td>0·04</td>
</tr>
<tr>
<td>9 years</td>
<td>22</td>
<td>28</td>
<td>1·12 (0·59–2·14)</td>
<td>0·73</td>
</tr>
<tr>
<td>10 years</td>
<td>24</td>
<td>16</td>
<td>2·14 (0·95–4·36)</td>
<td>0·03</td>
</tr>
<tr>
<td>11 or more years</td>
<td>74</td>
<td>72</td>
<td>1·47 (0·93–2·32)</td>
<td>0·10</td>
</tr>
</tbody>
</table>

*Pearson’s x²-test. †Reference category. Test for trend=p<0·0065.

Table 3: Number of full-term pregnancies versus nulliparity

of births than women without cancer (2-67 vs 1·72, respectively). On the basis of these data, we believe that if all women who were offered testing had accepted, we would have found an even stronger association between parity and breast-cancer risk.

Discussion

Women who were carriers of the BRCA1 or BRCA2 mutation who had had a full-term pregnancy were significantly more likely than nulliparous carriers to develop breast cancer by the age of 40. The risk was further increased with each birth up to three. This association was present in both BRCA1 and BRCA2 carriers, but the sample size for the mutation-specific subgroups were small. Our data support the hypothesis raised by Johannsson and colleagues; however, we found an excess risk of early-onset breast cancer in association with any previous pregnancy, not only those that occurred in the previous year.

Previous studies of associations between family history, parity, and breast-cancer risk have been inconsistent, and the mutation status of the patients was not known. Even among cases with a family history of breast cancer, few will carry a BRCA1 or a BRCA2 mutation. Lynch and colleagues found that pregnancy did not influence the risk of familial breast cancer in a panel of high-risk families, and no protective effect was seen from an early pregnancy. Colditz and colleagues found an adverse effect of a first pregnancy on breast-cancer risk: the risk was 50% greater among women with a family history of breast cancer than among women without a family history. In two other studies the effect of pregnancy on breast-cancer risk was similar for women with and without a family history of breast cancer. Others found that increasing parity protected against breast cancer in women with a family history of the disorder. Most cases of breast cancer related to BRCA1 or BRCA2 are diagnosed in young women, and parity may have differential effects on breast-cancer risk in younger and older women. Mccredie and colleagues studied breast cancer in Australian women under age 40, and reported an increase in breast-cancer risk with the first full-term pregnancy, but a decrease in risk with each livebirth thereafter. Their finding is compatible with the hypothesis that the breast is protected against the effects of increased cell proliferation during the second and subsequent pregnancies by the terminal differentiation that occurs during the first full-term pregnancy.

The mammary gland develops at puberty and undergoes additional changes during and after each pregnancy. During the first part of the pregnancy, there is rapid proliferation of the breast epithelium. Differentiation of the breast tissue takes place during the last months of pregnancy. Lobuloalveolar differentiation is stimulated by oestrogen, progesterone, placental lactogen, placental growth hormone, oxytocin, and prolactin. After delivery, lactation is initiated as a result of increasing prolactin concentrations. When prolactin...
concentrations decline, postlactational apoptosis occurs and induces glandular involution.\textsuperscript{2,14} Thus, in nulliparous women, the proliferation rate remains high, and the breast epithelium is poorly differentiated, whereas in parous women the proliferation rate is low and the breast epithelial cells are more differentiated.

Most breast cancers are thought to originate in the terminal end ducts or intralobular terminal ducts.\textsuperscript{19} These structures are most numerous in nulliparous women and diminish with the differentiation during pregnancy and lactation.\textsuperscript{20,21} Not all breast cells differentiate fully with the first pregnancy, and further differentiation may take place during latter pregnancies. Therefore, both age at first full-term pregnancy and number of total pregnancies are believed to protect against breast cancer. Parity may have a differential effect on breast-cancer risk in younger and older women,\textsuperscript{22} possibly reflecting a balance between the transient increase in risk after pregnancy, and the long-term reduction thereafter. Animal experiments show that the susceptibility of the mammary gland to cancer is related to the proliferation rate of breast epithelial cells, and is inversely related to the degree of differentiation.\textsuperscript{27} High proliferation rates have also been linked to human cancer risk.\textsuperscript{22}

The BRCA1 gene is expressed in rapidly proliferating cells undergoing differentiation. In the mammary gland, BRCA1 expression is induced during puberty and pregnancy, and is believed to counteract proliferation and promote differentiation. An in-vitro study of breast-cancer cells suggests that one of the functions of the BRCA1 protein is to suppress oestrogen-mediated cell proliferation.\textsuperscript{23} The expression of the BRCA1 gene is also regulated by oestrogen and progesterone in combination\textsuperscript{24} and women who carry a BRCA1 mutation may be susceptible to carcinogenesis during periods of high sex-hormone exposure, such as a pregnancy. BRCA2 expression is also tightly regulated during mammary epithelial proliferation and BRCA2-messenger RNA expression occurs simultaneously with BRCA1 expression.\textsuperscript{25}

Poor milk production has been reported in carriers of the BRCA1 mutation compared with female relatives without mutations, possibly reflecting impaired breast epithelial differentiation.\textsuperscript{26} Russo and colleagues\textsuperscript{27} have also reported that the breast architectural pattern in parous women with a family history of breast cancer resembles that of nulliparous women and is different from that in the general population. There is further evidence from mice with mammary-specific mutations that breast tissue with BRCA1 mutations does not differentiate during pregnancy.\textsuperscript{28}

Our study has important implications for risk assessment of women at high risk of breast cancer, both for genetic counselling and for clinical study design. Current models for integrating reproductive and familial risk factors may be inappropriate. For example, according to the model of Gail and colleagues,\textsuperscript{29} a nulliparous woman with two affected relatives would be at higher risk of developing breast cancer than a woman with two affected relatives who had a child before age 20. This model does not seem to apply to BRCA1 and BRCA2 carriers, for whom an early pregnancy increases the risk. To advise carriers of BRCA1 and BRCA2 mutations that early pregnancy may protect them against breast cancer is therefore inappropriate.

Contributors
Hélène Jernström initiated the study, provided the background information, contributed to the data analysis, and prepared the paper. Caryn Lerman generated the data and discussion about the patients who declined to receive results, coordinated the study for the Lombardi Cancer Center, and did mutation analysis. Parviz Ghadri supervised the study activities for women at the University of M ontreal hospitals. Henry Lynch provided background information and supervised the study activities for Creighton University. Barbara Weber, Judy Garber, M ary Daly, Olofumilayo Olopade, and William Foulkes supervised study activities for women at their centres (U niversity of Pennsylvania, Dana F arber Cancer Center, F ox Ch as e Cancer Center, U ni versity of C hicago, and M cG ill University) and did mutation analyses. Ellen Warner supervised the study activities for women at the T oronto-Sunnybrook R egional Cancer Centre, Jean-Sebastian Brunet was the data manager and primary statistical analyst. Steven N ard was the principal investigator, study coordinator, and the director of the Women’s College H ospital ophthalmology laboratory.

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26 Jernström H, Johannsson O, Borg Ä, Olsson H. Do BRCA1 mutations affect the ability to breast-feed?: significantly shorter length of breast feeding among BRCA1 mutation carriers compared with their unaffected relatives. Breast 1998; 7: 320–24.
Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial

Mitra B Drakulovic, Antoni Torres, Torsten T Bauer, Jose M Nicolas, Santiago Nogué, Miquel Ferrer

Summary
Background Risk factors for nosocomial pneumonia, such as gastro-oesophageal reflux and subsequent aspiration, can be reduced by semirecumbent body position in intensive-care patients. The objective of this study was to assess whether the incidence of nosocomial pneumonia can also be reduced by this measure.

Methods This trial was stopped after the planned interim analysis. 86 intubated and mechanically ventilated patients of one medical and one respiratory intensive-care unit at a tertiary-care university hospital were randomly assigned to semirecumbent (n=39) or supine (n=47) body position. The frequency of clinically suspected and microbiologically confirmed nosocomial pneumonia (clinical plus quantitative bacteriological criteria) was assessed in both groups. Body position was analysed together with known risk factors for nosocomial pneumonia.

Findings The frequency of clinically suspected nosocomial pneumonia was lower in the semirecumbent group than in the supine group (three of 39 [8%] vs 16 of 47 [34%]; 95% CI for difference 10·0–42·0; p=0·003). This was also true for microbiologically confirmed pneumonia (semirecumbent 2/39 [5%] vs supine 11/47 [23%]; 4·2–31·8, p=0·018). Supine body position (odds ratio 6·9 [1·7–26·7], p=0·006) and enteral nutrition (5·7 [1·5–22·8], p=0·013) were independent risk factors for nosocomial pneumonia and the frequency was highest for patients receiving enteral nutrition in the supine body position (14/28, 50%). Mechanical ventilation for 7 days or more (10·9 [3·0–40·4], p=0·001) and a Glasgow coma scale score of less than 9 were additional risk factors.

Interpretation The semirecumbent body position reduces frequency and risk of nosocomial pneumonia, especially in patients who receive enteral nutrition. The risk of nosocomial pneumonia is increased by long-duration mechanical ventilation and decreased consciousness.

Lancet 1999; 354: 1851–58
See Commentary page

Introduction
Pneumonia is the most frequent nosocomial infection among intensive-care-unit (ICU) patients. The frequency of nosocomial pneumonia in the ICU has been reported as between 9% and 70%, depending on the definition and the population studied. Additionally, the incidence of nosocomial pneumonia varies among types of ICUs and ranges from 4·7 cases per 1000 ventilator days for paediatric ICUs to 35 cases per 1000 ventilator days in burn ICUs. The incidence of nosocomial pneumonia in medical and surgical ICUs has been reported to range from 12·8 to 17·6 per 1000 ventilator days. The recognised pathogenetic sequence of nosocomial pneumonia is abnormal oropharyngeal colonisation and subsequent aspiration. The colonisation of the oropharynx may be augmented by regurgitation of colonised gastric content. Colonisation of the stomach is favoured by the use of systemic or local antacid drugs and enteral nutrition, which alkalise gastric secretions and hence facilitate bacterial growth. Although controversial, gastric reflux and subsequent aspiration to lower airways could play a part in the pathogenesis of nosocomial pneumonia.

Two studies with radioactively labelled gastric contents showed that reflux can be reduced and subsequent aspiration avoided by positioning mechanically ventilated patients in a semirecumbent position. In addition, an elevated head position (angle >30°) was also protective against nosocomial infection in an epidemiological study. Although pneumonia was the most common nosocomial infection in that study, data on nosocomial pneumonia alone were not available. Kollef described in a cohort study a three-fold risk of nosocomial pneumonia, in patients with a supine head position during the first 24 h of mechanical ventilation. Although the semirecumbent position has been strongly recommended by the US Centers for Disease Control and Prevention (CDC), the benefit for prevention of nosocomial pneumonia has never been proven in a randomised clinical trial. We therefore investigated the frequency of nosocomial pneumonia in intubated and mechanically ventilated patients, randomly assigned to either supine or semirecumbent body positions.

Methods
Patients
Patients were recruited from June 1, 1997, until May 31, 1998, in the Hospital Clinic, a 1000-bed tertiary-care university hospital in two ICUs, a six-bed respiratory ICU, and eight-bed medical ICU. All patients were routinely subjected to standard measures for general critical care and prevention of nosocomial pneumonia in mechanically ventilated patients, namely: sterile endotracheal suctioning; no change of mechanical ventilation tubing systems; stress ulcer prophylaxis with sucralfate (1 g every 4 h) given in patients who tolerated enteral feeding and intravenous ranitidine (50 mg every 6 h) or omeprazole (20 mg every 12 h) in patients receiving parenteral nutrition (in accordance with clinical
judgment, antacid medication was given in addition to sucralfate in some patients with present evidence or previous history of gastrointestinal bleeding.

Feeding was either parenteral or enteral depending on the decision of the physician in charge. Enteral feeding was continuous without rest period overnight and administered via two types of nasogastric tubes—small bore (2.85 mm, Flexiflow, Ross Laboratories, Columbus, OH, USA) and large bore (4.0 mm, Salam Sump, Sherwood M edical, T ullamore, Ireland). The composition of the enteral nutrition varied according to individual requirements and the total amount was calculated to provide 30–35 kcal/kg bodyweight per day. The initial delivery rate was 200 mL in 12 h and gastric aspiration was done every 4 h. The delivery rate was increased until individual requirements were met in the absence of problems associated with prolonged gastric emptying. The amount of enteral nutrition was within 1500–2000 mL per 24 h for all patients. Patients were classified as being on enteral nutrition if they had received at least 48 h of enteral feeding before pneumonia, extubation, or death.

A standard pressure area care protocol was followed in all patients, and a water-filled cushion was placed under the sacral region to minimise pressure. Selective digestive decontamination was not done in any patient. Surgical patients received perioperative antibiotic prophylaxis, if indicated.

Study design

The study consisted of three phases: start of the study protocol with the first weaning trial, extubation, permanent change in body position for more than 45 min or death; follow-up for an additional 72 h. Surveillance for clinical detection of pneumonia was done daily. Samples for microbiological diagnostic tests were taken, if infection was clinically suspected. Exclusion criteria were: recent abdominal surgery (<7 days); recent neurosurgical intervention (<7 days); shock refractory to vasoactive drugs or volume therapy; previous endotracheal intubation (<30 days). The study was approved by the ethics committee and conducted in accordance with its guidelines.

Informed consent was obtained for all patients from the next-of-kin before randomisation. Patients were randomly allocated to either semirecumbent (45°) or supine body position (0°) by a computer-generated list and all consecutive patients were included. The allocation table was generated and disclosed by an independent person. All medical care personnel were instructed not to change the position, unless for medical requirements—the correctness of the position was checked daily.

All relevant data from the patient’s medical records and bedside flow charts were reviewed on admission to the ICU: age, sex, smoking habits (current smoker, ex-smoker [<2 years], and non-smokers), chronic alcohol abuse (>80 g alcohol per day), intravenous drug abuse, cause of respiratory failure, and severity of underlying medical disease (non-fatal, rapidly fatal, ultimately fatal). 8 h after ICU admission clinical data for calculation of the APACHE II score, the Glasgow coma scale, and the level of consciousness induced by sedation were retrieved.

At the end of the protocol the following variables were recorded: duration of mechanical ventilation, duration and type of nasogastric intubation, nutrition, and stress ulcer prophylaxis; sedative treatment (any sedative agent given continuously for >24 h), antimicrobial treatment (administered intravenously for >24 h during the hospital stay), body position (according to definition), duration of hospital stay before ICU admission, length of ICU stay, comorbidities (cardiovascular disease, abnormal hepatic function, haematological diseases, polytrauma, diabetes mellitus, chronic obstructive pulmonary disease, malignant diseases, immunosuppression (corticosteroid treatment >5 mg/day, HIV infection, chemotherapy within the previous 45 days, neutropenia (neutrophil count <5 x 10⁹/L) or organ transplant recipient (kidney, liver, heart, or bone marrow) requiring immunosuppressive agents), and recent surgery.

Depending on the clinical situation a tracheobronchial aspirate, a protected specimen brush, or a bronchoalveolar lavage was done if pneumonia was suspected clinically. Tracheobronchial aspirate was collected without prior administration of saline in a standard sputum trap (Proclinics, Barcelona). For fiberoptic bronchoscopic examinations (Pentax FB18, Asahi Optical Ltd, Japan) patients were premedicated with propofol or midazolam. No local anaesthetics were administered and suction was avoided. Broncholarvalve lavage and protected specimen brush were done in the areas most prominently affected on chest radiograph or in one segment of the lower lobes in cases with diffuse infiltrates. Broncholarvalve lavage was done by instillation of three 50 mL volumes of non-bacteriostatic saline, and the first aspirated portion was discarded. Protected specimen brush (Mill-Rose Inc, 7310, M entor, OH, USA) samples were retrieved as previously described.

All samples were processed within 30 min. Samples were quantitatively plated on blood, chocolate, Wilkins-Chalgren and Sabouraud agar media in serial dilutions of 1 in 10, 1 in 100, and 1 in 1000. If negative, the plates were discharged after 3 days of testing for aerobic bacteria and after 4 weeks of testing for fungi. If positive, results were expressed as colony-forming units (cfu) per mL. Identification and susceptibility testing were done with standard methods. For purposes of analysis, only potentially pathogenic microorganisms were taken into account. The following microorganisms were excluded as non-pathogenic microorganisms: Streptococcus spp except Streptococcus pneumoniae, coagulase-negative staphylococci, N essaia spp, and Candida spp (thresholds of significant growth for pathogenic microorganisms were 10⁶ cfu/mL in tracheobronchial aspirate, 10³ cfu/mL in bronchoalveolar lavage, and 10² cfu/mL in protected specimen brush cultures).

Clinical suspicion of pneumonia was defined by new and persistent infiltrates on chest radiograph most likely to be associated with pulmonary infection and at least two of the following three criteria: fever (temperature >38.3°C); leucopenia or leucocytosis (white blood-cell count <4 x 10⁹/L or >12 x 10⁹/L); purulent tracheal secretions. Nosocomial pneumonia was regarded as microbiologically confirmed in the presence of clinical suspicion of pneumonia and at least one pathogenic microorganism in tracheobronchial aspirate, broncholarvalve lavage, or protected specimen brush, with bacterial growth above the defined thresholds for positive cultures of blood or pleural fluid, or both. The frequency of clinical and microbiologically confirmed nosocomial pneumonia was defined as number of cases per 100 patients and the rate was defined as the number of cases per 1000 ventilator days.

Statistical methods

The primary objective of this study was to test the frequency of clinically suspected pneumonia in semirecumbent and supine body position. A secondary objective was to compare the frequency of microbiologically confirmed pneumonia in both study groups. Initial calculations showed a sample size of 182 patients to show a 50% risk reduction by the semirecumbent position (confidence level [1-a] 95%, power level 80% [1-b], projected frequency in the supine group was 40%). One planned interim analysis, comparing the frequency of the primary study objective between the two study groups was done after inclusion of 50% of the patients. A stochastic curtailment was used to correct for multiple analyses. The interim analysis revealed a significant reduction of the frequency of clinically suspected pneumonia in the semirecumbent position (p=0.003) and the trial was stopped.

For the univariate analyses, frequencies were compared by means of x² test or Fisher’s exact test, where appropriate. Means were compared by unpaired Student’s t test, and corrected for inequality of variances (Levene’s test). Adjusted odds ratios and 95% CI were computed for variables significantly associated with pneumonia.

In the analytical procedures, all categorical attributes (such as presence or absence of particular manifestations) were initially regarded as individual variables and dimensional variables (such as age or APACHE II score) were initially maintained in...
Figure 1: Trial profile
dimensional form. The variables were then tested for significant differences between study groups and the results were reported in the original form.

All risk factors tested in this analysis had been previously described for ICU patients. The factors included in further analyses were then divided into extrinsic and intrinsic risk factors. The reasons behind this procedure were to reduce the number of candidate variables and to separate factors that can be influenced by the physician (extrinsic, eg body position) from those that cannot (intrinsic, eg age). All dimensional variables were dichotomised with the use of cut-off points that were either consistent with previously published definitions (eg, coma defined as Glasgow coma scale score <9), important for the cause vs (non-fatal vs fatal or ultimately fatal), number of comorbidities).

The following intrinsic risk factors of nosocomial pneumonia were tested: age (=65 years vs 65 years), mechanical ventilation (>7 days vs >7 days), hospital admission before ICU admission (<48 h vs >48 h), sex, APACHE II score on admission (<20 vs >20), Glasgow coma scale score on admission (>9 vs <9), sedation score (<4 vs >4), severity of the underlying disease (non-fatal vs fatal or ultimately fatal), number of comorbidities (one or none vs two or more), immunosuppression (not present vs present), and recent surgery. The following extrinsic risk factors were analysed: sedative medication, enteral nutrition, parenteral nutrition, bed of nasogastric tube (2-85 mm vs 6-0 mm), medication with sucralfate, ranitidine, or omeprazole, antibiotic medication for longer than 72 h, heated humidifiers, and supine body position.

For the multivariate analyses a logistic-regression analysis was done and precautions were taken to avoid common pitfalls associated with multivariable analysis.24 Stringent entry criteria (p<0-05 in univariate analyses) and separate analysis of intrinsic and extrinsic risk factors reduced the number of candidate variables to avoid overfitting. To correct for collinearity, a conditional stepwise forward model was chosen (p<0-05). Interactions were analysed pairwise by entering an interaction term into the logistic-regression analysis. Results are reported separately when interaction was found (p<0-05).

The K aplan-M eier method was used to display time-to-event data for clinically suspected pneumonia and death. Curves were compared by use of the log-rank test.

All data were processed with SPSS, version 7-5. Data are reported as counts or mean (SD) with the two-tailed level of significance.

Results

Patients
90 patients were randomly assigned with semirecumbent or supine body position (figure 1). Four patients were excluded from the analysis: one died during resuscitation 2 h after initiation of the protocol and three because of protocol violation (reintubated patients all in semirecumbent position).

A total of 86 patients (65 male and 21 female, mean age 65 years [SD 15]) completed the clinical trial. Among the 86 patients the reasons for termination of the protocol were: change in position for more than 45 min (seven/86, 8%), death during the protocol (13/86, 15%), and weaning trial (66/86, 77%). Overall 39/86 patients were in the semirecumbent position (45%) and persistent supine position was maintained in 47/86 patients (55%). Table 1 compares general data of patients in supine and semirecumbent position. Patients in supine position tended to be less well, but the difference in APACHE II score was not significant.

Incidence of clinically suspected pneumonia

Pneumonia was clinically suspected in 19 of the 86 patients (22%) and could be microbiologically confirmed in 13 (15%); the incidence rate for the former was 28-7 per 1000 ventilator days and 19-6 per 1000 ventilator days for the latter. Table 2 summarises the microorganisms recovered.

Pneumonia was clinically suspected in three (8%) of 39 patients in the semirecumbent group and 16 (34%) of 47 in the supine group (95% CI for difference 10-42, p=0-003). Microbiologically confirmed pneumonia occurred in two (5%) patients in the semirecumbent position.

Table 1: General data of patients in supine and semirecumbent position

<table>
<thead>
<tr>
<th></th>
<th>Supine (n=47)</th>
<th>Semirecumbent (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>67 (14)</td>
<td>63 (16)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>35 (75%)</td>
<td>30 (77%)</td>
</tr>
<tr>
<td>Current or ex-smokers</td>
<td>32 (66%)</td>
<td>27 (69%)</td>
</tr>
<tr>
<td>Chronic alcohol abuse</td>
<td>9 (19%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Intraavenous drug abusers</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Cause of acute respiratory failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>16 (34%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>Other pulmonary diseases</td>
<td>12 (26%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (13%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Drug over dose or neurological emergency</td>
<td>3 (6%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (21%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Severity of underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease fatal or ultimately fatal</td>
<td>44 (94%)</td>
<td>31 (80%)</td>
</tr>
<tr>
<td>Mean (SD) APACHE II score</td>
<td>23.8 (6.1)</td>
<td>21.3 (6.0)</td>
</tr>
<tr>
<td>Mean (SD) Glasgow coma scale score</td>
<td>9.4 (4.3)</td>
<td>10.3 (4.2)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) total (h)</td>
<td>171 (167)</td>
<td>145 (149)</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>18 (38%)</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Duration of ICU stay (days) mean (SD)</td>
<td>9-7 (7-8)</td>
<td>9-7 (7-2)</td>
</tr>
<tr>
<td>Heated humidifier</td>
<td>20 (43%)</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>Large bore nasogastric tube</td>
<td>41 (87%)</td>
<td>28 (72%)</td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>28 (60%)</td>
<td>22 (55%)</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>10 (21%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Medication before protocol termination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucralfate</td>
<td>35 (75%)</td>
<td>33 (83%)</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>29 (62%)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>6 (13%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Sedation</td>
<td>45 (96%)</td>
<td>37 (95%)</td>
</tr>
<tr>
<td>Antibiotic drugs</td>
<td>24 (51%)</td>
<td>18 (46%)</td>
</tr>
</tbody>
</table>

90% patients were randomly assigned with semirecumbent or supine body position (figure 1). Four patients were excluded from the analysis: one died during resuscitation 2 h after initiation of the protocol and three because of protocol violation (reintubated patients all in semirecumbent position).

A total of 86 patients (65 male and 21 female, mean age 65 years [SD 15]) completed the clinical trial. Among the 86 patients the reasons for termination of the protocol were: change in position for more than 45 min (seven/86, 8%), death during the protocol (13/86, 15%), and weaning trial (66/86, 77%). Overall 39/86 patients were in the semirecumbent position (45%) and persistent supine position was maintained in 47/86 patients (55%). Table 1 compares general data of patients in supine and semirecumbent position. Patients in supine position tended to be less well, but the difference in APACHE II score was not significant.

Incidence of clinically suspected pneumonia

Pneumonia was clinically suspected in 19 of the 86 patients (22%) and could be microbiologically confirmed in 13 (15%); the incidence rate for the former was 28.7 per 1000 ventilator days and 19.6 per 1000 ventilator days for the latter. Table 2 summarises the microorganisms recovered.

Pneumonia was clinically suspected in three (8%) of 39 patients in the semirecumbent group and 16 (34%) of 47 in the supine group (95% CI for difference 10–42, p=0.003). Microbiologically confirmed pneumonia occurred in two (5%) patients in the semirecumbent position.

Table 1: General data of patients in supine and semirecumbent position

<table>
<thead>
<tr>
<th></th>
<th>Supine (n=47)</th>
<th>Semirecumbent (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>67 (14)</td>
<td>63 (16)</td>
</tr>
<tr>
<td>Sex, male</td>
<td>35 (75%)</td>
<td>30 (77%)</td>
</tr>
<tr>
<td>Current or ex-smokers</td>
<td>32 (66%)</td>
<td>27 (69%)</td>
</tr>
<tr>
<td>Chronic alcohol abuse</td>
<td>9 (19%)</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Intraavenous drug abusers</td>
<td>0</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Cause of acute respiratory failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>16 (34%)</td>
<td>13 (33%)</td>
</tr>
<tr>
<td>Other pulmonary diseases</td>
<td>12 (26%)</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>6 (13%)</td>
<td>7 (18%)</td>
</tr>
<tr>
<td>Drug overdose or neurological emergency</td>
<td>3 (6%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (21%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Severity of underlying disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease fatal or ultimately fatal</td>
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<td>28 (60%)</td>
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<td>10 (21%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Medication before protocol termination</td>
<td></td>
<td></td>
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<tr>
<td>Sucralfate</td>
<td>35 (75%)</td>
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<tr>
<td>Ranitidine</td>
<td>29 (62%)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>6 (13%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Sedation</td>
<td>45 (96%)</td>
<td>37 (95%)</td>
</tr>
<tr>
<td>Antibiotic drugs</td>
<td>24 (51%)</td>
<td>18 (46%)</td>
</tr>
</tbody>
</table>
Extrinsic risk factors of pneumonia

Clinically suspected pneumonia was associated in the univariate analysis with enteral nutrition and supine body position (figure 2). The incidence rate of clinically suspected pneumonia was lower in the semirecumbent group (10·9 per 1000 ventilator days) than in patients with supine body position (41·2 per 1000 ventilator days). The incidence rate of microbiologically confirmed pneumonia revealed enteral nutrition (adjusted odds ratio 11·8 [1·4–98·5], p=0·022) and supine body position (6·1 [1·2–30·9], p=0·038) as independent risk factors.

Intrinsic risk factors of pneumonia

Mechanical ventilation for 7 days or more, an APACHE II score of 20 or greater a sedation score of 4 or greater, and a Glasgow coma scale of less than 9 were associated with clinical suspicion of pneumonia (table 5). Mechanical ventilation for 7 days or more (adjusted odds ratio 10·9 [3·0–40·4], p=0·001) and a Glasgow coma scale of less than 9 (4·0 [1·1–14·5], p=0·035) were independently associated with clinical suspicion of pneumonia in multivariate analysis.

Requirement for mechanical ventilation of 7 days or more, an APACHE II score of 20 or greater, and coma according to Glasgow coma scale of less than 9 were significantly associated with microbiologically confirmed pneumonia in the univariate analysis. The multivariate analysis showed only requirement for mechanical ventilation of 7 days or more (adjusted odds ratio 42·7 [5·2–354·0], p=0·001) as an independent factor associated with microbiologically confirmed pneumonia.

### Table 2: Microorganisms recovered on the day of clinical suspicion of pneumonia

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Supine</th>
<th>Semirecumbent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-negative bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus lugdunensis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Gram-positive bacteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Fungi</strong></td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Total number of samples: 10 (5 in each group).

Table 3: Clinical characteristics of patients with clinically suspected pneumonia and microbiologically confirmed pneumonia with regard to body position

<table>
<thead>
<tr>
<th>Body position</th>
<th>Supine</th>
<th>Semirecumbent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean (SD) age (years)</strong></td>
<td>62·8 (15·5)</td>
<td>55·3 (19·7)</td>
</tr>
<tr>
<td><strong>Mean (SD) APACHE II score</strong></td>
<td>24·3 (5·7)</td>
<td>18·0 (5·2)</td>
</tr>
<tr>
<td><strong>Duration of mechanical ventilation</strong></td>
<td>166·3 (155·7)</td>
<td>222·0 (132·4)</td>
</tr>
<tr>
<td><strong>Number of events in &gt;48 h</strong></td>
<td>15 (94%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td><strong>Number of events in &gt;96 h</strong></td>
<td>12 (75%)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td><strong>Mean (SD) duration of ICU stay, to discharge or death (h)</strong></td>
<td>295·5 (212·5)</td>
<td>339·0 (118·8)</td>
</tr>
</tbody>
</table>

*Student's t test. † Fisher's exact test. CI cannot be computed.

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Clinical suspicion of pneumonia

<table>
<thead>
<tr>
<th>Frequency of diagnosis</th>
<th>p</th>
<th>95% CI for odds ratio (95% CI)</th>
<th>Microbiologically confirmed pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>17/62  (27%)</td>
<td>0·210*</td>
<td>11/82 (13%)</td>
</tr>
<tr>
<td></td>
<td>2/4   (50%)</td>
<td></td>
<td>2/4 (50%)</td>
</tr>
<tr>
<td>No</td>
<td>16/60  (27%)</td>
<td>0·099†</td>
<td>12/50 (24%)</td>
</tr>
<tr>
<td></td>
<td>3/6   (50%)</td>
<td></td>
<td>1/6 (16%)</td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>Yes</td>
<td>5/13 (39%)</td>
<td>0·150†</td>
</tr>
<tr>
<td></td>
<td>14/73 (19%)</td>
<td></td>
<td>3/13 (23%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5/38 (13%)</td>
<td>0·100†</td>
</tr>
<tr>
<td></td>
<td>10/73 (14%)</td>
<td></td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Parenteral nutrition</td>
<td>Yes</td>
<td>3/17 (18%)</td>
<td>0·753†</td>
</tr>
<tr>
<td></td>
<td>16/69 (23%)</td>
<td></td>
<td>2/17 (12%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5/72 (7%)</td>
<td>0·190†</td>
</tr>
<tr>
<td></td>
<td>13/69 (19%)</td>
<td></td>
<td>11/69 (16%)</td>
</tr>
<tr>
<td>Nasogastric tube size</td>
<td>Large</td>
<td>3/17 (18%)</td>
<td>0·753†</td>
</tr>
<tr>
<td></td>
<td>Small</td>
<td>16/69 (23%)</td>
<td>2/17 (12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1/10 (10%)</td>
</tr>
<tr>
<td>Sucralfate medication</td>
<td>Yes</td>
<td>18/68 (27%)</td>
<td>0·063†</td>
</tr>
<tr>
<td></td>
<td>1/18 (6%)</td>
<td></td>
<td>0·001†</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>5/22 (23%)</td>
<td>0·124†</td>
</tr>
<tr>
<td></td>
<td>1/12 (9%)</td>
<td></td>
<td>0·312†</td>
</tr>
<tr>
<td>Antibiotic medication &gt;72 h before event</td>
<td>Yes</td>
<td>4/12 (33%)</td>
<td>0·451†</td>
</tr>
<tr>
<td></td>
<td>15/73 (21%)</td>
<td></td>
<td>10/74 (14%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>9/45 (20%)</td>
<td>0·624†</td>
</tr>
<tr>
<td></td>
<td>10/41 (24%)</td>
<td></td>
<td>5/45 (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8/41 (19%)</td>
</tr>
<tr>
<td>Omeprazole medication</td>
<td>Yes</td>
<td>10/41 (24%)</td>
<td>0·624†</td>
</tr>
<tr>
<td></td>
<td>15/73 (21%)</td>
<td></td>
<td>5/45 (11%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>4/12 (33%)</td>
<td>0·451†</td>
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<tr>
<td></td>
<td>15/73 (21%)</td>
<td></td>
<td>3/12 (25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10/74 (14%)</td>
</tr>
<tr>
<td>Body position</td>
<td>Sipune</td>
<td>16/47 (34%)</td>
<td>0·003†</td>
</tr>
<tr>
<td></td>
<td>Semirecumbent</td>
<td>6/2 (1·5–29·7)</td>
<td>0·018*</td>
</tr>
<tr>
<td></td>
<td>3/39 (8%)</td>
<td></td>
<td>2/39 (5%)</td>
</tr>
</tbody>
</table>

Odds ratios with 95% CI are reported for all variables entered into multivariate analysis (p<0·05). *Fisher’s exact test. †Two-tailed test.

Table 4: Univariate variable statistics for extrinsic risk factors of nosocomial pneumonia

Analysis of interactions

Enteral feeding and body position showed a significant interaction in the analysis of clinically suspected pneumonia (adjusted odds ratio for the interaction term 10·6 [2·5–41·1], p=0·001). The frequency of clinically suspected pneumonia was highest when enteral feeding was given in supine body position (enteral feeding and supine body position 14/67, 21%, vs 13/69 [19%] in the supine group (<7 days three/15, 20%, vs 14/69 (23%) in the supine group) (<7 days four/10, 40%; Glasgow coma scale <9 and mechanical ventilation <7 days one/43, 2%). In the analysis of microbiologically confirmed pneumonia the two extrinsic risk factors enteral nutrition and supine body position had also an significant interaction term (10·2 [2·5–41·1]; p=0·001). In accordance with the findings for clinically suspected pneumonia the interaction term was significant because the frequency of microbiologically confirmed pneumonia was highest when both risk factors were present (enteral feeding and supine body position ten/28, 36%; enteral feeding and semirecumbent body position two/22, 9%; no enteral feeding and supine body position one/19, 5%; no enteral feeding and semirecumbent body position zero/17).

Outcome

The overall mortality during the stay in the ICU was 20/86 (24%). The mean APACHE II score was 21·7 (SD 6·2) in survivors and 25·9 (4·7) in non-survivors (95% CI for difference 1·2–7·2, p=0·006). The length of mechanical ventilation until the end of the protocol did not differ significantly between survivors and non-survivors (108 [114] vs 131 [117] h [35·2 to 81·2], p=0·430). The mean duration of ICU stay was 9·0 (7·4) days in survivors and 11·0 (8·0) days in non-survivors (1·8 to 5·8, p=0·315). Mortality in the ICU was seven/39 (18%) in the semirecumbent group and 13/47 (28%) in the supine group (7·6 to 27·6, p=0·289), but also Kaplan-Meier statistics did not show a significant difference in survival between the two study groups (7·6 to 27·6, p=0·289), but also Kaplan-Meier statistics did not show a significant difference in survival between the two study groups (figure 3). Mortality was not significantly higher in patients with clinical suspicion of pneumonia compared with those without (six/19, 32% vs 14/67, 21%, 12·1 to 34·1, p=0·364). Accordingly, patients with microbiologically confirmed pneumonia tended to have a higher mortality, but this difference was also not statistically significant (five/13, 39% vs 15/73, 21%, 19·1 to 46·1, p=0·170).

Discussion

The pathogenesis of nosocomial pneumonia includes microaspiration to lower airways of abnormally colonised oropharyngeal or gastric contents, or both. However, the role of the gastric reservoir for the pathogenesis of bacterial nosocomial pneumonia is controversial. Some studies found no clear sequence of colonisation from the stomach...
to the pharynx or the airways, whereas other studies provided clear evidence of the contributing role of the gastric reservoir to the pathogenesis of late-onset nosocomial pneumonia.

Gastro-oesophageal reflux is a consistent finding in mechanically ventilated patients and may favour pneumonia by promoting retrograde oropharyngeal colonisation and aspiration to lower airways. The presence of a nasogastric tube seems to be a key factor facilitating gastro-oesophageal reflux, owing to the compromised function of the lower oesophageal sphincter.

We have clearly shown in our study that care of mechanically ventilated patients—with a nasogastric tube in place—in a supine body position increases the risk of nosocomial pneumonia. When patients were cared for in semirecumbent body position we observed more than 75% reduction of the rate of nosocomial pneumonia and the rate per 1000 ventilator days was reduced almost fourfold. In addition, we confirmed the increased risk of nosocomial pneumonia for patients in supine body position in a multivariate analysis together with enteral feeding, mechanical ventilation for 7 days or more, and coma on admission (Glasgow coma scale <9).

The mechanisms by which the semirecumbent position prevents nosocomial pneumonia are not fully understood. But the previous finding that this position decreases gastro-oesophageal reflux, abnormal oropharyngeal colonisation, and aspiration of gastric contents to lower airways supports the hypothesis that this measure prevents or at least slows the gastro-oropharyngeal route of pulmonary infection. This hypothesis is strongly supported by the analysis of interactions in our multivariate model, because 50% of all patients who received enteral feeding in the supine body position eventually developed clinical signs of pneumonia. Two previous studies showed that uncontrolled volume of enteral nutrition may promote gastro-oesophageal reflux and that reflux in intubated patients receiving enteral

The frequency of clinically suspected and microbiologically confirmed pneumonia in the presence and absence of each attribute are given together with the incidence in % and the univariable level of significance for this comparison. Odds ratios with 95% CI are reported for all variables entered into multivariable analysis (p<0·05). * Fisher's exact test. †  \chi^2   \text{test.}

Table 5: Univariable variable statistics for extrinsic risk factors of nosocomial pneumonia
nutrition is increased by the supine body position.18 Our study shows in a randomised clinical trial that a supine body position is associated with adverse outcomes and independent risk factors also for nosocomial pneumonia, especially when they are combined. This finding again strengthens the suggested pathogenesis involving reflux and aspiration and reinforces the potential role of the gastric reservoir in the acquisition of nosocomial pneumonia. Enteral nutrients are alkaline and may—depending on the gastric acidity—favour bacterial colonisation of the stomach.26

There are additional factors, however, that increase gastro-oesophageal reflux and aspiration. Among these, the nasogastric tube, the intragastric pressure, and the type of antacid medication could have important roles. Because the placement of a nasogastric tube was indicated in all patients we cannot comment on its potential contribution to the risk of nosocomial pneumonia. However, we used two different bores of nasogastric tubes in a well-balanced proportion and found no association with the development of nosocomial pneumonia. Intragastric pressure was controlled in our study by an incremental feeding schedule and frequent gastric aspiration, so differences in intragastric pressure are unlikely to have biased our results. The role of antacid medication in the development of nosocomial pneumonia is controversial. Initial studies raised the suspicion that antacids could promote pneumonia but we could not confirm this idea in a randomised trial.27 Our study cannot provide relevant evidence because gastroprotective treatment was given according to guidelines and was not randomised.28 In univariate analysis we even observed an increased risk of nosocomial pneumonia in the group of patients receiving sucralfate, but this risk is probably associated with enteral nutrition because these patients routinely received sucralfate.

Other additional risk factors for nosocomial pneumonia found in multivariate analyses deserve comment. Some risk factors such as the duration of mechanical ventilation (≥7 days) are obvious and have been shown before.29 Decreased consciousness has also been associated with a high incidence of nosocomial pneumonia,29 and Ewig and colleagues showed a distinct bacterial pattern in these patients.30 We observed a particularly high risk of nosocomial pneumonia in patients who had both risk factors. This finding can be explained by the fact that coma on admission facilitates aspiration and thus early-onset pneumonia, whereas long-duration mechanical ventilation increases the risk later on (late-onset pneumonia).29

We did not detect that morbidity or mortality decreased significantly when we cared for our patients in semirecumbent body position. By contrast, Kollef and colleagues showed that a supine body position during the first 24 h of mechanical ventilation was an independent risk factor of a poor prognosis in patients with nosocomial pneumonia.31 However, effects of body position on mortality should be caused by the attributable mortality of nosocomial pneumonia. In our study we did not find any differences in mortality between patients with and without nosocomial pneumonia. Larger sample sizes are needed to prove this idea and a study would have to accept significant differences in the nosocomial pneumonia rate that in the end might not translate into outcome differences.

The initial diagnosis in this study was based on clinical criteria that may have missed patients with nosocomial pneumonia. However, the operational characteristics of the method, as was shown, were independent. Because biopsy samples were taken immediately after death.32 Since the diagnostic methods were similar in both study groups, a bias is unlikely. The study was stopped before the calculated sample size was reached, which may be interpreted as a potential limitation because the small sample size might have suppressed the identification of other independent risk factors. However, statistical precaution was taken to avoid premature interpretation of interim results, which was a clear advantage for patients in the semirecumbent body position. The interpretation of the APACHE II and the Glasgow coma scale scores may have been hampered by the time in which the former was obtained and the inclusion of sedated patients into the calculation of the latter. Patients in the supine position were slightly less well at baseline as shown by the APACHE II score and the proportion of patients with predicted fatal or ultimately fatal diseases. Although these differences were not significant, they may have influenced our results. However, both measures were included in the multivariate analysis and the bias should therefore be limited. A multivariate time-to-event analysis (eg, Cox proportional-hazards model) would have been desirable for this type of data, but most of the candidate variables did not satisfy assumptions necessary for this type of analysis. Enteral feeding was clearly a risk factor for nosocomial pneumonia but was continuous in our units. Other feeding schedules, which support reacidification of the stomach or increase control of the intragastric pressure, do not decrease significantly the risk of nosocomial pneumonia.33 We did not observe any adverse effects of the semirecumbent body position in the patients included in this study. However, exclusion criteria applied, and protective measures for prevention of pressure ulcers, for example, were followed in our units. The semirecumbent body position is a low-cost and easy-to-apply measure to reduce the risk of nosocomial pneumonia in mechanically ventilated patients, especially when patients are receiving continuous enteral feeding through a nasogastric tube. In addition, physicians should also be especially alert to the possibility of nosocomial pneumonia in patients who are comatose when admitted or intubated and consecutively require mechanical ventilation for 7 days or more.

Contributors
M. Itra A D rakulovic was responsible for protocol design, recruitment of patients, data entry into the database, and assisted with writing of the manuscript. Antoni Torres was the study co-ordinator, and was involved in the design of the protocol, as well as writing and revision of the paper. Jose M. Nicholas, Santiago Nogué, and Miquel Ferrer enrolled patients into the study.

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References


Comparison of microwave endometrial ablation and transcervical resection of the endometrium for treatment of heavy menstrual loss: a randomised trial

Kevin G Cooper, Christine Bain, David E Parkin

Summary

Background Various new endometrial ablation techniques have emerged for the treatment of menorrhagia. We undertook a randomised controlled trial comparing one new technique, microwave endometrial ablation (MEA), with a proven procedure, transcervical resection of the endometrium (TCRE), for women with heavy menstural loss.

Methods 263 eligible and consenting women, referred for endometrial ablative surgery, were randomly assigned MEA (Microsulis plc, Waterlooville, Hampshire, UK; n=129) or TCRE (n=134). 230 participants were needed to give 80% and 93 (75%) in the TCRE group were totally or generally satisfied (all significantly).

Findings At 12 months, 89 (77%) women in the MEA group and 93 (75%) in the TCRE group were totally or generally satisfied with their treatment (95% CI for difference −12 to 17) and 109 (94%) versus 112 (90%) found it acceptable (−11 to 35). Mean operating times were shorter for MEA than for TCRE (11·4 vs 15·0 min, p=0·001) and the postoperative stay slightly but not significantly shorter. One blunt perforation occurred in each study group resulting in one immediate hysterectomy (TCRE group). Of eight health-related quality of life dimensions, all were improved after MEA (six significantly) and seven were improved after TCRE (all significantly).

Interpretation Both techniques achieved high rates of satisfaction and acceptability and both improved quality of life after 1 year. However, we cannot exclude a difference in satisfaction between the groups of less than 15% MEA seems a suitable alternative to TCRE.

Lancet 1999; 354: 1859–63

Introduction

Hysteroscopic endometrial destructive techniques, such as transcervical resection of the endometrium, are proven alternatives to hysterectomy for women with dysfunctional uterine bleeding.1·5 The most commonly used techniques in the UK are combination resection rollerball and laser ablation; patients' satisfaction with these techniques is high, recovery times are short, and the techniques are safe.6·7 However, specialist tuition is recommended before these hysteroscopic procedures are undertaken because they can be technically challenging. Various new ablative techniques have emerged; these methods are reported to be quick, safe, and easy to learn and use, yet as effective as traditional hysteroscopic surgery.8·10 In a series of cases treated by microwave endometrial ablation (MEA), the success rate was 83%, with a 56% rate of amenorrhoea, and very fast treatment times (1–2 min).9·10 These results were achieved in selected women in whom the uterus was of normal size and the endometrial cavity regular.

To appraise MEA formally we undertook a pragmatic11·12 randomised controlled trial comparing this technique with TCRE in terms of patients' satisfaction with their treatment.

Patients and methods

Participants

Approval from the local ethics committee was obtained to undertake a randomised controlled trial comparing MEA with TCRE for women complaining of heavy menstrual loss. The primary outcome measures were patients' satisfaction with and the acceptability of the two procedures. Secondary measures were comparisons of effect on menstrual status and health-related quality of life, and operative details and morbidity. Women who were referred to the gynaecology outpatient department of Aberdeen Royal Infirmary for endometrial destructive surgery were recruited between September, 1996, and February, 1998. Eligible patients were premenopausal, had dysfunctional uterine bleeding (uterine size equivalent to 10 weeks' pregnancy or less and no histopathological abnormalities of the endometrium), and gave informed consent to take part in the trial.

Procedures

Participants were given goserelin 3·6 mg to promote endometrial thinning,1·17 and underwent surgery 5 weeks later. Two specialist registrars (KGC and CB) undertook all but 11 of the operations. Each had previously undertaken at least 50 TCRE procedures. These researchers attended a training session to learn MEA and had each carried out five MEA procedures before the trial started.

Treatment allocation was obtained by telephone after the woman had given informed consent. A secretary opened the next in a series of sealed, opaque, sequentially numbered envelopes showing the treatment code in a one to one randomisation ratio. This sequence was predetermined by computer-generated random-number tables in balanced blocks of 20.
TCRE was carried out by a combination electrocautery technique, with 1.5% glycine as the distending medium. The uterine fundus and cornual regions were ablated with a rollerball, and a 90° loop of diameter 7 mm and depth 3 mm was used to excise endomyometrial strips from the walls.

Patients assigned M EA underwent ultrasonography for measurement of endometrial thickness and 5 mm gas hysteroscopy for identification of any fibroids and confirmation of placement in the endometrial cavity. For the M EA procedure (Microsulis plc, Waterlooville, Hampshire, UK), a microwave probe of diameter 8 mm was inserted until the tip reached the uterine fundus. The footswitch was then activated. Once the temperature of the tissue next to the probe tip reached 75°C, the probe was moved slowly from side to side and withdrawn with the temperature (visually displayed) maintained at 75°C–80°C. The technique effectively "paints" microwave energy with a maximum penetration of 6 mm over the whole surface of the uterine cavity. All procedures were done under general anaesthesia after cervical dilation to 9 mm and with antibiotic cover. Rectal analgesia with diclofenac or, if contraindicated, paracetamol was given at the end of all procedures.

A baseline clinical questionnaire and a questionnaire on health-related quality of life (short-term 36; SF-36), were completed by participants at recruitment. Women were asked to grade severity of bleeding and pain on a five-point scale for each day of their menstrual period, and these scores were added to obtain total bleeding and pain scores. Questions about bladder and bowel symptoms were included to establish any effect of microwave therapy on these organs. An operative questionnaire was completed that covered operating times, complications, requirements for postoperative analgesia, and length of stay. Hospital review was undertaken at 4 months and postal follow-up 12 months after the operation. The questionnaires used at baseline, with additional questions to assess satisfaction with and acceptability of treatment were completed by women again at follow-up.

Statistical analysis
We calculated that we would need to enrol 230 women to have an 80% chance of detecting a minimum 15% difference in satisfaction between the two techniques, which would be significant at $p=0.05$ (Instat 2, version 2.0). This calculation was based on known satisfaction rates of around 78% after TCRE.

Analysis was by intention to treat. SPSS for Windows (version 6.0) was used for data entry and statistical analysis. Independent and paired t tests were used to analyse continuous variables (independent and related) with a normal distribution. ANCOVA was used to adjust for baseline differences between the treatment groups in SF-36 scores. The Mann-Whitney U test was used for ordinal or continuous variables that did not show a normal distribution. We used the $\chi^2$ or Fisher’s exact test for independent nominal data, and McNemar’s and Wilcoxon’s ranked-sum tests for paired nominal data describing dichotomous and related variables, respectively. 95% CI were calculated for differences in means for normally distributed continuous variables and for differences in proportions for categorical data by the Confidence Interval Analysis programme (version 1.1).

Results
263 women were randomly assigned treatment—129 M EA and 134 T CRE (figure). The treatment groups had similar characteristics at baseline (table 1). 83 (65%) women assigned M EA and 80 (60%) assigned T CRE described their periods as very heavy, and 60% in both groups had had their problem for longer than 3 years. Sexual activity was severely affected in 56% and prevented by excessive bleeding in 51%, with just over 20% in each group also reporting dyspareunia.

Submucous fibroids of greater than 2 cm in diameter were present in 32 women (table 2). Of these women, all received their allocated treatment except one in the M EA group who underwent T CRE and one in the T CRE group who needed a two-stage procedure. Four women in the M EA group underwent T CRE because the microwave equipment failed. Operating times for M EA, which were significantly shorter than those for T CRE, included the hysteroscopic assessment but not the ultrasonographic examination. The mean fluid absorption at T CRE was 318 mL (median 200 mL). No patient had a glycine deficit of greater than 1500 mL, so there was no risk of electrolyte imbalance.

Blunt perforation with an inactive hysteroscope or microwave probe occurred once in each group. The M EA patient with perforation declined an attempt at a repeat procedure and requested a hysterectomy. The perforation in the T CRE patient caused bleeding into the broad ligament, which was managed by hysterectomy. A second

<table>
<thead>
<tr>
<th></th>
<th>M EA (n=129)</th>
<th>T CRE (n=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) age (years)</td>
<td>41.1 (6.7)</td>
<td>41.0 (8.4)</td>
</tr>
<tr>
<td>Mean (SD) weight (kg)</td>
<td>68.5 (14.0)</td>
<td>72.9 (17.4)</td>
</tr>
<tr>
<td>Menstrual symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irregular periods</td>
<td>66 (51%)</td>
<td>76 (57%)</td>
</tr>
<tr>
<td>&gt;7 days' bleeding</td>
<td>58 (45%)</td>
<td>54 (40%)</td>
</tr>
<tr>
<td>&gt;3 days' heavy bleeding</td>
<td>80 (60%)</td>
<td>82 (64%)</td>
</tr>
<tr>
<td>Dysmenorrhoea</td>
<td>91 (73%)</td>
<td>90 (68%)</td>
</tr>
<tr>
<td>Double or more sanitary protection required</td>
<td>111 (86%)</td>
<td>113 (84%)</td>
</tr>
<tr>
<td>Median (IQR) score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>27 (22–36)</td>
<td>27 (21–34)</td>
</tr>
<tr>
<td>Pain</td>
<td>19 (12–26)</td>
<td>16 (7–25)</td>
</tr>
<tr>
<td>Premenstrual symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloating</td>
<td>107 (87%)</td>
<td>115 (87%)</td>
</tr>
<tr>
<td>Breast discomfort</td>
<td>94 (76%)</td>
<td>103 (79%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>105 (86%)</td>
<td>117 (87%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>89 (75%)</td>
<td>93 (72%)</td>
</tr>
<tr>
<td>Depression</td>
<td>71 (612%)</td>
<td>79 (65%)</td>
</tr>
<tr>
<td>Work absence due to menses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13 (10%)</td>
<td>20 (15%)</td>
</tr>
<tr>
<td>None, but work suffers</td>
<td>54 (42%)</td>
<td>52 (39%)</td>
</tr>
<tr>
<td>1 day</td>
<td>14 (11%)</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>&gt;2 days</td>
<td>46 (36%)</td>
<td>49 (37%)</td>
</tr>
</tbody>
</table>

For some variables, a small number of women had missing data.

Table 1: Baseline characteristics of participants

Trial profile

<table>
<thead>
<tr>
<th></th>
<th>M EA (n=129)</th>
<th>T CRE (n=134)</th>
</tr>
</thead>
</table>
TCRE patient readmitted with abdominal and pelvic pain 2 weeks after the procedure also underwent hysterectomy. Bleeding occurred in five women in the TCRE group but none in the MEA group; this complication was managed by placement of a 14 gauge Foley catheter in the uterus for 6 h. Readmission was required for four women in the MEA group, three with minor secondary haemorrhage that responded to antibiotic therapy. Six women were readmitted in the TCRE group, three with pelvic pain, two to have repeat procedures, and one with chest pain. The repeat procedures were carried out uneventfully to complete treatment of a fibroid cavity in one patient and a large cavity in the second when the initial procedure was halted at 1500 mL glycine deficit. 87 (72%) of 121 women in the MEA group and 82 (66%) of 124 in the TCRE group felt that they had fully recovered within 4 weeks of their operation (p=0·83).

Follow-up data to 12 months were available for 240 women: 116 assigned MEA and 124 assigned TCRE. Hospital data confirm that no woman who did not complete the follow-up questionnaire has undergone further gynaecological surgery within Grampian region. Both techniques led to highly significant and equivalent reductions for all variables relating to bleeding (p<0·001), with amenorrhoea rates of 40% (table 3). The proportions of women with dysmenorrhoea or pelvic pain were significantly lower than at baseline in both groups (p<0·001) but did not differ between the groups. Similarly, the proportions with premenstrual symptoms were also much lower with both techniques (p<0·001). Both techniques led to significant reductions in work time lost due to menstrual symptoms (p<0·001).

Patients' satisfaction at 12 months is reported in table 4. Similar proportions of each group were totally or generally satisfied with the outcome and about 90% of each group found the treatment acceptable and would recommend it to others.

The baseline SF-36 scores of both groups were lower than normative values in women of equivalent age in the UK for six of the eight items. The baseline SF-36 pain scores are listed in table 3.

Table 2: Details of operative procedures

<table>
<thead>
<tr>
<th>Uterine characteristics</th>
<th>MEA (n=129)</th>
<th>TCRE (n=134)</th>
<th>95% CI for difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) cavity length (cm)</td>
<td>7.4 (0.9)</td>
<td>7.5 (0.8)</td>
<td>-0.3 to 0.07</td>
<td>0.2</td>
</tr>
<tr>
<td>Submucous fibroids &gt;2 cm</td>
<td>14 (11%)</td>
<td>18 (14%)</td>
<td>-5 to 10</td>
<td>0.1</td>
</tr>
<tr>
<td>Duration of procedure</td>
<td>11.4 (10.5)</td>
<td>15.0 (7.2)</td>
<td>-5.7 to 1.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean (SD) theatre time (min)</td>
<td>20.9 (11.3)</td>
<td>26.2 (8.7)</td>
<td>-7.7 to 2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intraoperative difficulties</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procedure abandoned</td>
<td>5 (4%)</td>
<td>5 (4%)</td>
<td>-4 to 5</td>
<td>0.57</td>
</tr>
<tr>
<td>Equipment failure</td>
<td>11 (9%)</td>
<td>3 (2%)</td>
<td>1 to 12</td>
<td>0.02</td>
</tr>
<tr>
<td>Blunt perforation</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>0</td>
<td>5 (4%)</td>
<td>0 to 7</td>
<td>0.06</td>
</tr>
<tr>
<td>Primary treatment received</td>
<td>123 (96%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEA</td>
<td>5</td>
<td>132 (98%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCRE</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative analgesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>90 (71%)</td>
<td>99 (74%)</td>
<td>-15 to 7</td>
<td>0.48</td>
</tr>
<tr>
<td>Oral</td>
<td>23 (18%)</td>
<td>19 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injectable</td>
<td>14 (11%)</td>
<td>16 (12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) postoperative stay (h)</td>
<td>13 (17-6)</td>
<td>16.7 (21.2)</td>
<td>-8.0 to 1.5</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Table 3: Menstrual status and symptoms at 12 months

<table>
<thead>
<tr>
<th>Menstrual status unchanged or worse</th>
<th>MEA (n=116)</th>
<th>TCRE (n=124)</th>
<th>95% CI for difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amenorrhoea</td>
<td>46 (40%)</td>
<td>49 (40%)</td>
<td>-14 to 20</td>
<td>0.23</td>
</tr>
<tr>
<td>1-3 days</td>
<td>15 (13%)</td>
<td>15 (12%)</td>
<td>-17 to 21</td>
<td></td>
</tr>
<tr>
<td>3-7 days</td>
<td>49 (42%)</td>
<td>51 (41%)</td>
<td>-11 to 13</td>
<td></td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>6 (5%)</td>
<td>9 (7%)</td>
<td>-17 to 35</td>
<td></td>
</tr>
<tr>
<td>Double or more sanitary protection required</td>
<td>14 (12%)</td>
<td>16 (14%)</td>
<td>-17 to 21</td>
<td>0.98</td>
</tr>
<tr>
<td>&gt;3 days of heavy bleeding</td>
<td>8 (7%)</td>
<td>7 (6%)</td>
<td>-10 to 31</td>
<td>0.79</td>
</tr>
<tr>
<td>Median (IQR) score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>3 (0-8)</td>
<td>3 (0-10)</td>
<td>-3 to 4</td>
<td>0.37</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (0-9)</td>
<td>1 (0-7)</td>
<td>-2 to 1</td>
<td>0.7</td>
</tr>
<tr>
<td>Dysmenorrhoea same or worse</td>
<td>24 (20%)</td>
<td>22 (18%)</td>
<td>-11 to 20</td>
<td>0.62</td>
</tr>
<tr>
<td>Prenovulatory symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast discomfort</td>
<td>64 (55%)</td>
<td>61 (49%)</td>
<td>-6 to 18</td>
<td>0.64</td>
</tr>
<tr>
<td>Blushing</td>
<td>75 (65%)</td>
<td>63 (51%)</td>
<td>1 to 26</td>
<td>0.03</td>
</tr>
<tr>
<td>Inturbidity</td>
<td>67 (58%)</td>
<td>65 (52%)</td>
<td>-6 to 19</td>
<td>0.4</td>
</tr>
<tr>
<td>Headaches</td>
<td>56 (48%)</td>
<td>54 (44%)</td>
<td>-7 to 17</td>
<td>0.46</td>
</tr>
<tr>
<td>Depression</td>
<td>42 (36%)</td>
<td>49 (40%)</td>
<td>-9 to 17</td>
<td>0.59</td>
</tr>
<tr>
<td>Work absence due to menses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>96 (83%)</td>
<td>101 (83%)</td>
<td>-14 to 18</td>
<td>0.93</td>
</tr>
<tr>
<td>None, but work suffers</td>
<td>31 (26%)</td>
<td>11 (9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>5 (4%)</td>
<td>4 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 days</td>
<td>4 (3%)</td>
<td>8 (7%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The baseline SF-36 scores of both groups were lower than normative values in women of equivalent age in the UK for six of the eight items. The baseline SF-36 pain
score was significantly lower in the MEA group than in the TCRE group (table 5). Changes in score showed improvements for all eight health scores after MEA (significant \(p<0.001\) for six items). Seven items showed significant improvements after TCRE \(p<0.05\;\text{to} \;0.001\). For physical role limitation and general health items the improvements were significantly greater with MEA than with TCRE. By ANCOVA, with correction for differences in baseline scores, only the improvement in physical role limitation differed significantly between the groups.

Sexual activity was equally and significantly improved by both interventions as were rates of dyspareunia (both Wilcoxon rank-sum test, \(p<0.001\)). At baseline, only 5% of women in each group could undertake leisure activities unaffected by their periods. After treatment, the corresponding proportions were 77% for MEA and 74% for TCRE (Wilcoxon’s rank-sum test, both \(p<0.001\)). Bowel and bladder symptoms were not affected by MEA or TCRE, as found previously for hysteroscopic surgery.

By 12 months, ten women in the MEA arm had undergone further surgery (hysterectomy in nine). 13 women in the TCRE group had further surgery (hysterectomy in 12).

**Discussion**

We adopted a pragmatic approach in this trial, which reflected usual clinical practice: entry was based on a subjective complaint of intolerable menstrual loss. Preoperative outpatient ultrasonographic and hysteroscopic examinations or an endometrial biopsy could not be obtained. We aimed to recruit a diverse population with presumed dysfunctional uterine bleeding, therefore increasing the general applicability of the results.

Operative times for TCRE were much shorter than previously reported. Even so, and despite the additional gas hysteroscopy, MEA was significantly quicker to complete than TCRE. No irrigation fluid is required for MEA, whereas one TCRE procedure was stopped once a 1500 mL glycine deficit had occurred. Technical failures with the equipment were significantly more common in the MEA group, and four women had to have TCRE instead. These findings all occurred early in the study with a prototype microwave generator. The perforation rate in this trial is similar to previously reported rates in national audits and studies, although none occurred with activated equipment since they were detected by hysteroscopy. Primary haemorrhage did not occur during MEA. Although three women had hysterectomies either immediately or within 6 weeks of their ablative procedures, two were at the patient’s request.

Rates of satisfaction with, and acceptability of treatment were high for both techniques, and similar to those in previous trials of endometrial ablation. The proportion of women with amenorrhoea after treatment was 40%, although this variable should not be used to define treatment success, since the most likely outcome is lighter menstruation. Women aware of and accepting of this fact will be more satisfied with the operative techniques than those expecting amenorrhoea.

The proportion of women with dysmenorrhoea was greatly decreased by both procedures, and regular new pelvic pain was reported by only 4% of the MEA group and 8% of the TCRE group. As reported previously after ablative procedures, MEA also significantly alleviated perimenstrual symptoms, although TCRE led to the largest changes. Whether this effect is achieved purely through a lessening of the anticipation of a heavy period, or whether an unknown endometrial product has been removed is unclear.

Heavy menstrual loss causes significant deterioration in general health and quality of life, which has been overlooked in the evaluation of treatment in many previous trials. The baseline SF-36 scores in this trial were lower than normative values for women of equivalent age in the UK, and are similar to those in previous studies of women with menorrhagia.

Table 4: Patients’ satisfaction and efficacy and acceptability of treatment

<table>
<thead>
<tr>
<th></th>
<th>MEA (n=116)</th>
<th>TCRE (n=124)</th>
<th>95% CI for difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Totally or generally satisfied</td>
<td>89 (77%)</td>
<td>93 (75%)</td>
<td>–12 to 17</td>
<td>0·88</td>
</tr>
<tr>
<td>Cure or acceptable improvement in symptoms</td>
<td>95 (83%)</td>
<td>94 (76%)</td>
<td>–11 to 18</td>
<td>0·76</td>
</tr>
<tr>
<td>Treatment acceptable</td>
<td>109 (94%)</td>
<td>112 (90%)</td>
<td>–11 to 35</td>
<td>0·34</td>
</tr>
<tr>
<td>Would recommend treatment to others</td>
<td>105 (91%)</td>
<td>110 (89%)</td>
<td>–16 to 25</td>
<td>0·68</td>
</tr>
</tbody>
</table>

Table 5: Baseline SF-36 scores and change in score at 12 months

<table>
<thead>
<tr>
<th></th>
<th>MEA (n=216)</th>
<th>TCRE (n=124)</th>
<th>95% CI for difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>84·6 (19·2)</td>
<td>82·2 (23·3)</td>
<td>...</td>
<td>0·40</td>
</tr>
<tr>
<td>Social functioning</td>
<td>60·1 (23·0)</td>
<td>60·1 (22·9)</td>
<td>...</td>
<td>0·99</td>
</tr>
<tr>
<td>Role—physical</td>
<td>56·5 (22·2)</td>
<td>62·9 (41·7)</td>
<td>...</td>
<td>0·24</td>
</tr>
<tr>
<td>Role—emotional</td>
<td>63·8 (18·5)</td>
<td>62·6 (43·2)</td>
<td>...</td>
<td>0·88</td>
</tr>
<tr>
<td>Mental health</td>
<td>63·6 (18·8)</td>
<td>63·8 (21·7)</td>
<td>...</td>
<td>0·92</td>
</tr>
<tr>
<td>Energyl fatigue</td>
<td>44·3 (22·6)</td>
<td>43·3 (24·3)</td>
<td>...</td>
<td>0·75</td>
</tr>
<tr>
<td>Pain</td>
<td>55·4 (22·2)</td>
<td>63·7 (26·1)</td>
<td>...</td>
<td>0·02</td>
</tr>
<tr>
<td>General health</td>
<td>69·7 (21·7)</td>
<td>73·0 (19·4)</td>
<td>...</td>
<td>0·22</td>
</tr>
</tbody>
</table>

Mean (SD) SF-36 score

<table>
<thead>
<tr>
<th></th>
<th>MEA (n=216)</th>
<th>TCRE (n=124)</th>
<th>95% CI for difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>84·6 (19·2)</td>
<td>82·2 (23·3)</td>
<td>...</td>
<td>0·40</td>
</tr>
<tr>
<td>Social functioning</td>
<td>60·1 (23·0)</td>
<td>60·1 (22·9)</td>
<td>...</td>
<td>0·99</td>
</tr>
<tr>
<td>Role—physical</td>
<td>56·5 (22·2)</td>
<td>62·9 (41·7)</td>
<td>...</td>
<td>0·24</td>
</tr>
<tr>
<td>Role—emotional</td>
<td>63·8 (18·5)</td>
<td>62·6 (43·2)</td>
<td>...</td>
<td>0·88</td>
</tr>
<tr>
<td>Mental health</td>
<td>63·6 (18·8)</td>
<td>63·8 (21·7)</td>
<td>...</td>
<td>0·92</td>
</tr>
<tr>
<td>Energyl fatigue</td>
<td>44·3 (22·6)</td>
<td>43·3 (24·3)</td>
<td>...</td>
<td>0·75</td>
</tr>
<tr>
<td>Pain</td>
<td>55·4 (22·2)</td>
<td>63·7 (26·1)</td>
<td>...</td>
<td>0·02</td>
</tr>
<tr>
<td>General health</td>
<td>69·7 (21·7)</td>
<td>73·0 (19·4)</td>
<td>...</td>
<td>0·22</td>
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</tbody>
</table>

Change in score to 12 months

<table>
<thead>
<tr>
<th></th>
<th>MEA (n=216)</th>
<th>TCRE (n=124)</th>
<th>95% CI for difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>0·7 (18·9)</td>
<td>2·4 (16·8)</td>
<td>–6·4 to 2·9</td>
<td>0·45</td>
</tr>
<tr>
<td>Social functioning</td>
<td>20·6 (26·5)</td>
<td>16·2 (24·4)</td>
<td>–2·1 to 10·9</td>
<td>0·18</td>
</tr>
<tr>
<td>Role—physical</td>
<td>23·9 (19·4)</td>
<td>11·3 (41·7)</td>
<td>1·0 to 24·3</td>
<td>0·03</td>
</tr>
<tr>
<td>Role—emotional</td>
<td>17·0 (48·5)</td>
<td>13·7 (47·9)</td>
<td>–9·1 to 15·6</td>
<td>0·59</td>
</tr>
<tr>
<td>Mental health</td>
<td>6·3 (19·5)</td>
<td>6·0 (22·2)</td>
<td>–4·9 to 5·7</td>
<td>0·89</td>
</tr>
<tr>
<td>Energyl fatigue</td>
<td>12·8 (31·7)</td>
<td>12·1 (23·0)</td>
<td>–4·2 to 6·5</td>
<td>0·80</td>
</tr>
<tr>
<td>Pain</td>
<td>14·8 (31·0)</td>
<td>7·2 (31·1)</td>
<td>–0·2 to 15·5</td>
<td>0·06</td>
</tr>
<tr>
<td>General health</td>
<td>2·4 (20·3)</td>
<td>–2·9 (20·0)</td>
<td>0·2 to 10·5</td>
<td>0·04</td>
</tr>
</tbody>
</table>

Table 5: Baseline SF-36 scores and change in score at 12 months
after both techniques; these benefits have been reported previously after hysteroscopic surgery. The ability to undertake leisure pursuits was greatly increased and the amount of time at work lost through menstrual symptoms decreased significantly.

The repeat surgery rates of around 10% for each group at 12 months are low and similar to some randomised trial data, but lower than rates obtained in other large trials and a national audit. Most treatment failures become apparent in the first year and retardation rates decline after this time. These findings are reassuring as regards our trial, since we have followed up the participants for at least 1 year.

The advantages of M E A over T C R E are that the operative technique is very easy to learn and that hysteroscopic surgical skills are not essential. M E A takes significantly less time than T C R E, is at least as safe, and should be amenable to outpatient management. These results should be widely applicable because virtually all of the procedures were undertaken by specialist registrars after short, though structured, preparatory training in M E A. Although hysterectomy was undertaken in this study with the aim of identifying fibroids, we believe that it should be mandatory immediately before M E A (or any blind ablative technique), to ensure correct siting of the probe in an intact endometrial cavity. As with all new surgical techniques, long-term monitoring of its performance is necessary.

Contributors

Kevin Cooper devised the study protocol and methods, did half of the operations, undertook the statistical analysis, and wrote the paper. Christine Bain coordinated the study, undertook recruitment and follow-up of the patients, did half of the operations, compiled the database and entered data, and edited the paper. David Parkin initiated the trial concept, obtained funding, recruited patients, provided theatre time and advice; and M.irosulis plc for supplying the microwave equipment for this trial and for financial support (to CB).

Acknowledgments

We thank the women who took part; Ann Fitzmurice (Dugald Baird Centre for Research in Women’s Health, Aberdeen) for statistical help and advice; and M.irosulis plc for supplying the microwave equipment for this trial and for financial support (to CB).

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T H E L A N C E T • V o l 3 5 4 • N o v e m b e r 2 7 , 1 9 9 9

1863
Cardiac arrhythmias in children during outpatient general anaesthesia for dentistry: a prospective randomised trial

M R Blayney, AF Malins, G M Cooper

Summary

Background Deaths in children associated with outpatient general dental anaesthesia may be attributable to sudden cardiovascular collapse precipitated by ventricular arrhythmias. A causal link between halothane anaesthesia, ventricular arrhythmias, and deaths has been suggested. We did a prospective, randomised trial to investigate the frequency and character of arrhythmias during anaesthesia with halothane and the alternative anaesthetic agent, sevoflurane.

Methods 150 children, aged 3–15 years, who needed dental extraction under general anaesthesia were randomly assigned sevoflurane or halothane supplementation of 66% nitrous oxide in oxygen with spontaneous ventilation. The halothane group (n=50) received halothane introduced in 0–75% increments, every two to three breaths, to a maximum of 3–0%, with maintenance at 1–5%. The incremental sevoflurane group (n=50) received sevoflurane introduced in 2% increments increased to a maximum of 8%, with maintenance at 4%. The 8% sevoflurane group (n=50) received sevoflurane introduced at 8%, with maintenance at 4%.

Findings 24 (48%) children receiving halothane had arrhythmias compared with four (8%) receiving incremental sevoflurane (difference 40% [95% CI for differences 24–56] p<0·0001), and eight (16%) receiving 8% sevoflurane (difference 32% [15–50] p=0·0013). Halothane-associated arrhythmias occurred during dental extraction or emergence and were mainly ventricular. Six (12%) children in the halothane group had ventricular tachycardia. The methods of sevoflurane administration did not differ significantly for the frequency of arrhythmias (p=0·357). Sevoflurane-associated arrhythmias were mainly single supraventricular ectopic beats.

Interpretation There was a strong association between halothane and ventricular arrhythmias, especially ventricular tachycardia. The use of sevoflurane in preference to halothane could contribute to a decline in morbidity and mortality associated with dental anaesthesia.

Introduction The use of general anaesthesia in dentistry has substantially decreased in the past 30 years. More than 300 000 general anaesthetics are, however, still administered each year in the UK. Most of these anaesthetics are administered to children requiring dental extractions. Inhalational induction and maintenance of anaesthesia with halothane supplementation of nitrous oxide and oxygen is the most popular technique. Mortality from dental general anaesthesia has not fallen, despite efforts to improve standards of practice and to discourage use of general anaesthesia in dentistry. The cause of death is generally either respiratory difficulty or sudden cardiovascular collapse. The latter may be due to unrecognised vasovagal syncope or ventricular arrhythmias. Arrhythmias are commonly associated with dental extractions and anaesthetic factors, such as hypoxia, hypercarbia, light anaesthesia, and inhalational anaesthetic agents. Ventricular arrhythmias may be involved in the initiation of ventricular fibrillation. Halothane has an established propensity to cause arrhythmias, with a frequency of up to 75% during dental anaesthesia. Sevoflurane is a suitable alternative to halothane. Two different induction techniques can be used with sevoflurane: incremental induction by gradual increase in inspired concentration by 2% every two to three breaths, to a maximum of 8%, or induction with a maximum concentration of 8% for a more rapid effect. In a study that compared sevoflurane and halothane anaesthesia, a lower rate of arrhythmias with sevoflurane was reported on visual analysis of single-lead (lead II) electrocardiographic rhythm strips undertaken by a physician. We did a similar pilot study but found the quality of the recordings to be poor, which made visual analysis difficult and inaccurate.

We did a prospective randomised trial to compare the frequency and characteristics of arrhythmias during anaesthesia was induced and maintained with halothane or sevoflurane. Because of the results of our pilot study, we used a Holter electrocardiograph, which produced better quality recordings than single-lead rhythm strips. This electrocardiograph is manufactured according to performance criteria approved by the American National Standards Institute, and enables objective real-time arrhythmia analysis through automated computer processing.

Patients and methods

Patients

The study was done at the Birmingham Dental Hospital, Birmingham, UK. We obtained local ethics committee approval, written parental consent, and, when appropriate, verbal consent from children. We recruited 156 healthy children not receiving any medication, aged 3–15 years, scheduled to undergo outpatient dental extractions for which inhalational induction of anaesthesia was requested.
mouth) and oral pack were inserted before dental extractions.

Local-anaesthetic infiltrations or blocks, with or without

Children sevoflurane or halothane supplementation of 66%

electrocardiography.

Labelled with randomisation numbers to mask the technician to
device (Oxford Instruments, Abingdon, UK). Continuous
After the last extraction, 100% oxygen was administered. We

Anaesthesia at or around 4%. Group 3 (8% sevoflurane) received

Nitrous oxide in oxygen. No premedication was used. After

Epinephrine, were used. Electrocardiography was stopped when

Patients’ treatment groups. A full electrocardiographic record

Recorded the timings of induction, gag insertion, start of

Extractions, and introduction and cessation of 100% oxygen. No

Premedication was used. After preoperative assessment, chest electrodes were applied and connected to an Oxford Medilog MR 4000 III Holter recording device (Oxford Instruments, Abingdon, UK). Continuous electrocardiographic recordings were produced throughout the perioperative period and stored on a numbered tape. In addition, we monitored children with standard digital pulse oximetry and electrocardiography.

Anaesthesia was administered via nasal masks and a non-

Rebreathing system, with children in the semi-reclining position.

We used recently calibrated vaporisers to deliver the anaesthetic. Group 1 received halothane in 0.75% increments, increased every two to three breaths, to a maximum of 3.0%, with maintenance of anaesthesia at or around 2.5%. Group 2 (incremental sevoflurane) received sevoflurane introduced in 2% increments to a maximum of 8%, with maintenance of anaesthesia at or around 4%. Group 3 (8% sevoflurane) received sevoflurane introduced at 8%, with maintenance of anaesthesia at or around 4%. After induction, a Ferguson gag (to open the mouth) and oral pack were inserted before dental extractions.

After the last extraction, 100% oxygen was administered. We recorded the timings of induction, gag insertion, start of extractions, and introduction and cessation of 100% oxygen. No local-anaesthetic infiltrations or blocks, with or without epinephrine, were used. Electrocardiography was stopped when the patient woke.

The tapes of electrocardiograms were analysed by a trained cardiology technician on an Oxford Holter analyser. Tapes were labelled with randomisation numbers to mask the technician to patients’ treatment groups. A full electrocardiographic record and arrhythmia summary were produced for each patient.

Methods
We used random computerised number generation to assign children sevoflurane or halothane supplementation of 66% nitrous oxide in oxygen. No premedication was used. After preoperative assessment, chest electrodes were applied and connected to an Oxford Medilog MR 4000 III Holter recording device (Oxford Instruments, Abingdon, UK). Continuous electrocardiographic recordings were produced throughout the perioperative period and stored on a numbered tape. In addition, we monitored children with standard digital pulse oximetry and electrocardiography.

Aerohanaesthesia was administered via nasal masks and a non-

Rebreathing system, with children in the semi-reclining position.

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After the last extraction, 100% oxygen was administered. We recorded the timings of induction, gag insertion, start of extractions, and introduction and cessation of 100% oxygen. No local-anaesthetic infiltrations or blocks, with or without epinephrine, were used. Electrocardiography was stopped when the patient woke.

The tapes of electrocardiograms were analysed by a trained cardiology technician on an Oxford Holter analyser. Tapes were labelled with randomisation numbers to mask the technician to patients’ treatment groups. A full electrocardiographic record and arrhythmia summary were produced for each patient.

Results
All three groups were similar for age, weight, number of teeth extracted, and duration of anaesthesia (table 1). Six children were excluded from the study (four who were to receive halothane and two who were to receive incremental sevoflurane) because of lack of cooperation during the setting-up of electrocardiography (figure). No arrhythmias other than occasional supraventricular ectopic beats were seen before anaesthesia was started. Mean maximum and minimum heart rates were similar in all groups, as was the degree of recording artefact (table 2).

The frequency of arrhythmias (all classifications) was higher in the halothane group than in the incremental sevoflurane group (24 [48%] vs four [8%] children; difference 40% [95% CI difference for difference 24–56], p<0.0001) and in the 8% sevoflurane group (eight [16%] children; difference 32% [15–50], p=0.0013). The two sevoflurane groups did not differ significantly (p=0.357).

There was no difference in the incidence of supraventricular ectopic beats between the halothane and the two sevoflurane groups (halothane vs incremental sevoflurane [95% CI difference in rate –3 to 12], p=0.268; halothane vs 8% sevoflurane [-1 to 18], p=0.773; and incremental sevoflurane vs 8% sevoflurane [0·2 to 2·4], p=0.096).

Ventricular arrhythmias (all classifications) occurred in 20 (40%) children receiving halothane compared with only single ventricular ectopic episodes occurring in three (6%) children in the incremental sevoflurane group (20–50, p<0.0001) and in no child in the 8% sevoflurane group. Ventricular couplets and bigeminy occurred exclusively in children who received halothane. In addition, six (12%) children in the halothane group had short runs of ventricular tachycardia. The longest run of tachycardia lasted 5·5 s (16 beats) and the shortest 0·8 s (three beats). One child had 13 separate runs of ventricular tachycardia. Ventricular tachycardia was defined as three or more successive ventricular ectopic beats during which two beat-to-beat intervals exceed 110 beats per min. These episodes of ventricular tachycardia, in common with the other halothane-induced ventricular arrhythmias, occurred during extraction (five children)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Halothane (n=50)</th>
<th>Incremental sevoflurane (n=50)</th>
<th>8% sevoflurane (n=50)</th>
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<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD) age (years)</td>
<td>6±8 (2·3)</td>
<td>7±6 (2·8)</td>
<td>6±6 (2·7)</td>
</tr>
<tr>
<td>Mean (SD) weight (kg)</td>
<td>25±8</td>
<td>26±11</td>
<td>23±9</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>33 (66%)</td>
<td>30 (60%)</td>
<td>28 (56%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>27 (54%)</td>
<td>32 (64%)</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Asian</td>
<td>16 (32%)</td>
<td>12 (24%)</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (12%)</td>
<td>6 (12%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Chinese</td>
<td>1 (2%)</td>
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<tr>
<td>Dentistry data</td>
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<tr>
<td>Mean (SD) duration of anaesthesia (s)</td>
<td>206±74 (2·9)</td>
<td>232±89 (2·9)</td>
<td>228±72 (2·7)</td>
</tr>
<tr>
<td>Mean (SD) number of teeth extracted</td>
<td>3±6 (2·2)</td>
<td>3±0 (1·9)</td>
<td>3±0 (2·3)</td>
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</table>

Table 1: Characteristics of patients

<table>
<thead>
<tr>
<th>Heart rate (beats/ min)</th>
<th>Halothane (n=50)</th>
<th>Incremental sevoflurane (n=50)</th>
<th>8% sevoflurane (n=50)</th>
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</thead>
<tbody>
<tr>
<td>Mean (SD) maximum</td>
<td>144±20</td>
<td>160±22</td>
<td>161±21</td>
</tr>
<tr>
<td>Mean (SD) minimum</td>
<td>73±8.9</td>
<td>73±13</td>
<td>75±12</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All arrhythmias</td>
<td>24 (48%)</td>
<td>4 (8%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>20 (40%)</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>6 (12%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Couplets</td>
<td>11 (22%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bigeminy</td>
<td>17 (34%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Single ventricular ectopic beats</td>
<td>13 (26%)</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Single supraventricular ectopic beats</td>
<td>6 (12%)</td>
<td>2 (4%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Artefact*</td>
<td>9 (18%)</td>
<td>5 (10%)</td>
<td>7 (15%)</td>
</tr>
<tr>
<td>Transient hypoxia</td>
<td>2 (4%)</td>
<td>2 (4%)</td>
<td>3 (6%)</td>
</tr>
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</table>

*Defined as any activity on electrocardiography not part of PQRS complex.

Table 2: Frequency of arrhythmias during anaesthesia in children who had at least one episode
and emergence from anaesthesia (one child). All episodes resolved spontaneously.

Transient episodes of hypoxaemia (oxygen saturation <90% but >88%) happened in seven children. They were related to breath-holding during induction and emergence from anaesthesia, or partial airway obstruction during surgery, which resolved spontaneously or on repositioning of the oral pack. The frequencies were similar in all groups. In the halothane group, two children had relative hypoxaemia and simultaneous ventricular arrhythmias. In the incremental sevoflurane and 8% sevoflurane groups, two and three children, respectively, had hypoxaemia, with no associated arrhythmias.

Discussion

The safety of general anaesthesia in dentistry has received substantial attention in the past decade from Royal colleges and government committees. Despite implementation of recommendations on safe practice identified in the Poswillo report, there has been no decrease in mortality. About two patients die each year, and there were five deaths in 1998. According to data from the National Health Service Executive, about 50% of the known deaths in the past 10 years have been among patients younger than 16 years.

We showed clearly a high frequency of arrhythmias, mainly ventricular, throughout the operative period and during early recovery with use of halothane anaesthesia. It is of particular concern that 12% of children in this group had episodes of ventricular tachycardia. With such a high frequency of ventricular arrhythmias, that reported mortality is so low is perhaps surprising especially since rapid focal ventricular activity may predispose to ventricular fibrillation.

Since most of the ventricular arrhythmias were brief and resolved spontaneously, other complicating factors (eg, undiagnosed hypertrophic cardiomyopathy, viral myocarditis, or high circulating concentrations of endogenous catecholamines associated with fear) may be involved. The possible involvement of other complicating factors in the progression of ventricular arrhythmias, especially ventricular tachycardia, to pulseless ventricular tachycardia, ventricular fibrillation, or both may lead to sudden and unexpected cardiovascular collapse. Although evidence is currently insufficient to substantiate the idea that transient arrhythmias associated with halothane in dental anaesthesia can lead to an established cardiac arrest, we suggest that sustained ectopic ventricular activity even if self-limiting, cannot be ignored. Such arrhythmias, ventricular tachycardia in particular, result in compromised cardiac output and, therefore, decreased oxygen delivery to vital organs. We have shown that such ventricular arrhythmias do not occur during sevoflurane anaesthesia. In addition, inhalational induction with 8% sevoflurane, which allows more rapid induction of anaesthesia, is not associated with any increased likelihood of arrhythmias compared with an incremental induction. We believe, therefore, that sevoflurane is the anaesthetic agent of choice for dental anaesthesia in children. However, the need to lower the number of unnecessary general anaesthetics administered remains important.

Contributors

Michael Blayney, Andrew M alins, and Griselda Cooper all contributed to the background research, and design of the study. Michael Blayney and Andrew M alins supervised recruitment of patients, administration of anaesthesia, and collection of clinical data. All investigators contributed to the writing and critical revision of the paper.

Acknowledgments

We thank the dental and nursing staff of the Day Stay and General Anaesthetic Department, Birmingham Dental Hospital, for their cooperation, Leslie Hubbard, Senior Medical Technical Officer, Cardiorespiratory Unit, George Eliot Hospital, Nuneaton, for analysis of the Holter tapes, and Peter Nighstingale, Statistician, Wolston Computer Laboratories, University of Birmingham, for help with statistical analysis. Oxford Instruments (UK) Ltd provided the Holter recorder and Abbott Laboratories Limited gave financial support.

References

Neuroanatomy of comorbid schizophrenia and learning disability: a controlled study

T L Sanderson, J J K Best, G A Doody, D G Cunningham Owens, E C Johnstone

Summary

Background Reasons for the higher frequency of schizophrenia in learning-disabled populations are uncertain. We investigated the neuroanatomical basis for this phenomenon by structural magnetic resonance imaging (MRI) in patients with learning disability and schizophrenia, learning-disabled patients, and patients with schizophrenia.

Methods Age-matched and sex-matched patients with learning disability (20 cases), schizophrenia (25), and both disorders (23) underwent MRI scans of the brain. Whole brain areas and specific regions of interest were examined. 29 normal controls were also scanned.

Findings The scans of the group with both disorders were closely similar to those of the schizophrenic group, in terms of both general structures and the structure of the amygdala-hippocampus. However, the amygdala-hippocampus was significantly smaller on both sides than that of normal controls (left 4.1 vs 4.5 cm³, p=0.011; right 4.2 vs 4.99 cm³, p<0.0001). The brains of learning-disabled patients were generally smaller than those of the other three groups, but the amygdalohippocampal complexes were larger.

Interpretation In terms of brain structure, patients with comorbid learning disability and schizophrenia resemble patients with schizophrenia and not those with learning disability. We suggest that the higher frequency of schizophrenia in learning-disabled patients is due to a greater tendency of schizophrenic patients to develop cognitive deficits, and that within the learning-disabled population there may be individuals whose deficits result from undiagnosed schizophrenia.

Introduction

Epidemiological studies consistently show that people with mild learning disability have a higher frequency of mental disorder than the general population. The prevalence of mild learning disability in northern Europe is about 0.5%. The point prevalence of schizophrenia in these individuals is about 3%—ie, three times that in the general population. The reasons for this higher frequency are uncertain, but possibilities include that the presence of schizophrenia (whether diagnosed or destined to develop) increases the likelihood of an individual being diagnosed as having learning disability, and that the presence of learning disability increases the likelihood of an individual being diagnosed as having schizophrenia. The former possibility is consistent with the view that cognitive dysfunction, and sometimes motor and social impairment, in childhood may be the initial features of severe schizophrenia. The latter possibility implies that the cognitive deficits of some individuals with learning disability convey an increased susceptibility to develop the impairments associated with schizophrenia. By way of analogy, people with deafness are more susceptible to the development of paranoid psychoses, and the suggested mechanism behind this association is the overload on comprehension imparted by partly understood stimuli.

Knowledge of the biological basis of schizophrenia remains limited, although the view that there are underlying structural brain abnormalities in a large proportion of cases of schizophrenia is widely accepted. Evidence of structural brain abnormalities provided by imaging and post-mortem studies has been assessed alongside data on perinatal events, minor physical anomalies, and childhood development in individuals destined to develop schizophrenia in adult life. These elements have been drawn together to form the basis of the neurodevelopmental hypothesis of schizophrenia. If the view that comorbid learning disability and schizophrenia represents schizophrenia in a very severe form is correct, individuals with this disorder would be expected to have particularly profound neurodevelopmental deficits and to show an exaggeration of the findings in individuals with schizophrenia alone.

We investigated this issue in terms of structural imaging, by examining matched groups of patients with comorbid learning disability and schizophrenia, schizophrenia alone, and learning disability alone. Initial reports of structural imaging in patients with schizophrenia showed enlarged ventricles and reduced brain substance, and these findings have been widely replicated. Such general findings are, of course, not diagnosis-specific, but several structures, particularly the amygdala and hippocampus, are affected to a greater extent than would be expected from the overall reductions in brain volume. The structural brain changes in schizophrenia may thus be classified as general (ie, reduction of brain volume, ventricular enlargement, cortical sulcal dilatation) and focal (eg, reductions in...
We postulated that if comorbid learning disability and schizophrenia represents a particularly severe form of schizophrenia of neurodevelopmental origin, the focal changes in schizophrenia (i.e., the reduction in amygdalo-hippocampal size), will appear in an exaggerated form, and, in general, the brains of the group with both disorders will resemble those of the schizophrenic group. If, on the other hand, the schizophrenic psychosis in the comorbid group is a result of a tendency of people with learning disability to develop psychotic symptoms, probably as a consequence of overload imposed by partial comprehension, the focal changes in the comorbid group will be less than those of the schizophrenic group, and, in general, the brains of the comorbid group will resemble those of the learning-disabled group. Brain structure in all three groups will differ from that of an appropriately matched control group of normal individuals, but the nature of the difference will vary.

**Methods**

**Patients**

We studied patients who took part in a clinical comparison of matched patients with learning disability and schizophrenia, schizophrenia alone, and learning disability alone. The patients with both schizophrenia and learning disability had been identified from the database held by the Information and Statistics Division of the Scottish Health Service. We identified from this database 248 individuals with at least one episode of inpatient care in one of two Scottish health districts between 1970 and 1993, with discharge diagnosis of mild learning disability and schizophrenia. For inclusion in the study, patients were required to be between 16 and 65 years of age, to fulfil research diagnostic criteria for schizophrenia, and to have a premorbid IQ of between 50 and 70 (and thus to have attended remedial education). 39 individuals fulfilled these criteria, were successfully traced, and were willing to participate in the clinical study. Each patient was matched for age (to within 5 years) and sex to both a schizophrenic group, and, in general, the brains of the learning-disabled group. Brain structure in all three groups will differ from that of an appropriately matched control group of normal individuals, but the nature of the difference will vary.

The patients underwent magnetic-resonance-imaging (MRI) scanning on a 1 T Siemens (Erlangen, Germany) Magnetom scanner. Midline sagittal localisation was followed by two sequences to image the whole brain. The first was a turbo spin-echo sequence, which gave simultaneous proton density and T2 weighted images (T R=3500 ms; T E=19 ms and 93 ms; 20 contiguous 5 mm slices acquired in the T alairach plane; field of view 230 mm; matrix size 256×192) which was used to exclude any gross brain lesions. The second scan, for the volumetric analysis, was a three-dimensional turboFLASH (MPRAGE) sequence consisting of an inversion pulse followed by a FLASH collection (flip angle 12°; T R=10 ms; T E=4 ms; T 1=200 ms; relaxation delay time 500 ms; field of view 250 mm), giving 128 contiguous 1.88 mm thick slices in the coronal plane, orthogonal to the T alairach plane.

### Table 1: Volumetric brain analyses in patients and controls

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Mean (SD) raw volume (cm³)</th>
<th>Comorbid group (n=23; group 1)</th>
<th>Learning-disability control group (n=19; group 2)</th>
<th>Schizophrenia control group (n=25; group 3)</th>
<th>Normal controls (n=29; group 4)</th>
<th>One-way ANOVA and post hoc LSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain volume</td>
<td></td>
<td>1236.0 (42.7)</td>
<td>1137.5 (32.0)</td>
<td>1249.3 (133.8)</td>
<td>1326.7 (108.0)</td>
<td>4.99 ≤ 3.62, 3.2, 1.6</td>
</tr>
<tr>
<td>Prefrontal lobe left</td>
<td></td>
<td>65.0 (12.9)</td>
<td>59.3 (13.1)</td>
<td>64.5 (11.3)</td>
<td>70.1 (9.7)</td>
<td>4.92 ≤ 3.62, 3.2, 1.6</td>
</tr>
<tr>
<td>Prefrontal lobe right</td>
<td></td>
<td>72.1 (14.5)</td>
<td>64.4 (11.7)</td>
<td>67.6 (9.8)</td>
<td>74.2 (10.3)</td>
<td>4.6 3.6 3.2 1.6</td>
</tr>
<tr>
<td>Temporal lobe left</td>
<td></td>
<td>74.8 (9.9)</td>
<td>69.3 (13.1)</td>
<td>77.7 (9.8)</td>
<td>79.4 (9.6)</td>
<td>3.6 3.6 3.2 1.6</td>
</tr>
<tr>
<td>Temporal lobe right</td>
<td></td>
<td>77.9 (10.2)</td>
<td>70.9 (11.9)</td>
<td>79.2 (7.7)</td>
<td>82.6 (7.3)</td>
<td>1.6 3.6 3.2 1.6</td>
</tr>
<tr>
<td>Caudate nucleus left</td>
<td></td>
<td>4.8 (0.7)</td>
<td>4.4 (0.9)</td>
<td>5.0 (0.8)</td>
<td>4.3 (0.4)</td>
<td>1.6 3.6 3.2 1.6</td>
</tr>
<tr>
<td>Caudate nucleus right</td>
<td></td>
<td>4.7 (0.7)</td>
<td>4.3 (0.9)</td>
<td>4.9 (0.8)</td>
<td>4.2 (0.5)</td>
<td>1.6 3.6 3.2 1.6</td>
</tr>
<tr>
<td>Lenticular nucleus left</td>
<td></td>
<td>6.5 (1.1)</td>
<td>5.6 (1.3)</td>
<td>6.9 (1.0)</td>
<td>4.7 (0.6)</td>
<td>1.6 3.2 3.4</td>
</tr>
<tr>
<td>Lenticular nucleus right</td>
<td></td>
<td>6.7 (0.9)</td>
<td>5.7 (1.0)</td>
<td>6.9 (0.9)</td>
<td>4.8 (0.6)</td>
<td>1.6 3.2 3.4</td>
</tr>
<tr>
<td>Thalamic nuclei left</td>
<td></td>
<td>6.9 (0.8)</td>
<td>5.6 (1.3)</td>
<td>6.3 (0.6)</td>
<td>6.4 (0.6)</td>
<td>1.6 3.2 3.4</td>
</tr>
<tr>
<td>Thalamic nuclei right</td>
<td></td>
<td>5.9 (0.8)</td>
<td>5.6 (1.3)</td>
<td>6.2 (1.1)</td>
<td>6.1 (0.6)</td>
<td>3.2 3.2 3.4</td>
</tr>
<tr>
<td>Amygdalohippocampal complex left</td>
<td></td>
<td>4.1 (0.7)</td>
<td>4.2 (0.7)</td>
<td>4.3 (0.6)</td>
<td>4.5 (0.5)</td>
<td>4.1 3.2 3.4</td>
</tr>
<tr>
<td>Amygdalohippocampal complex right</td>
<td></td>
<td>4.2 (0.7)</td>
<td>4.3 (0.7)</td>
<td>4.4 (0.6)</td>
<td>4.9 (0.7)</td>
<td>4.1 3.2 3.4</td>
</tr>
<tr>
<td>Lateral ventricle left</td>
<td></td>
<td>7.9 (0.8)</td>
<td>12.7 (5.6)</td>
<td>6.7 (3.4)</td>
<td>5.1 (3.7)</td>
<td>2.3 3.4</td>
</tr>
<tr>
<td>Lateral ventricle right</td>
<td></td>
<td>7.1 (0.2)</td>
<td>11.6 (12.4)</td>
<td>5.6 (3.0)</td>
<td>5.0 (3.6)</td>
<td>2.3 3.4</td>
</tr>
<tr>
<td>Third ventricle</td>
<td></td>
<td>0.6 (0.4)</td>
<td>0.6 (0.6)</td>
<td>0.7 (0.4)</td>
<td>0.4 (0.3)</td>
<td>3.4 3.4</td>
</tr>
<tr>
<td>Fourth ventricle</td>
<td></td>
<td>0.6 (0.2)</td>
<td>0.7 (0.4)</td>
<td>0.5 (0.3)</td>
<td>0.7 (0.4)</td>
<td>2.3 3.4</td>
</tr>
<tr>
<td>Total ventricular volume</td>
<td></td>
<td>16.1 (2.1)</td>
<td>25.6 (28.5)</td>
<td>13.5 (6.3)</td>
<td>11.1 (7.4)</td>
<td>2.3 3.4</td>
</tr>
</tbody>
</table>

LSD=least significant difference.

* n=20, t=22.
Results
Scans were carried out on 23 patients with learning disability and schizophrenia, 20 learning-disabled patients, 25 schizophrenic patients, and 29 normal controls. The mean ages of the individuals were 48·6 years (SE 1·9), 46·3 years (2·4), 51·1 years (1·7), and 42·8 years (1·8), respectively (normal controls p<0·01). The proportions of male individuals were 57%, 45%, 60%, and 45%, respectively.

Whole brain volume could be measured in all 97 scans. The scan of one patient in the learning-disabled group showed substantial disturbance of cerebral anatomy, probably as a result of brain surgery in the postnatal period, and regions of interest could not be assessed. The putamen and globus pallidus could not be measured in one patient in the group with both disorders who had high-intensity signal lesions over the lentiform nuclei. The cause and clinical significance of these findings were uncertain.

The results of the volumetric brain analyses are shown in table 1. The significance levels ranged from 0·0001 to 0·05. Multiple testing was not corrected for since the imposition of an a-priori hypothesis would have been inappropriate in this little-studied area.22 Whole brain volumes in the comorbid and schizophrenic groups were similar to each other, but they both differed significantly from those in the learning-disabled group. The brains of normal controls were significantly larger than those of any other group (figure 1).

The learning-disabled group had the largest ventricular volumes; there were significant differences between this group and the schizophrenic group, except in the case of the third ventricle. Similarly to whole brain volume, the comorbid group resembled the schizophrenic group more closely than the learning-disabled group (figure 1).

Table 2: Comparison of the raw volumes of the amygdalohippocampal complexes showed that there were no significant differences between the groups with schizophrenia, learning disability, or both. Normal controls had the largest amygdalohippocampal complexes.
However, after control for the effects of whole brain volume, the analysis showed that both the left and right amygdalohippocampal complexes were significantly smaller in the comorbid group than in both the learning-disabled group and in normal controls. There was no significant difference between the comorbid and schizophrenic groups in this respect (figure 2). The reason for the greater right/left difference in amygdalohippocampal size in the normal controls is unclear, although the effect of head tilt may be an important factor.

Discussion

Many studies have examined the brain structure of schizophrenic patients by neuroimaging, but studies of patients with learning disability (with or without comorbid psychosis) have been few, and the numbers of patients examined have been small.

The main aim of this study was to assess the extent to which the scans of the comorbid group resembled those of the schizophrenic group and of the learning-disabled group in terms of general brain structure (eg, total brain volume and ventricular size), and the structure of focal areas such as the amygdalohippocampal complex. In schizophrenic patients, these focal areas are smaller than would be expected from the overall reductions in brain volume. Table 1 shows that in terms of the general structures, the comorbid group closely resembles the schizophrenic group. In the learning-disabled group, however, whole brain size is significantly less than that in the other three groups, several structures are smaller than those in one or both of the other groups, and the ventricular spaces are generally larger. When the volumes of focal structures are regarded as a proportion of whole brain volume, the values in the comorbid group are similar to (although slightly smaller than) those of the schizophrenic group, and significantly smaller than those of the learning-disabled group on the left side.

Overall, the structural findings in this study show that the brains of the group with both disorders are very like those of the schizophrenic group, and possibly show greater decreases in volume in the areas where these would be expected. On the other hand, these brains are different from the brains of patients with learning disability in terms of both the general and focal areas addressed. The general areas of the brain are significantly smaller in the learning-disabled group than in the comorbid group, but the focal areas of the brain (ie, the amygdalohippocampal complexes) are significantly larger. These findings support the view that comorbid learning disability with schizophrenia is a severe form of schizophrenia, rather than a consequence of learning disability.

Reduction of amygdalohippocampal size in schizophrenia has been shown in many studies. In an investigation carried out in our department, structural scans of young individuals judged to be at high risk of schizophrenia for genetic reasons were compared with those of age-matched normal individuals with no family history of serious mental disorder, and with age-matched individuals with first-episode schizophrenia. Amygdalohippocampal volume, particularly on the left, was smallest in the confirmed cases; however, volumes in the high-risk individuals were significantly smaller than those in the normal controls. The present study similarly indicates that decreased amygdalohippocampal volume is a feature of schizophrenia, and not of learning disability, although reduction of whole brain volume was shown in individuals with learning disability, as would have been expected from previous work. Although various studies have shown that decreased amygdalohippocampal volume is a feature of schizophrenia, decreased size of medial temporal structures, including the amygdala and hippocampus, has been associated with other disorders, including Alzheimer’s disease and epilepsy. However, such a feature does not seem to be associated with learning disability. The normal control group in this investigation adds clarity to the differences observed between the schizophrenic and comorbid group by highlighting both the general and focal areas where volumetric abnormalities exist in these populations.

The results suggest that within the young learning-disabled population there is a group of patients whose cognitive deficits stem from schizophrenic illness yet to be diagnosed or to become manifest. We studied patients with an IQ of 50–70. Schizophrenia can be reliably diagnosed in individuals with IQs in this range, although in patients with lower IQs, the diagnosis can be difficult. Whether or not some such individuals have an undiagnosed schizophrenic illness (which might be improved by treatment) is a possibility that has yet to be explored.

Contributors

T Sanderson coordinated the scanning procedure and analysed the scans; J Best designed and supervised scanning aspects of the study; G D oody obtained the clinical samples, provided clinical assessments, and analysed data; D C Cunningham Owens provided supervision and training for G D oody; and E Johnstone designed the study, and wrote the first draft of the paper.

Acknowledgments

This study was supported by a project grant from the Wellcome Trust. We thank Julia K estelman and Andrew M cintosh for providing normal control scans; all the patients and controls for their participation; and the many supporting staff for their assistance.

References


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A 26-year-old woman with fever, headache, and a dry cough was admitted in September, 1998, to the Hyogo College of Medicine Hospital with multiple nodules on her chest radiograph. She had no relevant medical history and was in good general health. She had not travelled abroad. Her job was in an electrical appliance shop. Examination on admission showed cervical lymphadenopathy, leucocytosis 16.8×10⁹/L, and eosinophilia (61%). There were no neurological abnormalities and her optic fundae were normal. Chest radiography and computed tomography (CT) showed multiple nodules in both lung fields. The size and location of these shadows changed during her stay in hospital. CT, magnetic resonance imaging (M RI), and ultrasonography of the liver were done. Non-contrast CT showed multiple low-density hepatic nodules. Hepatic-arterial-dominant phase-contrast CT showed several well-defined hepatic nodules. Portal-venous-dominant phase-contrast CT showed homogeneous enhancement of the lesions. M RI findings also suggested an inflammatory process, not a malignant tumour or haemangioma. Histological examination of specimens obtained from liver biopsy and transbronchial lung biopsy showed only extensive eosinophilic infiltration. There were elevated concentrations of immunoglobulin E (IgE, radioimmunosorbent test 1·81 UA/mL). Ouchterlony's double diffusion test showed a precipitin band against the larval excretory-secretory antigen of Toxocara canis. ELISA with the larval excretory-secretory antigen of T canis was positive. There was a small brown itchy nodule on her left ankle on admission. This was thought to be prurigo and was treated unsuccessfully with topical steroids. Similar skin lesions then appeared on the opposite leg.

Histological examination of a skin biopsy specimen showed a focus of eosinophilic and lymphocytic infiltration in the mid to lower dermis. In the centre of the focus was a toxocara larva (figure). She admitted eating raw beef liver in the previous year. She was treated with mebendazole and tiabendazole, but soon stopped treatment because of side-effects. When last seen in October, 1999, she had a slight cough without fever or skin nodules.

Tissue invasion by toxocara larvae was first described in the liver by Beaver.¹ The migration of T canis larvae is usually to the liver and lungs.² Granulomatous lesions in the liver are frequently seen as multiple hypoechoic areas on ultrasonography.³ Pulmonary involvement is characterised by the pulmonary infiltration with eosinophilia syndrome.⁴ T canis larvae can also lodge in the eye, producing endophthalmitis.⁵ Skin lesions in patients with toxocariasis have previously been diagnosed as urticaria due to an allergic reaction.⁶ They are generally associated with eosinophilia, hypergammaglobulinaemia, and fever. T toxocara larvae are the major causative agent of visceral larva migrans in human beings. The parasite invades via the intestines. Other larvae that cause creeping eruptions or cutaneous larva migrans generally invade the skin directly. These larvae do not migrate to the visceral organs at the time of cutaneous infection. Beaver coined the term “visceral larva migrans” to differentiate the condition from cutaneous larval infections.⁷ Although the signs and symptoms of toxocara infection of the liver and lung have been reported, direct detection of toxocara larvae is rare; the diagnosis is usually based on serological tests. The skin may be a previously overlooked target for toxocara larvae.

References
Colorectal hyperplastic polyps and risk of recurrence of adenomas and hyperplastic polyps

Steven P Bensen, Bernard F Cole, Leila A Mott, John A Baron, Robert S Sandler, Robert Haile, for the Polyps Prevention Study Group

We examined data from two large colorectal chemoprevention trials for possible associations of hyperplastic polyps and adenomas with subsequent development of these lesions. Hyperplastic polyps do not predict metachronous adenomas. Hyperplastic polyps are common colonic lesions that are generally considered not to be premalignant, although they may act as markers for the subsequent development of colorectal cancer. Little has been reported on the risk of metachronous adenomas in patients with hyperplastic polyps. We examined data from two large randomised colorectal chemoprevention trials for possible associations of hyperplastic polyps and adenomatous polyps with subsequent development of these lesions.

Patients were participants in two large, multicentre, randomised trials of potential chemopreventive agents for the recurrence of colorectal adenomas in patients with a history of adenomas. In the first trial, 864 patients were randomly assigned treatment in a two-by-two factorial design: placebo, β-carotene, vitamin C and vitamin E, and vitamins C and E plus β-carotene. In the second trial, 930 patients were randomly assigned treatment with calcium carbonate versus placebo. In both studies, patients had at least one histologically-confirmed adenoma removed within 3 months of study entry, with the entire large-bowel mucosa examined and judged free from remaining polyps. Patients were then randomly assigned chemopreventive agents and followed up endoscopically for the development of new polyps. Follow-up colonoscopic examinations were planned for about 1 year after study entry (first surveillance examination) and 3 years later (second surveillance examination). All polyps found on follow-up were biopsied and removed, and histologically reviewed by a pathologist who classified them as neoplastic (adenoma) or non-neoplastic (hyperplastic polyp, lymphoid follicle, &c).

Uniform data were not available about the presence or absence of hyperplastic polyps at initial examination. We therefore studied polyp occurrence after the first surveillance examination, according to the presence or absence of hyperplastic polyps or adenomas at that examination. Of the 1794 patients randomised in the two trials, 1583 completed two follow-up colonoscopies, and are considered in this analysis. We computed crude rates of incidence on hyperplastic polyps and adenomas over the 3-year follow-up after the first surveillance examination with polyp status (type and number) at that examination as predictors. The number of polyps on the first surveillance examination was classified as none, one, or at least two polyps. We used logistic regression analysis to calculate odds ratios of recurrence, and randomised treatment group. Interactions between the main effects were considered through product terms tested with likelihood ratio methods. Separate analyses for the two prevention trials were similar to the combined results, and therefore, only the combined results are presented. All p values are two-sided.

There were more men than women in both studies; however, the characteristics of patients in both trials were similar in age, sex, smoking status, and number of adenomas removed before study entry. Mean length of follow-up after the first surveillance examination was also very similar. At the first surveillance examinations, the starting point for this analysis, 929 (59%) of 1583 patients had no polyps. Patients who had both types of polyps were also more likely to have multiple adenomas or multiple hyperplastic polyps. Of the 126 with both types of polyps, 84 (67%) had two or more adenomas or two or more hyperplastic polyps, while among the remaining 1506, only 183 (12%) had multiple adenomas or multiple hyperplastic polyps.

During the 3-year follow-up, 320 (20%) had one or more hyperplastic polyps detected, and 564 (36%) had one or more adenomas. Crude rates of polyp occurrence during follow-up are shown in table 1 according to polyp status at the first surveillance examination. Patients with hyperplastic polyps at the first surveillance examination had a higher risk of any hyperplastic polyp recurrence on follow-up than those without hyperplastic polyps (odds ratio 3.67, p<0.001). Similarly, patients with adenomas at the first surveillance examination had a higher risk of adenoma recurrence than those without adenomas (2.08, p<0.001). However, the presence of hyperplastic polyps at the first surveillance examination was not significantly associated with adenoma occurrence during follow-up, nor was the presence of adenomas significantly associated with subsequent hyperplastic polyps occurrence. Patients with adenomas and hyperplastic polyps at the first surveillance examination had a particularly high recurrence risk for both types of polyp (table 1). This effect was largely due to the high prevalence in this group of multiple polyps at the first surveillance examination: patients with two or more polyps of either type had particularly high risks of subsequent polyps of the same type, but no substantial increase in risk

<table>
<thead>
<tr>
<th>Polyp status at the first surveillance examination</th>
<th>Hyperplastic polyps on follow-up</th>
<th>Adenomas on follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Odds ratio* (95% CI)</td>
</tr>
<tr>
<td>No polyps</td>
<td>929</td>
<td>137 (15)</td>
</tr>
<tr>
<td>Hyperplastic polyps only</td>
<td>168</td>
<td>73 (43)</td>
</tr>
<tr>
<td>Adenomas only</td>
<td>360</td>
<td>45 (13)</td>
</tr>
<tr>
<td>Both</td>
<td>126</td>
<td>65 (52)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, clinical centre, time between study examinations, and treatment group.

Table 1: Crude rates of polyp occurrence during follow-up and adjusted odds ratios according to polyp presence at first surveillance examination
Polyp multiplicity status at the first surveillance examination

<table>
<thead>
<tr>
<th>Number of hyperplastic polyps</th>
<th>N</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1289</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>198</td>
<td>3.67 (2.62–5.14)</td>
</tr>
<tr>
<td>≥2</td>
<td>96</td>
<td>6.91 (4.38–10.88)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of adenomas</th>
<th>N</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1097</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>228</td>
<td>0.92 (0.64–1.32)</td>
</tr>
<tr>
<td>≥2</td>
<td>198</td>
<td>1.03 (0.69–1.53)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, clinical centre, time between study examinations, and treatment groups.

Table 2: Odds ratios of polyp occurrence during the follow-up according to polyp multiplicity at first surveillance examination of the other type of polyp (table 2). There were no significant interactions among polyp-multiplicity variables when predicting risk of hyperplastic polyp (p=0.4) or adenoma (p=0.3).

The strength of this study is that we evaluated incident polyps in a well-defined population, and patients were followed up uniformly. The limitation of this study is that it does not assess the risk of subsequent adenomas or hyperplastic polyps in patients with no history of adenomas. Several lines of evidence are consistent with the hypothesis that hyperplastic polyps act as markers for synchronous or metachronous colorectal neoplasia. However, we found that adenomatous and hyperplastic polyps did not predict each other’s occurrence. This suggests that hyperplastic polyps and adenomatous polyps reflect different biological processes.


Epidemic of obesity in UK children

John J Reilly, Ahmad R Dorosty

Data from a nationally representative sample of 2630 English children show that the frequency of overweight ranged from 22% at age 6 years to 31% at age 15 years and that of obesity ranged from 10% at age 6 years to 17% at age 15 years. The definition of obesity in childhood and adolescence has been debated, but now use of body-mass index (BMI; weight/height²) is recommended. In children BMI must be interpreted in relation to population reference data. The consensus is that children and adolescents with BMI above the 85th centile should be defined as overweight, and those with BMI above the 95th centile defined as obese. The obesity definition has clinical meaning: children with BMI above the 95th centile are likely to be relatively fat, and obesity defined in this way has a strong tendency to persist and is associated with morbidity. The aim of our study was to provide current estimates of overweight and obesity prevalence in English children and adolescents.

Correspondence to: Dr Steven P Benson

<table>
<thead>
<tr>
<th>Age-group</th>
<th>n</th>
<th>Proportion overweight (%)</th>
<th>Proportion obese (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>154</td>
<td>22.1</td>
<td>11.7</td>
</tr>
<tr>
<td>Girls</td>
<td>144</td>
<td>21.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Total</td>
<td>298</td>
<td>21.8</td>
<td>10.4</td>
</tr>
<tr>
<td>7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>144</td>
<td>25.7</td>
<td>9.0</td>
</tr>
<tr>
<td>Girls</td>
<td>136</td>
<td>17.6</td>
<td>11.8</td>
</tr>
<tr>
<td>Total</td>
<td>280</td>
<td>21.8</td>
<td>10.4</td>
</tr>
<tr>
<td>8 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>136</td>
<td>24.3</td>
<td>11.8</td>
</tr>
<tr>
<td>Girls</td>
<td>159</td>
<td>20.7</td>
<td>13.2</td>
</tr>
<tr>
<td>Total</td>
<td>295</td>
<td>22.4</td>
<td>12.5</td>
</tr>
<tr>
<td>9 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>131</td>
<td>25.2</td>
<td>13.0</td>
</tr>
<tr>
<td>Girls</td>
<td>116</td>
<td>19.0</td>
<td>9.5</td>
</tr>
<tr>
<td>Total</td>
<td>247</td>
<td>22.3</td>
<td>11.3</td>
</tr>
<tr>
<td>10 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>135</td>
<td>23.0</td>
<td>9.6</td>
</tr>
<tr>
<td>Girls</td>
<td>117</td>
<td>23.9</td>
<td>11.1</td>
</tr>
<tr>
<td>Total</td>
<td>252</td>
<td>23.4</td>
<td>10.3</td>
</tr>
<tr>
<td>11 years</td>
<td></td>
<td></td>
<td></td>
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All observed frequencies were significantly different from expected values of 15% (overweight) and 5% (obesity) at p<0.01, except for overweight prevalence in 7-year-old and 9-year-old girls.

Prevalence of overweight and obesity

The Health Survey for England 1996 (Data Archive, University of Essex) was a cross-sectional survey in a representative sample of English children and adolescents. Height (to 0.1 cm with a portable stadiometer) and weight (to 0.5 kg, with portable scales, in light indoor clothing) were measured in 2630 children aged 6–15 years. The survey was approved by relevant ethics committees. BMI was compared with UK reference data for BMI by means of software provided by the Child Growth Foundation (London). These reference data represent a compilation of 11 UK surveys carried out between 1978 and 1990. Current recommendations set the expected frequency of overweight at 15% (BMI >85th centile) and obesity at 5% (BMI >95th centile). Changes in BMI reference data to take account of secular trends in BMI would obscure those trends so the UK reference data were used as a baseline against which subsequent surveys of obesity prevalence should be compared. Differences between observed and expected frequencies above the cut-offs for overweight and obesity were tested for significance by χ² goodness-of-fit tests.

Frequencies of overweight and obesity significantly (p<0.01) exceeded expected frequencies in almost all age-groups (table). Differences in the frequency of obesity between boys and girls were not significant. The frequency of obesity was generally higher in the older age-groups (figure). These findings show that the epidemic of obesity in the UK is not confined to adults, and that overweight and obesity are...
much more common than expected in English children and adolescents. We have described elsewhere a high frequency of obesity in children and adolescents in the UK, and this study shows that the frequency increases throughout childhood (figure). Our results do not provide encouragement that public-health targets aimed at reducing obesity can be met.

We have described a rapid increase in overweight and obesity, between the construction of the UK 1978–90 reference data and the time of the Health Survey (1996). This increase reflects a rapid shift towards positive energy balance resulting from societal changes in lifestyle, which altered population energy intake, energy expenditure, or both. As in the USA, these changes are apparent once children reach the age of 3–4 years, and the evidence for lower energy expenditure is stronger than that for increased energy intake. In UK children aged 1.5–4.5 years, mean energy intake fell by 20% between 1967 and 1992, yet the frequencies of overweight and obesity increased during this period. Although there are no comparable data for older children and adolescents in the UK, this trend constitutes strong, if indirect, evidence for reduced habitual physical activity as the major cause of increasing obesity in children and adolescents.

Inactivity, particularly watching television, is predictive of subsequent overweight and obesity in children and adolescents, and the amount of time spent watching television by 4–15-year-olds in the UK has doubled since the 1960s. In certain diseases of childhood, such as childhood leukaemia, lifestyle changes associated with lower habitual activity are also known to promote obesity.

Our study will have underestimated the magnitude of the obesity problem in children and adolescents in the UK for several reasons. First, secular trends in fatness of children suggest that prevalence of obesity will be higher in Scotland than in England. However, no Scottish data on obesity prevalence are available (children were not included in the equivalent health survey for Scotland). Second, the definition of obesity we used, based on BMI, underestimates obesity prevalence. The BMI is a proxy for excessive fatness rather than a direct measure of fatness, and is specific (identifies few non-obese children as such) but insensitive (fails to identify large numbers of excessively fat children). Finally, we analysed the most recently available Health Survey data (1996), but a continuation of the trends we have described would lead to even higher prevalence of overweight and obesity. In view of the adverse health implications of obesity in childhood and adolescence, and increasing evidence that childhood overweight and obesity make significant contributions to adult disease, greater public-health efforts to address the problem should be contemplated.

We thank Jan Love for statistical advice, and Lawrence Weaver and Alison Wood for helpful comments on the paper. AD is funded by the Iranian Ministry of Health and Medical Education. Data from the Health Survey for England were used with the permission of the Data Archive, University of Essex. The Health Survey was carried out by the Joint Health Survey Unit, Social and Community Policy Research, University College London. The survey was funded by the Department of Health.

Association between cerebral palsy and coagulase-negative staphylococci

Robert Mittendorf, Nancy Roizen, Atef Moawad, Babak Khoshnood, Kwang Sun Lee

Coagulase-negative staphylococci were cultured from the space between the placental membranes at delivery in four of five neonates who were later diagnosed with cerebral palsy, and in 26 of 102 neonates who were not found to have the disorder (p=0.02). During the past few years, several investigators, most notably Nelson and colleagues, have shown that certain indicators of perinatal infection, such as chorioamnitis and premature rupture of the placental membranes, predict cerebral palsy independently of low birthweight and preterm birth. However, no specific bacteria have been significantly associated with cerebral palsy.

To study further this relation, we took cultures from the placental chorioamniotic space of mothers taking part in the Magnesium and Neurologic Endpoints (MagNET) Trial immediately after preterm delivery. With a technique modified from that of Hillier and colleagues, which avoids bacterial contamination from the vagina, we obtained cultures for aerobes, anaerobes, ureaplasma, mycoplasma, and chlamydia, by aseptic separation of the amnion from the chorion; we then cultured the inner surfaces distant from the opening in the membranes. Of the preterm neonates studied in the MagNET trial, the presence or absence of cerebral palsy at 18 months of age was known in 122. We obtained cultures from 107 (88%) of these neonates. Babies from whom cultures were not obtained did not differ in any substantial way from those in whom cultures were obtained.

Of the 107 cultures, 37 grew no microorganisms, 41 grew pure isolates of one species, and 29 grew mixed isolates. Coagulase-negative staphylococci were the bacteria most commonly cultured at delivery: 30 of 107 cultures were positive. Escherichia coli, mycoplasma, and ureaplasma were the next most prevalent, being found in 14 of 107, 13 of 107, and seven of 107, respectively. At the 18-month assessment,
five of 107 children from whom membrane cultures were obtained and who remained in the trial for follow-up, were found to have cerebral palsy (one additional child found to have cerebral palsy had no culture sample obtained at delivery). Two of these children had mild hemiplegia, one had moderate hemiplegia, two had diplegia and mild hemiplegia, and one had spastic quadriplegia and extrapyramidal involvement (mixed cerebral palsy). All assessments were done by a developmental paediatrician (N R) who was unaware of the bacteriological results. Membrane cultures for four of the five children with cerebral palsy grew isolates of coagulase-negative staphylococci, whereas only 26 of 102 children without cerebral palsy had positive cultures (p=0.02, two-sided Fisher’s exact test). Two of the four isolates from children with cerebral palsy were pure cultures of coagulase-negative staphylococci, and two were mixed cultures of coagulase-negative staphylococci and other bacteria. In the one case of cerebral palsy in which the chorioamniotic culture grew no microorganisms, a microscopic review of the culture discovered grape-like clusters of gram-positive cocci. Thus, coagulase-negative staphylococci may have been present at delivery in the membranes of this child as well.

To find out whether potential confounding, such as birthweight, might account for this association, we assessed 16 suspected or known predictors of cerebral palsy. By univariate analysis, we found that five of these 16 possible risk factors had p values less than 0.10 (coagulase-negative staphylococci, p=0.02; neonatal seizures or abnormal electroencephalogram, p=0.01; and non-verbal presentation, p=0.07). In a multivariate logistic regression model in which we controlled for these variables, the presence of coagulase-negative staphylococci in the chorioamniotic space remained highly significant (adjusted odds ratio 37.7 [95% CI 3.0–377], p=0.003).

The hypothesis we have generated—an association between coagulase-negative staphylococci and cerebral palsy—requires further testing, and large future studies may find significant associations between cerebral palsy and other species of bacteria. From these data, however, only coagulase-negative staphylococci were associated with cerebral palsy. Despite the fact that these bacteria are commonly thought of as contaminants, recent published studies have shown the substantial pathogenicity of their virulence factors, which include hyaluronidase, deoxyribonuclease, and adhesins.
Suicide among patients with cancer cared for at home by palliative-care teams

Carla Ripamonti, Antonio Filiberti, Amadio Totis, Franco De Conno, Marcello Tamburini

Patients with terminal cancer are thought to be at high risk of committing suicide. In a population of 17 964 patients with terminal cancer cared for at home by 12 palliative-care teams, five patients committed suicide. We speculate that further treatment or contact with the health-care system is not possible to determine whether the frequency of suicide differs with respect to those patients who did not use home palliative-care programmes because we have not included a control group for ethical reasons. Rates of suicide in the general population resident in the same area (Lombardy) yield standardised mortality ratios (SMR=observed suicides/expected suicides) of 15 for men (0·027%) and 33 for women (0·026%) were recorded (figure). Of these, two were women (breast cancer, melanoma) and three were men (bladder, lung, and unknown primary cancer site). Mean age was 65 years (range 50–76) and the duration of home care by the palliative-care team was a median 30 days. Two patients jumped out of a window, two shot themselves, and one took an overdose of morphine. Patients were usually seen every day, which makes the underestimation of suicide unlikely even if this occurred by drug overdose.

Our findings are similar to a study carried out on 72 633 patients with terminal cancer admitted to 43 palliative-care units over 5 years, which reported 21 suicides (0·029%). It is not possible to determine whether the frequency of suicide differs with respect to those patients who did not use home palliative-care programmes because we have not included a control group for ethical reasons. Rates of suicide in the general population resident in the same area (Lombardy) yield standardised mortality ratios (SMR=observed suicides/expected suicides) of 15 for men (3/0·2) and 33 for women (2/0·06). The expected number of suicides was estimated by multiplying age-specific and sex-specific suicide
mortality rates from the Lombardy region from 1986–87 by the corresponding person-years of observation. The frequency of suicide in our patients was lower than that of patients near the time of diagnosis. For example, from 1987 to 1994, in central Italy, 18,566 patients with cancer died and 41 (0·2%) of these cases were registered as suicides. The highest risk was during the first 6 months after diagnosis.1

Our study shows that suicide among patients with terminal cancer is rare. We cannot state whether this is due to the input of palliative-care service, but can only speculate that an adequate and continuous symptomatic treatment and psychosocial support given to these patients may reduce the risk. However, comparative data are required.


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Role of microvascular decompression in trigeminal neuralgia and multiple sclerosis

Giovanni Broggi, Paolo Ferroli, Angelo Franzini, Mauro Pluderi, Loredana La Mania, Clara Milanese

An excellent outcome after microvascular decompression for medically intractable trigeminal neuralgia in patients with multiple sclerosis is reported in seven of 15 cases. A dual cause could be hypothesised in some patients with multiple sclerosis and trigeminal neuralgia, and that microvascular decompression can be a therapeutic option.

Due to the efficacy of microvascular decompression, vascular compression of the trigeminal root is considered the main contributory factor in idiopathic tic douloureux. In patients with multiple sclerosis (MS), a demyelinating lesion at the trigeminal-root entry zone is the accepted cause, and MS has long been thought to be a contraindication to microvascular decompression. With approval from the institutional ethics board and informed consent, 15 patients with MS by Poser’s criteria and medically intractable typical trigeminal neuralgia underwent microvascular decompression, between 1994 and 1998.

All patients underwent magnetic resonance imaging (MRI; sagittal T1 [axial and coronal intermediate]; and T2-weighted images). In ten patients, sequences for magnetic resonance tomographic angiography were obtained to disclose possible vascular compression. Trigeminal neuralgia was the presenting symptom of MS in six patients. All patients had previously been given medical treatment (carbamazepine, phenytoin, baclofen). Five percutaneous radiofrequency rhizotomies and five percutaneous balloon microcompressions had been done previously. Four patients had been given steroids at the onset of trigeminal neuralgia. Five had immunosuppressants. The trigeminal nerve was exposed through a small, key-hole, retromastoid craniectomy, and was examined microsurgically for vascular compression at trigeminal-root entry zone and along the whole cisternal course. Vascular compression was defined as severe (clear groove on the trigeminal root) or mild (contacts without root distortion) by the surgeon (GB) and by a retrospective independent observer on videotapes. Any compressive artery was dissected free and maintained away from the nerve and its root entry zone through small teflon pads. Compressive veins were electrocoagulated and divided. The outcome was graded by an independent reviewer. Mean follow-up was 25 months (table).

In one patient, complete pain relief was obtained after a second microvascular decompression, 10 months after the first operation. In patients with medically tractable recurrence, postoperative drug dose was lower than before. The mean recurrence time was 13·5 months. Six patients with medically intractable recurrence were compared with nine patients with complete pain relief without medication (n=7) or with medically tractable recurrence (n=2). The mean duration of trigeminal neuralgia was 5·8 years versus 5·0 years and the mean duration of MS was 16·0 years versus 12·6 years. The clinical course of MS was relapsing remitting in three versus five, secondary progressive in three versus two, and primary progressive in none versus two patients. The preoperative expanded disability status scale was 4·5 versus 3·5 and MRI T2-hyperintensity along pontine trigeminal pathways was observed in three versus two patients.

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pontine trigeminal pathways was present in six versus six patients. Vascular compression was severe in two versus seven and steroids at onset of trigeminal neuralgia were given to one versus six patients. Preoperative immunosuppressant therapy was administered in one versus four patients (table). Variables were compared with two-sample t test or Fisher's exact test, as appropriate. No significant prognostic factor was found. There was no mortality or long-term morbidity.

The high incidence of vascular compression at trigeminal-root entry zone suggests a causal relationship rather than a chance association, whereas the 40% of failures of microvascular decompression in our series questions the possible causative role of vascular compression in patients with MS and trigeminal neuralgia. The causal role of vascular compression is debated even in trigeminal neuralgia and a simple cause-effect mechanism has not yet been established. A more complex balance between the excitability threshold of neurons of the trigeminal nucleus, and possible pathological inputs from the compressed trigeminal root of entry zone might be considered. In patients with MS and trigeminal neuralgia, with vascular compression at operation, a dual cause could be hypothesised; the action of vascular compression might be facilitated by the underlying hyperexcitability of trigeminal pathways due to evolving demyelination. This might explain not only the higher incidence of trigeminal neuralgia in patients with MS, but also the worse results obtained by both microvascular decompression and percutaneous procedures in patients with MS and trigeminal neuralgia than in the series of essential trigeminal neuralgia. A direct relation between post-operative sensory deficits and the cure rate still limits percutaneous methods in patients with MS. Disease progression is likely to cause neurological deficits and recurrences of trigeminal pain; the possibility of obtaining long-term relief of trigeminal neuralgia without damaging the nerve should not be denied to patients with MS. An ad-hoc M RI protocol should be used to select MS patients with MS and trigeminal neuralgia as surgical candidates.


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Treatment of traumatic bleeding with recombinant factor VIIa

Gilli Kenet, Raphael Walden, Arieh Eldad, Uri Martinowitz

Surgical intervention failed to stop life-threatening bleeding caused by injury complicated by severe coagulopathy. Administration of recombinant factor VIIa immediately corrected the coagulopathy and bleeding stopped.

A 19-year-old soldier was admitted with a high-velocity rifle injury. The bullet tore the inferior vena cava at L5 level causing extensive damage to paravertebral muscles at the exit wound. He was admitted in a critical condition with profound hypovolaemic shock, ketoacidosis, hyperthermia, and disseminated intravascular coagulation. Ligation of the inferior vena cava was done immediately, yet surgical attempts to achieve haemostasis (including repeated packing) and attempts to correct the ketoacidosis and hyperthermia failed to control bleeding. He received 5 L packed cells, 3 L fresh frozen plasma, 20 units of platelets, and 10 units of cryoprecipitate with tranexamic acid. He continued to bleed at a rate of 300 mL/min and a fatal outcome seemed inevitable.

In a desperate attempt to control the bleeding, 60 µg/kg of recombinant factor VIIa were given intravenously. 10 min after injection, coagulation tests improved markedly, the rate of bleeding decreased to 10–15 mL/min but slow oozing from all wound surfaces continued. After 1 h a repeat dose of recombinant factor VIIa (60 µg/kg) was given. The oozing stopped immediately with a return to normal of coagulation tests, enabling surgeons to identify and ligate some small vessel tears. Fibrin sealant was sprayed over the area to prevent rebleeding. The patient’s condition remained stable, and he had no further blood loss.

Recombinant factor VIIa is an effective treatment for patients with haemophilia with inhibitors. Its mode of action is not completely clear. Some studies suggest tissue-factor-dependent mechanisms, whereas others emphasise the role of factors Xa and IXa on the surface of activated platelets. These studies relate thrombin generation on activated platelets to the high level of recombinant factor VIIa binding to platelet surfaces. Therapeutic doses of recombinant factor VIIa are not established; different doses have been used during surgery in patients with haemophilia and inhibitors. The use of recombinant factor VIIa has been reported to control bleeding in patients with thrombocytopenies, liver disease, liver transplantation, and patients undergoing cardiac surgery. Due to its thrombogenic potential, recombinant factor VIIa has been contraindicated for use in patients with severe disseminated intravascular coagulation or crush injuries. The successful use of recombinant factor VIIa in Dengue fever with bleeding and in the case we report suggests that this contraindication should be re-evaluated.


2 Monroe DM, Hoffman M, Oliver JA, Roberts HR. Platelet activity indication should be re-evaluated.


5 The 5th Novo Nordisk Symposium on the treatment of bleeding and thrombotic disorders. Copenhagen, Denmark, M ay 7–8, 1999

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Topical N-acetylcysteine for lamellar ichthyosis

Pedro Redondo, Ana Bauzá

The antioxidant N-acetylcysteine has an antiproliferative effect on a culture of human keratinocytes. We report a patient with lamellar ichthyosis satisfactorily treated with topical N-acetylcysteine.

Topical therapy of ichthyosis consists of emollient creams, ointments, and bath oils. In addition, keratolytic agents such as α-hydroxy acids, propylene, and urea preparations can produce some improvement. Topical retinoids have been shown to help, although they should be used cautiously to avoid irritation. N-acetylcysteine (NAC) is a thiol that reacts with reactive oxidative intermediates and replenishes the intracellular cysteine necessary for the production of glutathione, an endogenous antioxidant.1

Cultures of keratinocytes were prepared from the skin of human female breast.2 To examine the effect of NAC on cell proliferation, second-passage keratinocytes were incubated under serum-free, low-calcium conditions, with 0.5–30 mmol/L NAC and cell numbers determined. NAC dose-dependently suppressed the incorporation of 3H-thymidine in keratinocytes (figure 1). Median inhibitory concentration for NAC was 10 mmol/L, and the inhibitory effect of NAC was time dependent (data not shown). Cell viability as determined by trypan-blue exclusion assay and propidium-iodide staining indicated that 95% of cells were viable after incubation with 20 mmol/L NAC for 3 days. Inhibition of keratinocyte proliferation by NAC is therefore not due to the cytotoxic effect of this drug.

A 33-year-old woman with lamellar ichthyosis had been treated for 2 years with 30 mg acitretin daily and topical urea lotions. She presented large and dark scales with a 10% NAC (Sigma, Madrid, Spain) was prepared. Placebo consisted of the same emulsion without NAC. She was instructed to apply each preparation twice daily on the skin of opposite forearms (initially randomly selected). Preparations were applied without occlusion and followed thoroughly. 5 weeks later, there was outstanding improvement. No changes were observed in placebo-treated areas (figure 2).

NAC has been used as a mucolytic agent in various pulmonary disorders and as an antidote for acetaminophen overdose.3 Lamellar ichthyosis is a congenital disorder, associated with a greatly increased epidermopoiesis.4 The dermatological usefulness of NAC has not been previously reported, although topically applied NAC can prevent skin irritation resulting from radiotherapy5 and protects from sun-induced erythema. NAC is labile and tends to break down, releasing sulphur-containing compounds. The water-in-silicone emulsion improves stability and reduces malodour. Recent studies show that NAC suppresses proliferation of NIH3T3 fibroblast cells, and this antiproliferative effect is mediated by reversible blocking cell-cycle progression in G1 phase.6 Because NAC is an atoxic and hypoallergenic aminoacid derivative with successful therapeutic uses and rare side-effects, it may be useful in the treatment of hyperproliferative skin disorders.


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NEWS

Dexfenfluramine side-effects confirmed in new study

Dexfenfluramine, the appetite-suppressing drug, is associated with an increase in abnormal valve regurgitation, confirms a new study. The valve problems seem to regress when drug therapy is stopped but, says lead author Bruce Shively, “that this drug increases the risk of valve regurgitation at all renders it unsuitable for the treatment of obesity”.

COX-2 inhibitors gain more support for use in arthritis

Cyclo-oxygenase-2 (COX-2) inhibitors cause fewer gastrointestinal side-effects than non-steroidal anti-inflammatory drugs (NSAIDs) in people with arthritis? Two new studies suggest that they do, but an accompanying editorial warns that these agents should be reserved for patients at high risk of gastrointestinal problems.

In the first study, 1149 patients with rheumatoid arthritis were randomly assigned the COX-2 inhibitor celecoxib, the NSAID naproxen, or placebo. Both drugs were better than the placebo at improving the symptoms of arthritis. However, 26% of patients receiving naproxen developed gastroduodenal ulcers, compared with 4-6% of patients taking celecoxib and 4% taking placebo (JAMA 1999; 282: 1921–28).

The second study compared rofecoxib, another COX-2 inhibitor, to placebo and various NSAIDs in 5435 patients with osteoarthritis. The cumulative frequency of upper gastrointestinal perforations, ulcers, and bleeding during 12 months was less than 8 months before assessment, but in only 15-7% of patients who had not taken the drug in the previous 8 months (Circulation 1999; 100: 2161–67).

After being in use for 10 years, dexfenfluramine was withdrawn from the market in the USA and Europe in 1997, when reports of its link with valve abnormalities were published. André Scheen (Division of Diabetes, Nutrition and Metabolic Disorders, University of Liège, Belgium) agrees that the 7-6% prevalence of abnormal valve regurgitation shown by Shively’s study is “unacceptable” and Shively concludes that dexfenfluramine’s side-effects, its patchy results in inducing long-term weight loss, and its inability to alter any obesity-related outcome make it “history”. The news on Nov 23 that a US judge has given preliminary approval to a US$3-75-billion settlement between American Home Products and people who took their anti-obesity therapy containing dexfenfluramine adds to this view.

Kathryn Senior

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Neuritic plaques detected non-invasively

Researchers in the USA have used magnetic resonance microscopy (MRM) to produce the first three-dimensional, images of neuritic plaques in necropsy tissue from patients with Alzheimer’s disease. The plaques look like “small round balls, basically spots of garbage, floating in space”, says lead investigator Helene Benveniste (Duke University Medical Center, Durham, N.C., USA). It may be possible to use the technique to follow the progression of amyloid-positive brain lesions in vivo but Benveniste warns that neuritic plaques may not be the best marker for early Alzheimer’s disease.

Benveniste and co-workers used MRM, a technique which produces much higher resolution images than conventional MRI, to study hippocampal tissue from five patients with Alzheimer’s disease and three non-demented people within hours of death. Because of variability in specimen preparation, “we were lucky to find two specimens that were solid”, admits Benveniste. But despite “loose ends”, the study shows that plaques can be imaged non-invasively, she concludes (Proc Natl Acad Sci USA 1999; 96: 14079–84). MRM studies in transgenic mice which overexpress β-amyloid are now underway to try to document brain changes over time.

Paul Coleman, head of the University of Rochester Alzheimer’s Disease Center (NY, USA), notes that “the paper starts with the statement that neuritic plaques are the neuropathological hallmark of Alzheimer’s disease, but that is not universally agreed to”. A recent consensus conference “emphasised the [neurofibrillary] tangles, not the plaques. Even if we grant the statement about plaques, the method only shows amyloid deposits, which may or may not be associated with the dystrophic neurites of neuritic plaques”.

Benveniste agrees that plaques may not be a causal factor in Alzheimer’s disease, but “if you can visualise the plaque in vivo to see how its development relates to cognitive behaviour, you can answer the question of cause and effect”. However, she says, there are suggestions that hippocampal atrophy might be a better early marker of disease than plaques. And though “we don’t have the resolution yet to see plaques in the mice, we can see the progression of atrophy over time, and this seems to correlate with the hippocampal atrophy seen in people with Alzheimer’s disease”. If this is the case, she says, it might be possible to use mice to test new drugs for Alzheimer’s disease. Perhaps so, says Coleman, “but only if transgenic mice making plaques represent an adequate model of the human condition”.

Marilyn Larkin

Embryonic grafts have long-term benefits in Parkinson’s disease

Dopamine release has been restored to normal rates, and disease symptoms have markedly improved in a patient with Parkinson’s disease who received embryonic nigral transplants 10 years ago, report Paola Piccini (Imperial School of Medicine, London, UK) and co-workers.

In 1989, Piccini and colleagues implanted dissociated ventral mesencephalic tissue (taken from human embryos at routine suction abortions) into the right putamen of a 59-year-old man with Parkinson’s disease resistant to conventional treatment. The patient showed a marked clinical improvement during the first 3 postoperative years; levodopa and immunosuppressive drugs were stopped at 32 and 64 months, respectively. However, owing to axial progression of symptoms and in the limbs ipsilateral to the graft, low-dose levodopa was restarted at 74 months, to which the patient responded well; motor functions and levodopa dose remained unchanged thereafter. 10 years on, he has no rigidity, only minor hypokinesia, intermittent resting tremor, and no “on-off” fluctuations (Nat Neurosci 1998; 2: 1137–40).

To measure dopamine release from the graft, the researchers studied binding of the dopamine D2 receptor antagonist [3H]-raclopride using positron emission tomography. [3H]-raclopride binding was normal in the grafted putamen, but was 43·7% higher than that of normal individuals in the non-grafted putamen.

According to Roger Barker (University of Cambridge, UK), “the really important messages” of the study are that “such grafts can survive for a decade in the Parkinsonian brain (whilst the patient’s own dopaminergic neurons continue to be lost), and continue to exert a clinical benefit, releasing dopamine in a tonic and regulated fashion”.

Steve Dunnett, also of the University of Cambridge, says “it is an elegant piece in a puzzle. It is not a ‘breakthrough’, but then neither are 99% of the ‘breakthroughs’ proclaimed by the media. It is a fine study nevertheless”.

Khabir Ahmad

Unusual case of identical triplets reported

The assisted-reproduction team at C línica Quirón, Barcelona, Spain, announced on Nov 10 the rare case of identical triplets who shared a placenta yet had their own amniotic membranes.

After in-vitro fertilisation by means of intracytoplasmic sperm injection, four embryos had been introduced into the womb of a 37-year-old patient; only one implanted. Serial ultrasonographs done after embryonic implantation showed first a bipartition and then a tripartition. At 34 weeks’ gestation, three identical boys were born by caesarean section. After the births, genetic tests confirmed that the triplets had an identical genetic make-up.

Marisa López-Tejón, a specialist at the Assisted Reproduction Unit, says that this case is like a “natural cloning” and that only one similar case has been previously reported in France in 1995. She explains that the pregnancy, as with any multiple pregnancy, was defined as high risk. However, because each triplet developed in its own amniotic membrane, the babies’ chances of surviving were probably improved.

López-Tejón points out that 98% of triplets come from different ova, and hence each embryo has its own placenta and amniotic membrane. However, in the 2% of cases where triplets arise from a single ovum, the three fetuses develop within one or two amniotic membranes. So the unusual aspect of this case is that each triplet had its own membrane. In López-Tejón’s opinion, this sort of unusual tripartition may be triggered by the manipulation techniques and the ovarian hyperstimulation used in assisted-reproduction procedures.

Xavier Bosch
Few therapies exist for drug addiction, and unfortunately one agent that has shown promise—the plant alkaloid ibogaine—is mostly given in unsafe settings by addict self-help groups, says Deborah Mash (University of Miam, FL, USA).

This means there is a 'poverty of clinical data' on the effects of the preparation. However, Mash now has preliminary findings from almost 100 patients, and at a series of talks in the UK this month, she presented her results and called for further research to be top priority.

Ibogaine's anti-addictive properties have been shown in animals; in human beings, ibogaine often causes "dream-like states" at treatment doses but is quickly cleared from the bloodstream. The persistent metabolite noribogaine should act to raise mood, ward off craving, and help an addict enter long-term therapy via its actions on both the serotonin transporter and on opiate receptors µ and κ (see Lancet 1998; 352: 1298).

After a single treatment, Mash's team found that Beck Depression Inventory scores improved significantly (mean 18 vs 4), and remained low for at least a month. There were also significant decreases in craving scores and in physician-rated signs of opiate withdrawal.

Adverse events during the acute treatment phase were nausea, vomiting, mild tremors, and transient ataxia; initial drops in heart rate and blood pressure occurred in a few patients, mainly "crack" cocaine abusers. "Whether the visions are profound experiences associated with ibogaine that can be life-transforming", notes Mash, "but there are very profound experiences associated with ibogaine that can be life-transforming".

Despite these promising results, further drug development is likely to be hindered by continuing controversies. Ongoing litigation over patent rights between the University of Miami and Howard Lotosf, the discoverer of ibogaine's anti-addictive effects, seems likely to deter potential investors. In addition, some experts have reported cerebellar Purkinje-cell loss in rats treated with high doses of ibogaine. However, Mash found no such damage at necropsy of one former patient who died from other causes. Finally, proponents of ibogaine believe that clinical use of a US schedule-I drug is politically unpalatable in the USA, despite evidence of the lack of abuse potential.

Kelly Morris

**End of the story for Di Bella cancer treatment?**

Results published this month confirm that the unconventional Di Bella cancer treatment (see Lancet 1999; 353: 1289-90) does not prolong the survival of patients.

Italian researchers examined Di Bella's files on 3076 patients treated between 1971 and 1997. Only 248 patients were evaluable and had complete follow-up. All but four of the patients had received conventional therapy as well as the Di Bella treatment. Date of diagnosis and histology were confirmed for each patient from cancer registries, and each was matched with cases from a pooled database of Italian cancer registries. 5-year survival in patients older than 14 years of age for all cancers combined was 21% for patients using the Di Bella therapy but 49% for controls. For childhood leukaemias, survival rates were 21% and 70%, respectively (p=0.001 for both comparisons; Cancer 1999; 86: 2143-49).

Although it is possible that patients with a poor response to conventional therapy might have been more likely to try alternative therapies, first author Eva Buiatti (Unità Sanitaria Locale, Firenze, Italy) concludes that the results "do not support any evidence of the efficacy of the treatment proposed by Di Bella". Ten Italian phase II clinical trials of Di Bella's treatment have also yielded negative results, and Paul Calabresi (Brown University, Providence, RI, USA) congratulates Italian institutions in an editorial for "demonstrating unequivocally, in less than 1 year, that [Di Bella's therapy] is ineffective".

Bruno Simini

**News in brief**


Caffeine and miscarriages? A new study shows that mean serum concentrations of paraxanthine (a caffeine metabolite) were significantly higher in women who had miscarriages than in those with live-births. However, the risk of miscarriage was raised only in women with extremely high paraxanthine concentrations (more than 1845 ng/mL; N Engl J Med 1999; 341: 1639-44).
Probiotics strain for credibility

T he UK launch in September of a “probiotic version” of an established multivitamin product epitomises what is wrong with the commercialisation of probiotics, says Gregor Reid of the Lawson Research Institute (London, Ontario, Canada). “Apparently, it’s being promoted for use in irritable bowel syndrome, gut disorders, and thrush—the latter being a clever way of implying it prevents or treats yeast infections. Where is the scientific evidence for these stated or implied claims?”, says Reid, who is investigating the use of probiotics to prevent urogenital infections and who reported on the scientific basis of probiotics at the International Congress on Microbial Ecology and Disease (San Francisco, CA, USA; Sept 23–24).

“Probiotics have been reduced to a very naïve and simplistic level in order to market products, but we will never have good explanations of their health-giving potential until we know more about the normal intestinal microflora”, adds Gerald Tannock (University of Otago, Dunedin, New Zealand), editor of Probiotics: A Critical Review (1999, Horizon Scientific Press, Norfolk, UK).

Could lactobacillus be behind his longevity?

The concept of probiotics—live microbial food ingredients that have a beneficial effect on human health—was first proposed in the early 1900s by Russian Nobel Prize winner Elie Metchnikoff who suggested that Bulgarian peasants lived long healthy lives because they consumed fermented milk products. Lactobacillus, he proposed, had a positive effect on the microflora of the colon, decreasing toxic microbial activities. Today, bifidobacterium, Escherichia coli, Saccharomyces boulardii, and enterococci are also being investigated for their probiotic potential.

But although probiotics have been available commercially for years, data on their benefits are inconclusive, says Mary Ellen Sanders (California Polytechnic State University, San Luis Obispo, CA, USA). “There are too few properly controlled human trials”, she says. “We know from studies in animals that the endogenous flora influences health but we still must find out if feeding healthy people exogenous microbes will be of benefit.”

Nevertheless, there is evidence that probiotics may be useful in some disorders. For example, there are data that indicate that consumption of an inoculum of $10^9-10^{10}$ specific probiotic bacteria per day can ameliorate the symptoms of bacterial antibiotic-associated diarrhoea, notes Richard Hull (Baylor College of Medicine, Houston, TX, USA). When taking antibiotics, he explains, “you lose a lot of normal flora and if they are replaced by harmful bugs, or if there’s a harmful bug already there and it can now bloom, then you get diarrhoea. Replacement of the normal flora with a temporary coloniser such as lactobacillus can stop the bad guys getting in.”

The “other side of probiotics”, continues Hull, involves colonising a body site which is normally sterile, but prone to infection, to keep out harmful bacteria. This is the basis of his work in catheterised hospital patients who get frequent urinary tract infections. Hull and co-workers in Sweden gave eight women with recurrent infections a strain of E coli known to colonise the bladder without causing symptoms; the women remained symptom-free. In another study, says Hull, men treated similarly remained symptom-free for up to 3 years. The strategy could help people with spinal-cord injury, or frail elderly patients, but is not for prevention of infection in healthy adults, he says. “You don’t want to take somebody with a sterile bladder and intentionally contaminate it.”

The rationale behind Hull’s experiments is well rooted in science, but probiotics are being touted for many conditions besides infections. Data on the use of probiotics in cancer, hypertension, allergies, and immune function are “intriguing, but they are not comprehensive”, says Sanders. And “none of the studies says anything about the value of probiotics in healthy adults”, which is the main market for these products. “How do studies in Peruvian children with diarrhoea translate to a healthy 45-year-old woman taking the product?”, she asks. And though some studies show that probiotic intake can increase phagocytic activity and cytokine concentrations, “does that mean people will get fewer colds? Or have a decreased risk of cancer? We simply don’t know”.

Another worry is that probiotic products—eg, freeze-dried supplements, “enhanced” yoghurt—are not subject to stringent quality control and labelling standards, so “it’s hard to know what you’re buying”, says Sanders. Most labels do not adequately identify the microbes in the product. And they give the number of viable cells at the time of manufacture, rather than at the expiry date. Many factors affect probiotic survival, she warns, so until full information is provided routinely for each product, doctors who suggest probiotics to their patients should contact the manufacturer and ask what is known about the product.

Proposed pathways of action include inhibition of pathogen growth or colonisation, and stimulation of host immune responses, but the mechanisms need to be clarified, says Sanders. And, adds Tannock, probiotic effects, if any, generally last only as long as someone takes the product. “The concept of permanently changing the intestinal microflora is one we can forget about”, he says. “We all have our own strains of bacteria, and though we probably share a core of bacterial species, there is tremendous variability from person to person.” Tannock and his colleagues have shown that about 40–50% of people have a stable lactobacillus population. For these people, he says, “an exogenous strain probably won’t influence their microflora very much. But other people have an unstable population and for them, it might be easier to get the probiotic strain to predominate”. These findings, warns Tannock, mean it will be important to know which strains are native to individuals before exogenous strains are added. And, he notes, although the pathogenicity of lactobacilli is generally low, one case has been reported in which a probiotic lactobacillus was found associated with a liver abscess. “I used to say nobody’s ever harmed by a probiotic, so if you think it may be helpful, why not try it? But now I’d be a bit nervous if they were used by somebody with a serious disease without medical supervision.”

Marilynn Larkin
LONDON  Old cash problems in Labour’s new National Health Service

Only 16 months ago it was being heralded by UK health managers and finance directors as a spending package “beyond our wildest dreams”, but just 6 months into Labour’s 3-year comprehensive spending plan for health, the newspaper headlines tell a different story: “NHS heads for worst cash crisis in 10 years.”

The financial package was announced in July, 1998, just a few weeks after the National Health Service (NHS) celebrated its 50th birthday with a series of conferences and parties at which the Prime Minister pledged a serious government commitment to the modernisation of the system.

When the spending review was unveiled, health was the clear winner, achieving a bigger cash increase than education which Labour had identified as its first priority. The £21 billion increase was described by ministers as “the biggest cash increase ever”, which was true, although the Conservatives introduced an even bigger real-terms increase during 1991–94 to ensure their new internal market for health did not collapse. Yet even the most sceptical commentators were impressed with the Labour package at the time. It promised an average annual real increase of 4.7% over 3 years for a service that historically has averaged only 3%. Better still, it provided 5.7% in the first year, 4.5% in the second, and 3.9% in the third. There was a promise of 7000 more doctors and 15 000 more nurses, although no details as to how these numbers fitted in with increases already being planned. There was particular praise from managers because they could now look ahead to the next 3 years, rather than limp from year to year.

The new spending era began in April but, by the end of the second quarter of the financial year according to a recently published survey of health authorities by the Healthcare Financial Management Association, a serious deterioration in funding had already occurred with finance directors forecasting a £200-million deficit by the end of the year. Health managers were even more worried. Stephen Thornton, chief executive of the NHS Confederation, which represents health authorities and hospital trusts, told reporters that he expected the deficit to be about £400 million.

He was even more worried about next year: “Areas of the NHS with

“NHS heads for worst cash crisis in 10 years”

emerging cash problems are usually balanced by other bits with enough cash. It is called brokerage and it has happened for years. All the messages I am hearing from regional directors of finance are that the number of people needing cash is likely to exceed the number that have got cash. It means it might not be possible for the NHS to pay itself. I don’t believe the NHS will allow that to happen. But the very fact that it might be contemplated shows how serious the problem is.”

Unlike earlier governments, this government has earmarked funds much more systematically to ensure its own initiatives succeed. The cash flowing to routine services has been much less than the initial announcement suggested. Moreover, another winter approaches. The NHS has enjoyed two successive winters with low influenza outbreaks. It cannot expect to be lucky for a third successive year.

Ministers have dismissed recent reports as “alarmist”. A £200-million deficit represents just 2 days of NHS spending. Yet it is also clear that the squeeze on NHS resources that began in 1993–94 and continued for the first 2 years of Labour administration during 1997–99 is still having effects. A National Audit office report in May showed that an underlying deficit of £700 million had been accumulated by last year.

The Conservative media has recently suggested the £21 billion extra involves triple accounting. No one in the professional press had been fooled, recognising the real increase is not worth £21 billion but will be nearer to £10 billion by the end of the third year.

The future is not totally hopeless. The British economy continues to expand, generating annual government budget surpluses in excess of £3 billion. Some Labour ministers have been stung by an analysis done by Tony Travers, a London School of Economics academic, which shows that Labour is projected to spend less on public welfare as a proportion of national income than any government for 35 years.

Ministers have already talked privately of a second 3-year spending programme, overlapping with the first programme in its third year. Labour knows its first 2 years of squeeze on the NHS has caused political harm. Leaks have suggested another big boost to health and education will be announced next summer with the aim of embarrassing the Tories who have been calling for tax cuts. But best of all, a new election approaches. Elections always help boost health expenditure.

Malcolm Dean

TOKYO  Japan set to make first legal prohibition on life-sciences research

Japan is set to tighten its restrictions on human cloning after a government advisory panel recommended on Nov 18 that such research should be banned. “Neither economic nor research benefits are to be gained from cloning human beings”, said Yoshiho Okada, chairman of the Osaka-based Senri Life Science Foundation and head of the panel.

Okada’s panel recommended new laws to penalise scientists who do human cloning experiments.

However, the panel deferred a decision about whether to prohibit cultivation of embryonic stem cells. It also suggested that legislation should be reviewed after 3-5 years to take into account shifts in public opinion or new scientific developments.

Next month, the panel’s report will be submitted to the life ethics committee of the science and technology council that advises Prime Minister Keizo Obuchi. According to Japanese media reports, the government will put a bill to parliament in January based on the panel’s recommendations.

If enacted, it would be the first legal prohibition on life-science research in Japan, where regulations usually take the form of administrative guidance that does not specify penalties for violators. Existing guidelines prohibit research into human cloning but have proved difficult to enforce.

Jonathan Watts
HIV/AIDS cases in 1999 set to keep increasing into the next century

The Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO estimated that 32.4 million adults and 1.2 million children will be living with HIV/AIDS at the close of this century at the simultaneous launch of their AIDS epidemic update report in London, UK, and Geneva, Switzerland, on Nov 23.

In the past year, 5.6 million children and adults have been infected with HIV, and 2.6 million people have died—a higher global total than in any year since the beginning of the epidemic. The latest estimates, which UNAIDS points out are provisional and are constantly reviewed, indicate that by the end of 1999, a cumulative total of 11.2 million children who will have lost their mothers to AIDS by the age of 15 years.

Since the epidemic began, sub-Saharan Africa has been worst affected region in the world. This area is home to 10% of the world’s population but has 70% of the global total of HIV-infected people. At the end of 1999, in the 15–49 year age group, HIV-positive women will outnumber HIV-positive men: 12.2 million women compared with 10.1 million men.

In the 1990s, life expectancy in southern Africa was 59 years but UNAIDS states that it expects this figure to drop back to 45 years between 2005 and 2010. By comparison, people in south Asia can expect to live 22 years longer by 2005.

Peter Piot: executive director of UNAIDS

UNAIDS underlined the scale of the epidemic in sub-Saharan Africa by noting that the “continent’s lead in terms of child infection is more compelling than ever…nearly 90% of the half million children born with the virus or infected through breast feeding in 1999 were living in sub-Saharan Africa”.

Despite this region’s grim statistics the executive director of UNAIDS, Peter Piot, is optimistic that even here, “we will see stronger, more effective responses to AIDS in more many sub-Saharan African nations”.

The most new cases of HIV in 1999 were reported in the newly independent states of the former Soviet Union, revealed the report. Piot told The Lancet: “In absolute terms we are talking about 360,000 infected individuals for the total region. I must say that [in this region] AIDS is not recognised as a priority…because most people are healthy because they have been recently infected. The impact is very invisible and the disease is highly stigmatised because it is associated with drug abuse.”

Piot warned that even though “we are working very hard with local authorities, in, for example, Ukraine… the response does not really match the urgency, and this is a region of the world where one can make a difference today. There is a window of opportunity”.

Haroon Ashraf

Family-planning restrictions written into US law

For 3 years President Bill Clinton has steadfastly resisted demands from the Republican Congress to reinstate the “Mexico City” policy that forbids US funding of international family-planning organisations that advocate for abortion. But, faced with the prospect of the USA losing its vote in the United Nations (UN) General Assembly for failure to pay its dues, Clinton capitulated on Nov 14, trading the payment of UN dues for agreeing to restrictions on family planning. Technically, anti-abortion lawmakers won in that this represents the first time the restrictions will be written into law. The Mexico City policy, in effect from 1984 until 1993, was merely a Presidential order issued by Ronald Reagan, which Clinton was able to rescind. Clinton is still able to waive the restrictions, but to do so would result in an automatic cut in the international family-planning budget and transfer of funds to child-survival programmes. More significantly, however, the language will not be written into permanent law, but will be in effect for only the fiscal year that ends on Sept 30, 2000, leaving the two sides to resume the fight next year.

Julie Rovner

Spain chastised for failing to implement WHO’s Health for All 2000

Health inequalities cause 35,000 premature deaths each year in Spain. This is the blunt message of a report released by the Spanish Society of Public Health and Health Administration (SEPSAS) on Nov 18.

The report says that Spain has ignored most of the 38 objectives in WHO’s Health for All 2000. In addition to inequalities, Spain has also failed to tackle cancer, motor and occupational accidents, mental illness, and suicide. It has also failed to create an environment policy with suitable public-health objectives. The report noted that improvements have been made in only three WHO-designated areas: reduction of disease transmission, child health, and healthy ageing.

Carlos Alvarez-Dardet, professor of preventive medicine at the University of Alicante and president of SEPSAS’s scientific committee, pointed out that there are “serious problems of health equity depending on the north-south and east–west axes” of Spain. “Citizens living in south-western regions such as Andalusia, Extremadura, and the Canary Islands have worse health indices than those living in the north-eastern axis such as Catalonia and Navarra”, he said.

The SEPSAS report revealed that the health inequalities are especially clear when noting that the inhabitants of poor neighbourhoods of Spain’s cities can have a life expectancy 10 years shorter than people living in richer areas. Worse still, said Alvarez-Dardet, is that these health inequalities “are growing and, unlike in other European countries, … Spain has no specific policies to face them”.

Xavier Bosch
Patient-directed drug advertising puts pressure on US doctors

Physicians often accede to patient requests for drugs advertised in the lay media, reported US researchers at a meeting of the American Association of Pharmaceutical Scientists (New Orleans, LA, USA; Nov 14–18).

The researchers were examining whether direct-to-consumer advertising (DTCA) influences prescribing habits as part of larger study of factors that encourage physicians to prescribe. Co-researcher, John Bentley, assistant professor of pharmacy administration (University of Mississippi, MS, USA), said the study indicates physicians’ growing acceptance of DTCA, and marks the trend toward more informed patients and managed care based on patient satisfaction. Nevertheless, he added, how DTCA affects health care, the doctor-patient relationship, costs, and outcomes remains equivocal.

Pharmacist Michael Cohen, president of the Institute for Safe Medication Practices (Philadelphia, PA, USA), pointed out that “DTCA has definitely increased the use of drugs by patients while we are having a growing battle against adverse drug events”. He added, “I’m not so sure that doctors are all that thrilled about direct-to-consumer advertising. The fact that they are pressured to some degree and may cave in to consumer requests doesn’t mean that doctors see DTCA in a favourable light”.

The study showed that only 9% of physicians reported feeling no pressure to prescribe from patients informed by advertising; 38% felt very little pressure, 47% felt a little pressure, and 6% felt a lot of pressure. Family physicians (42%) were also more likely than internists (32%) to acquiesce to patients’ prescription requests.

The American Medical Association (AMA) had opposed DTCA until 1992 when, in collaboration with the US FDA, AMA issued guidelines for DTCA that called for accurate information that balanced claims of product effectiveness with risk information. Since 1997, the US FDA has issued draft guidance for broadcast advertising that seems to have resulted in a surge of DTCA in both print and broadcast media. AMA reports that in 1998 US$1·3 billion was spent on DTCA and that the trend for more DTCA continues.

Condoms banned from Israel’s anti-AIDS campaign

Israel’s Health Minister Shlomo Benizri incited the wrath of AIDS experts on Nov 17 by unilaterally declaring that photographs of condoms be excluded from the ministry’s International AIDS Day, which is held on Dec 1. Benizri, of the Shas religious party, personally instructed his office not to use pamphlets and posters showing a man holding a rolled-up condom in his hand.

Ministry official, Yair Amikam, said that Benizri was responding to “public demand for modesty while educating in detail” about sexually transmitted diseases. “Israeli citizens—Jewish, Arab, religious, secular—have indicated that pictures of condoms are offensive and embarrassing”, added Yoram M alka, a Health Ministry spokesman. Malka told The Lancet that “many booklets, films, demonstrations, and advertisements throughout the media, sponsored or produced by the ministry, contain explicit detail about the value and use of condoms without having to show pictures of someone holding a rolled-up condom in his hand”.

But AIDS experts were not placated. “Condoms are the main protection against AIDS, and we have to overcome social reticence, to displace the Pavlovian association of condoms with immorality and illicit sex, with condoms as medicine. I have no doubt that showing the condom habituates the public to this message”, said Zvi Bentwich, head of Kupat Holim Clalit’s Kaplan Hospital AIDS Centre, the largest AIDS centre in Israel. “The bottom line is that we need to increase awareness well beyond what is already being done if we want to prevent the level of AIDS in Israel from increasing”, he said.

The head of Israel’s AIDS taskforce, T K Hassman, noted that “if you are talking about health and medical care, Israel is similar to Europe, but if you are talking about prevention and education, Israel is more similar to Africa”. “In the States, Europe, and Australia they spend US$1·69 per capita per annum. In Africa it’s seven cents and Israel it’s about 13 cents”, he added.

The ministry spent an unprecedented NIS 2·1 million ($513 000) on this campaign. “Never in my 3 years in the ministry have we allocated more than $322 000 for any individual campaign, including cancer and heart disease”, said Amikam.

Rachelle H B Fishman

Needle exchange advocated for Canada’s prisons

With hepatitis C (HCV) and HIV-infection rates rising in Canada’s prisons, a Correctional Service study has concluded that the time may be ripe for the introduction of a needle-exchange programme in the nation’s jails. The recommendation puts correctional officials in a quandary because drug use and trafficking are officially prohibited.

“One significant advantage of a needle and syringe exchange programme in a prison setting is that old, damaged, and home-made syringes that have the potential to harbour pathogens will be removed from circulation”, says the study, a summary of which was released on Nov 14. A Correctional Service team visited 18 prisons as part of an evaluation of the agency’s programmes that distribute condoms and needle-cleaning bleach kits. The report notes that one third of all inmates are estimated to have hepatitis C. Similarly, the rate of HIV infection in prisons is estimated to be ten times that of the general population. But the review team concluded that it has “no confidence” that the distribution of bleach alone reduces infection rates caused by use of contaminated needles for tattooing, body piercing, or drug injection.

The findings will be assessed by a federal working group which has been created to determine measures required to address health and drug problems within the prison system.

Wayne Kondro
Despair as sanctions against Afghanistan start

Sanctions against Afghanistan went into effect on Nov 14 following the Taliban’s failure to surrender the Saudi exile, Osama bin Laden, for trial on charges of plotting the bombings of US embassies in Kenya and Tanzania last year.

The Taliban have refused to expel Osama who was a favourite of the West, particularly of the USA, during Afghanistan’s war with the USSR.

The sanctions, which were imposed by the UN Security Council on Oct 15 with a 1-month deadline, freeze the Taliban’s financial assets. In addition, aeroplanes owned, leased, or operated by the Taliban are banned from taking off or landing internationally.

“...Our head hangs in shame...a body that claims to be fighting poverty, disease, and ignorance has instead resorted to supporting a punitive action that impoverishes, malnourishes and kills human beings”, a senior UN official told The Lancet. The official predicted that the sanctions would undo all the efforts that had been aimed at defeating malnutrition, ill health, and illiteracy.

The sanctions sparked widespread protests across Afghanistan with protesters attacking UN offices and vehicles. On Nov 17, four staff members of the World Food Programme (WFP) in Afghanistan were robbed and beaten. Just 2 days before the sanctions were imposed, six bombs targeted US and UN buildings in Islamabad, the capital of neighbouring Pakistan. The UN has strongly condemned all these attacks.

All non-governmental organisations (NGOs) and UN agencies working in Afghanistan have expressed deep concern at the sanctions that have already started to affect the people of a country that has been ravaged by war for more than 20 years. The Afghan National Airline, Ariana, that conveyed medicine, food, and health-care providers to Afghanistan has been grounded. Several NGOs have started rolling back their programmes because of withdrawal of donors’ support and the sanctions-induced insecurity.

According to the UN, NGOs are providing more than 70% of health-care services in the country. The sanctions have unleashed humanitarian crises in a country with high rates of infant, child, and maternal mortality and malnutrition. Malaria, pneumonia, diarrhoeal diseases, war and landmines related accidents, and leishmaniasis are still rampant.

Khabir Ahmad

Bristol inquiry told that status came before care

The anaesthetist who “blew the whistle” on poor results for paediatric cardiac surgery in Bristol, UK, in the 1980s alleged on Feb 23 that the hospital’s status was put before patients’ safety.

Stephen Bolsin, a former consultant anaesthetist at the Bristol Royal Infirmary, was giving evidence at the ongoing public inquiry which started last year after three of the hospital’s medical staff had been severely disciplined by the General Medical Council.

“The analogy that Bolsin uses is of a train where occasional passengers were falling off, and the train had to keep moving in order to attract funding”, Bolsin said when explaining the attitudes of senior hospital personnel whom he believed were keen for the hospital to remain one of the country’s 12 specialist units for paediatric cardiac surgery. Bolsin had accused senior staff of refusing to investigate his concerns.

During Bolsin’s evidence, it was revealed that he had attended group counselling with the two paediatric cardiac surgeons at Bristol whose mortality rates he had criticised. Asked whether attending counselling with James Wisheart and Janardan Dhasmana had been helpful, Bolsin replied:

“I am not sure that getting psychiatrists in to resolve differences of opinion was necessarily an appropriate step, but it was one that was proposed by the Chief Executive.”

Sarah Ramsay

News in brief

Class-action by Bhopal victims

Exasperated by the tardy pace of criminal cases in India against the Union Carbide Corporation and its former head, Warren Anderson, the surviving victims of the 1984 Bhopal gas explosion filed a class-action lawsuit in a New York District Court on Nov 15. Following a compensation settlement of US$470 million in 1989, the Indian Supreme Court had allowed criminal cases to be pursued against Union Carbide. The complainants allege that the efforts of the Indian judicial authorities have been met with stony indifference by both the company and Anderson.

“Smoking kills” in Europe

Anti-smoking legislation proposed by the European Commission on Nov 16 will reduce from 12mg to 10mg per cigarette the maximum permitted level of tar and impose a new limit of 1mg of nicotine content. Manufacturers will have to declare any additives in their products. Potentially misleading brand descriptions such as “light” and “mild” are likely to be regulated, while current health warnings will be replaced by the blunt message “Smoking kills”.

Pakistan to tackle vitamin A deficiency

Pakistan will launch nationwide vitamin A supplementation as part of its polio immunisation programme which starts on Nov 30. An estimated 30% of children in Pakistan are vitamin A deficient. About 25 million children will be given megadoses of vitamin A to protect against night blindness, blinding xerophthalmia, and other complications of deficiency.

Recent work indicates that most of Pakistan’s ophthalmologists fail to diagnose clinical vitamin A deficiency because of inappropriate postgraduate training.

World Humanitarian Day

On Nov 23, UN Secretary-General Kofi Annan launched World Humanitarian Day. The day marked joint appeals from various UN agencies to raise US$2·4 billion to aid 25·4 million of the world’s poorest countries or regions. This is the second year that the agencies have held a joint appeal and the aim is to make it a yearly event.
How the World Trade Organisation is shaping domestic policies in health care

David Price, Allyson M Pollock, Jean Shaoul

High up on the agenda of the World Trade Organisation (WTO), an international body founded in 1995 to expand free trade and the free market, is the privatisation of education, health, welfare, social housing and transport. The WTO’s aim is to extend the free market in the provision of traditional public services. Governments in Europe and the US link the expansion of trade in public services to economic success, and with the backing of powerful medical-pharmaceutical, insurance, and service corporations, the race is on to capture the share of gross domestic product that governments currently spend on public services. They will open domestic European services and domestic markets to global competition by government procurement agreements, dispute-settlement procedures, and the investment rules of global financial institutions. The UK has already set up the necessary mechanisms: the introduction of private-sector accounting rules to public services; the funding of public-sector investment via private-public partnerships or the private finance initiative; and the change to capitation funding streams, which allows the substitution of private for public funds and services. We explain the implications of these changes for European public-health-care systems and the threat they pose to universal coverage, solidarity through risk-pooling, equity, comprehensive care, and democratic accountability.

On Nov 29, 1999, trade ministers from 134 member states will meet in Seattle, USA, for the latest round of talks at the World Trade Organisation (WTO), an international body established in 1995 to expand free trade and the free market. The meeting will trigger the arrival of more than 1100 public-interest groups from 87 countries who intend to put forward “the real critique” of the WTO. Seattle will be the setting for an unprecedented worldwide campaign in which consumer groups, trade unions, environmentalists, and public-health activists will highlight the global economic implications of the WTO trade talks, not the leaft of which is the dismantling of European socialised welfare provision with its publicly stated goals of universality and solidarity.

Many governments are deregulating and privatising public-service funding and delivery (www.imf.org/external/pubs/ft/fandd/1999/03/thobani.htm, available November, 1999). The transformation is being engineered through policy initiatives such as New Public Management, contracting out of services, compulsory competitive tendering (best value), and public infrastructure privatisation through public-private partnerships known variously as the private finance initiative (PFI), build-own transfer (BOT), or build, own, operate, and transfer (BOOT). These policies are generally presented as technical and, therefore, neutral adjustments. There has been little public debate about the way in which the privatisation of public services at national level is linked to the global trade-expansion policies of international institutions, such as the WTO, the International Monetary Fund, and the World Bank. There is even less understanding of the huge implications of these policies for European traditions of democracy and community risk-sharing.

WTO’s expansion of the free market into public-sector service provision

The Geneva-based WTO was established during the Uruguayan round of the General Agreement on Trade and Tariffs. Its aim is economic growth and stability based on free markets and minimum governmental interference. Although the WTO’s membership includes 134 nation states (at February 1999), the transnational corporations that sit on all the important advisory committees decide detailed policy and set the agenda. WTO trade agreements have been described as a bill of rights for corporate business.1,2

The WTO talks in Seattle will focus on revision of the General Agreement on Trade in Services (GATS), a system of international law intended to expand private-enterprise involvement in the increasingly important service sector. According to the WTO, 160 service sectors are covered by GATS, including telecoms, transport, distribution, postal, insurance, environment, tourism, entertainment, and leisure services. What few people realise is that health care, social services, education, housing, and other services run by government agencies are also included (www.wto.org/wto/services/services.htm, available November, 1999).1

The WTO’s focus on the service industry reflects the sector’s growing commercial importance. As profitability in manufacturing has declined because of international competition, US and European corporations have turned to services as an alternative source of profit. According to the European Commission “The service sector accounts for two thirds of the [European] Union’s economy and jobs, almost a quarter of the EU’s total exports and a half of all foreign investment flowing from the Union to other parts of the world”.3 In the USA, more than a third of economic growth over the past 5 years has been because of service exports.4 The World Bank has calculated that in less-developed countries alone, infrastructure development involving some private backing rose from US$15·6 billion...
in 1990 to $120·0 billion in 1997. Around 15% was direct foreign investment in public schemes. Governments in Europe and the US link the expansion of trade in public services to economic success, and, with the backing of powerful coalitions of transnational and multinational corporations, the race is on to capture the share of gross domestic product governments currently spend on public services. The European Community has set up the European Services Network of multinational industry representatives, led by Andrew Buxton, chairman of Barclays plc, to “advise European union negotiators on the key barriers and countries on which they should focus. . .” (www.gats-info.eu.int/, available November, 1999).

In the USA, the Coalition of Service Industries is calling for a majority foreign ownership to be allowed for all health facilities. “We believe we can make much progress in the negotiations to allow the opportunity for US businesses to expand into foreign health care markets . . . . Historically, health care services in many foreign countries have largely been the responsibility of the public sector. This public ownership of health care has made it difficult for US private-sector health care providers to market in foreign countries. . .” (www.uscsi.org; available November, 1999).

The US trade delegation goes even further. “The United States is of the view that commercial opportunities exist along the entire spectrum of health and social care facilities, including hospitals, outpatient facilities, clinics, nursing homes, assisted living arrangements, and services provided in the home.”

Waiting in the wings of the WTO talks are the US multinationals, including the pharmaceutical industry, long-term-care sector, and the health-maintenance organisations. Known in the mid-1990s as “the darlings of Wall Street,” the multibillion dollar business of health-maintenance organisations depends heavily on a mixture of public funding, private health insurance, and user charges. Much of its impressive profitability was brought about by the acquisition of non-profit hospitals in the USA.

However, by 1997, the stock-market boom in health-maintenance organisations had ended; and earnings by these businesses of $700 million in 1996 turned into $768 million losses by 1998. Profits fell because of market saturation, government strategies to contain health-care costs, and high-profile scandals. To restore profitability, the industry has begun to lower benefits, increase premiums, and withdraw from selected markets. It has also tried to capture new markets abroad by acquiring publicly run facilities. The industry has received influential backing for its foreign-acquisitions policy from the US government, the World Bank, and multilateral financial institutions such as the Inter-American Development Bank. These bodies have supported “managed care initiatives that convert public health care institutions and social insurance funds to private management, private ownership, or both.”

Health-maintenance organisations target the public funding behind foreign health-care systems. Multibillion-dollar social-security or tax pools are effectively privatised when public health care is redirected through private-sector organisations.

Intention to open public services to international global markets through GATS

Expansion of the private services sector depends on the opening of markets in the traditional areas of public provision. The WTO and the World Bank have carefully created policies to ensure that such changes take place. But the WTO has found progress slow in health care. When GATS was introduced in 1995, only 27% of WTO members agreed to open hospital services to foreign suppliers.12 According to the WTO secretariat, some governments have resisted making the hospital sector commercial because they think of hospitals as part of their country’s “national heritage.” Consequently, 5 years into GATS, the public-service basis of many health-care systems has not been accessible to transnational corporations.

GATS permits member countries to force the removal of barriers to foreign participation in the service industries of other member countries. The WTO now has three main objectives: to extend coverage of GATS, to toughen procedures for dispute settlements so that member states can more easily be brought into line, and to change government procurement rules to create market access.

Extension of GATS—Articles 1.3, 13, and 19

The previous round of WTO ministerial talks (the Uruguay round) allowed governments to protect health and social services from GATS treatment by defining them as government services. According to GATS Article 1.3, a government service is one “which is supplied neither on a commercial basis, nor in competition with one or more service suppliers”. Article 19 of GATS is, however, intended to end this protection. “Members shall enter into successive rounds of negotiations . . . . with a view to achieving a progressively higher level of liberalisation.”

The WTO secretariat has argued that services to be classified under Article 1.3 they should be provided free. Many governments initially protected health services from GATS treatment by defining them in this way. But the WTO has highlighted the inconsistencies in this approach. “The hospital sector in many countries . . . is made up of government-owned and privately-owned entities which both operate on a commercial basis, charging the patient or his insurance for the treatment provided. Supplementary subsidies may be granted for social, regional, and similar policy purposes. It seems unrealistic in such cases to argue for continued application of Article 1.3, and/or maintain that no competitive relationship exists between the two groups of suppliers of services.” In addition, Article 13 of GATS calls for the end of subsidies that distort trade and requires members to negotiate procedures to combat them.

Therefore, according to the WTO, wherever there is a mixture of public and private funding, such as user charge or private insurance, or there are subsidies for non-public infrastructure, such as public-private partnerships or competitive contracting for services, the service sector should be open to foreign corporations. Health-care systems across Europe are vulnerable on all these counts.

Dispute settlement

The WTO uses dispute settlement to implement market access. These procedures enable states to force changes in the domestic laws of other states and to impose retaliatory trade sanctions in areas unconnected with the disputed practice. Current proposals will enable transnational corporations to take legal action against governments that frustrate their foreign-investment aspirations. Dispute settlement is an important means of US influence and a vital weapon in its trade expansion. According to Ambassador Charlene Barshefsky, leader of the US trade delegation and chairperson of the Seattle round, “the
United States has demonstrated a record as the most aggressive user of the WTO dispute resolution process. Dispute settlement is a form of attack on government powers. The procedures promote the least trade-restrictive regulation, which is voluntary rather than compulsory, involves consumer information rather than prohibition, and puts individual before public responsibility. The US trade delegation has announced that it will be supporting the introduction of regulation in the service sector that "promotes rather than restrains competition".

Creation of market access: government procurement rules

The WTO proposes to use a reformed government procurement agreement as the primary mechanism for opening public services to the private sector. Government procurement rules supply the legal and regulatory framework within which public bodies contract for goods, services, and investment funds. This procedure opens up domestic services and markets to international competition. The influential European Union reform proposals focus on "[unlocking] new potential markets" by extension of private firms' involvement with public services and by creation of contracting rules to ensure "acceptable returns for investors".

Use of government-procurement-agreement reforms to shape health-care policy in the UK

The World Bank has famously described public services as a barrier to the abolition of world poverty. It maintains that "if market monopolies in public services cannot be avoided then regulated private ownership is preferable to public ownership". The WTO sees one of its roles as coordinating the international transfer of such policies. It asks "How can WTO Members ensure that ongoing reforms in national health systems are mutually supportive and, whenever relevant, market-based?"

The UK provides a fascinating insight into the assimilation of the WTO agenda into domestic policy. The UK was one of the first states among more-developed countries to take up two key recommendations of global financial institutions: the introduction to the public sector of commercial accounting and appraisal of commercial investment. Procurement reforms are being used to breach socialised provision to enable private firms to exploit the public-funding base of traditional public services.

Changes to resource allocation

Money now follows the individual to the point of service. In 1991, the National Health Service internal market replaced resource allocation based on area needs with capitation funding. Payments per person are generally seen simply as a cost-containment strategy because they provide organisations with an incentive to withhold care (necessary and unnecessary). However, per-person payments, which are fixed sums of money that lend themselves to copayments and consumer purchases in the private sector, also facilitate the substitution of private funding for public funding (through private insurance and user charges) and private services for public services. Capitation models are promoted by the World Bank (www.worldbank.org/nor/class/module/sec7i.chm 7i).

In the UK, the devolution of capitation payments to family-physician fundholders has enabled the substitution of private health insurance and user charges for some publicly funded care (eg, pharmaceuticals, elective surgery) as well as the diversion of public funds into the private sector (eg, elective surgery, private outpatient clinics, podiatry, physiotherapy, and capital infrastructure). The introduction of primary-care groups and primary-care trusts in April, 1999, will accelerate this process. Primary-care groups will have an incentive to expand private health insurance and user charges or copayments when their National Health Service per-person budgets are capped, and they will have more freedom to use the private sector.

A copayment template is about to be tried in the UK by the department of employment and education. Next year the department will give a UK£10 000 "individual learning account" to school-leavers to pay for education after age 18 years, as well as training costs in the public or the private sector. Public funds will be triggered by private contributions.

Service delivery changes in creation of corporations

In the UK, National Health Service entities have been re-established on private-sector lines, or corporatised, by the imposition of commercial accounting practices. For example, the sole statutory duties of National Health Service provider trusts (hospital and community services) are financial and not health-care duties; National Health Service bodies must break even after having made a profit for their owners (the government) equivalent to a 6% return on capital. The same will apply to primary-care trusts, which will also be made to behave commercially if they have shareholders. This resource accounting, which is shortly to be introduced throughout all UK public services, makes public and private sectors seem interchangeable. Resource accounting is a prerequisite for public-private partnerships.

Public-private partnerships

The UK government is outsourcing labour-intensive services and capital-intensive infrastructure projects through public-private partnerships (or private finance initiative in the National Health Service). These changes give the private sector access to public funds, but are presented as offering the public sector access to private funds. The privatisation of public funds has been achieved by almost eliminating new public funding for capital projects such as hospital refurbishment through the introduction of direct government subsidies to the private sector; and through creation of revenue that can be diverted to the private sector as rental income.

These policies are occurring to a greater or lesser degree in all UK public services and are being widely copied in other more-developed countries.

Implications for health and health care

These structural changes in the financing and delivery of health-care conflict with the principles of universal coverage and shared risk that tax-funded or social-insurance-funded systems generally uphold. The changes provide insurers and providers with the means and making maximum profit the incentive to engineer favourable risk pools. Experience in the USA and more recently in Latin America is that the viability of public and voluntary hospitals and health services is threatened when they have to compete with commercial providers for per-person public funds, private insurance, and copayments.
Democracy versus consumerism

In the UK, the substitution of market mechanisms and competition has fractured the traditional mechanisms for local accountability. National health Service providers are governed by trust boards, with no democratic or legal mechanisms to ensure that they uphold the interests of the local communities from which they draw patients. Increasingly, the goals of universality and equity are being replaced by consumer sovereignty. This effect is reflected in the growing governmental emphasis on league tables, performance measures, and quality frameworks, rather than on substantive health-care rights, such as to a universal, comprehensive health-care service.

The cumulative effect of these market-based reforms in the UK is a decrease in the supply of publicly funded services. An early example of this was the long-term-care sector. Later, despite government recognition of major shortages in the labour force and physical capacity, the introduction of the private finance initiative to the acute hospital sector in the National Health Service has resulted in a reduction of 30% in capacity at the hospitals concerned and of 20% in clinical budgets and workforce.

Inequalities in health

Income and health inequalities continue to widen in the UK. The restrictions on national sovereignty imposed by the WTO through GATS will make it increasingly difficult to reverse these trends. As the UK trade minister, Richard Caborn, goes to Seattle, the UK Government has yet to adopt the first recommendation of its own Independent Inquiry into Inequalities in Health that "all policies likely to have a direct or indirect effect on health should be evaluated in terms of their impact on health inequalities ... and formulated ... to reduce such inequalities". Resource accounting, private finance initiatives, outsourcing, capitation, and corporatisation continue to be imposed under the modernisation programme of the "third way", but the government has yet to sponsor a thorough assessment of their impact on health inequalities.

Conclusion

The WTO is stage-managing a new privatisation bonanza at Seattle. Multinational and transnational corporations, including the pharmaceutical, insurance, and service sectors, are lining up to capture the chunks of gross domestic product that governments currently spend on public services such as education and health. The long tradition of European welfare states based on solidarity through community risk-pooling and publicly accountable services is being dismantled. The US and European Union governments are aggressively backing this project in the interests of their business corporations.

Typically, the public sector has been left to bear the risk for more vulnerable populations but with diminished risk-pools (or pooled funding) to finance care. Competition for per-person funds among autonomous providers leads to competition for patients. Evidence from the UK shows that such competition has destabilised the provision of care and diverted planning and service priorities away from the needs of their local populations. For example, private-finance-initiative business cases show that hospitals are currently being planned according to trusts' financial needs and not local clinical need: access capacity as the hospitals concerned and of 20% in clinical services at the hospitals concerned is a decrease in the supply of publicly funded services. An early example of this was the long-term-care sector. Later, despite government recognition of major shortages in the labour force and physical capacity, the introduction of the private finance initiative to the acute hospital sector in the National Health Service has resulted in a reduction of 30% in capacity at the hospitals concerned and of 20% in clinical budgets and workforce.

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Conclusion

The WTO is stage-managing a new privatisation bonanza at Seattle. Multinational and transnational corporations, including the pharmaceutical, insurance, and service sectors, are lining up to capture the chunks of gross domestic product that governments currently spend on public services such as education and health. The long tradition of European welfare states based on solidarity through community risk-pooling and publicly accountable services is being dismantled. The US and European Union governments are aggressively backing this project in the interests of their business corporations. But the assault on our hospitals and schools and public-service infrastructure depends ultimately on a promise from one government to another to expand private markets. Such promises can be kept only if domestic opposition to privatisation is held in check. We need to constantly reassert the principles and values on which European health-care systems are based and resist the WTO agenda.

We thank Meri Koivusalo.

References

Global trade and access to medicines: AIDS treatments in Thailand

David Wilson, Paul Cawthorne, Nathan Ford, Saree Aongsanwang

The process of increasing globalisation is dominated by market influences that have a negative effect on public health in less-developed countries. Laws that govern the importing of medicines and the patent protection of new discoveries are subject to an increase in globalisation. The possible effects in terms of access to medicines are well defined.

In May, 1999, WHO was given a mandate to monitor the public-health consequences of international trade agreements. Several less-developed countries have been under pressure from western governments to make changes in trade laws that would restrict their ability to produce or import drugs (www.cptech.org, accessed Nov 15, 1999). Non-governmental organisations have an important part to play in increasing awareness of these issues, and Médecins Sans Frontières has been active in bringing these issues to public attention.

The World Trade Agreements
The World Trade Agreements, signed in 1994, were a decisive step towards a worldwide free-trade economy. In signing these agreements, member states of the World Trade Organisation have to abide by several multilateral agreements, of which the TRIPS agreements (Trade-Related Aspects of Intellectual Property Rights) probably has the greatest effect on access to medicines. TRIPS deals with patent law and sets some minimum standards such as 20-year patent protection for pharmaceuticals. In certain instances, such as public-health emergencies or unfair-pricing practices, TRIPS allows for the production of medicines by companies other than the patent holder (compulsory licensing). TRIPS also allows for the importing of medicines from countries other than the country of manufacture (parallel importing). Compulsory licensing and parallel importing are both widely practised by western countries. However, some less-developed countries have been pressured by western governments to ban compulsory licensing and parallel imports. We focus here on Thailand, where US trade pressure has limited access to affordable treatment for patients with HIV and AIDS.

Access to HIV treatment in Thailand
1 million people in Thailand (which has a population of 61 million) are infected with HIV. In 1995, a World Bank and WHO review advised Thailand to focus its limited drug resources for HIV on the prevention of perinatal HIV infection and management of opportunistic infections. The Thai Ministry of Public Health (MOPH) identified the need to formulate a policy of rational use of antiretroviral drugs and issued guidelines for the clinical management of HIV infection that focused on prevention and treatment of opportunistic infections. Short-course zidovudine to limit perinatal transmission is to be implemented as a result of a study by the Centers for Disease Control and Prevention. The MOPH also funds small-scale research projects but these benefit small numbers only and do not guarantee long-term treatment for participants. In reality few patients can afford antiretroviral treatment. The monthly price for a course of zidovudine, lamivudine, and indinavir is $US575, whereas the typical monthly wage of an office-worker is $US120.

Generic drugs in Thailand
There are legitimate concerns about the quality of therapeutic agents in less-developed countries. In Thailand, there have recently been reports of deaths as a result of a new rabies treatment. Although a limited study by UK researchers did not find any pattern of substandard quality for pharmaceuticals imported from less-developed countries, the researchers commented that improved control at a regulatory level with less-developed countries is required. A critical assessment of the extent of the problem is needed.

The generic pharmaceutical industry in Thailand formulates and packages drugs from imported raw materials. Bioequivalence studies are required for generic product registration. Reports on Thailand’s pharmaceutical industry are available from the website of the UN agency in charge of industrial development (www.unido.org, accessed Nov 15, 1999).

Fluconazole is a key drug in the management of cryptococcal meningitis, an opportunistic infection that affects one in five patients with AIDS in Thailand. Until recently, Pfizer was the sole supplier of fluconazole in Thailand, charging a daily price (dosage of 400 mg) of $US1.4. In 1998, fluconazole was released from the safety monitoring programme (the safety monitoring programme confers a period of market exclusivity) in Thailand and is now supplied by three local pharmaceutical companies. The price has fallen to 5% of the 1998 price, which represents a potential annual saving to Thailand of $US53.1 million in the treatment of cryptococcal meningitis. Compliance with treatment has also improved because more patients can afford the drug.

This example shows the difference that generic competition can make in terms of price and accessibility of medicines in less-developed countries.

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Antiretroviral drugs are cost-effective in a less-developed country. Thailand’s Government Pharmaceutical Organisation has supplied generic zidovudine since 1993. The resulting competition has led to a fall in monthly cost ($60 per day) from $US524 in 1992 to $US587 in 1995.

Attempts to produce other drugs have been less successful, such as the Government Pharmaceutical Organisation’s plan to supply generic didanosine. Research and development of didanosine was funded by the US National Institutes of Health and exclusive production rights in the USA were granted to Bristol-Myers Squibb. The planned production of didanosine in Thailand was supervised by Bristol-Myers Squibb but buffer formulation in production was blocked when Bristol-Myers Squibb secured a product patent for the new formulation in 1998. This company remains the sole supplier in Thailand selling didanosine at a monthly cost ($400 per day) of $US136. The agreement between the US National Institute of Health and Bristol-Myers Squibb includes a reasonable-pricing clause, which seems to have been overlooked in this case. In response to our requests, the US Department of Health and Human Services has verbally agreed to review implementation of this clause.

US pressure to change patent law in Thailand Thailand is capable of producing good-quality cheap generic drugs, but local production has been limited by trade pressure from the US government. The US government regards TRIPS as a minimum standard, and in bilateral discussions commonly asks for additional commitments, with threats of trade sanctions to achieve its objectives. The USA is the destination of a quarter of exports from Thailand, so these threats are taken very seriously.

In 1992, under threat from the USA to limit textile imports, the Thai government passed a law to introduce product patent protection. As a safeguard, the Thai government created the Pharmaceutical Patent Review Board, which had authority to collect economic data, including the production cost of pharmaceuticals. The US Trade Representative Office objected and in 1998, under threat of increased tariffs on imports of wood products and jewellery, the Pharmaceutical Patent Review Board was disbanded and measures were taken that led to limiting of the right to issue compulsory licenses for pharmaceuticals.

The role of WHO

At the World Health Assembly in May, 1999, WHO was given a mandate to monitor the public-health consequences of International trade agreements. This new responsibility is contained within the Revised Drug Strategy, the WHO policy designed to ensure equitable access to essential drugs and to good treatment. The Revised Drug Strategy is a comprehensive policy that addresses all those involved, including member states and industry. The role of WHO, however, seems to be limited to monitoring the consequences of the World Trade Organisation agreements such as TRIPS. This will be of little comfort to countries subjected to international trade pressure.

After the adoption of the Revised Drug Strategy, a statement from the Thai delegation to WHO strongly recommended that the WHO support access to drugs by actions in areas of technology transfer, local production, elimination of counterfeit drugs, and human-resource development. The delegation also identified the need to develop indicators to assess the positive and negative effects of trade agreements on public health in less-developed countries. Assessment of the future effect of the Revised Drug Strategy will not be possible without such indicators.

The United Nations Development Programme (UNDP) has pointed out that less-developed countries are merely passive recipients of the effects of globalisation rather than its beneficiaries, and in 1992 and 1998 Thailand responded passively to trade pressure from the USA. However, the terms of the Revised Drug Strategy require member states to initiate requests for help; this help is unlikely to have a significant effect in less-developed countries unless consumer and advocacy groups pressure governments into action.

Conclusion

Pressure from the US government has forced Thailand to limit compulsory licensing and parallel importing, both of which are rights allowed for under TRIPS and used to great extent by western governments, including the US. Other less-developed countries have been subjected to similar pressure, in particular South Africa (for a list of countries, see www.cptech.org). An attempt to confer to WHO a role in monitoring international trade agreements was strongly opposed at the 1998 World Health Assembly: US State Department representatives threatened to withdraw WHO funding when faced with aggressive WHO support for improved access to patented medicines in less-developed countries. The adoption by unanimous consensus of the Revised Drug Strategy this year was, therefore, welcome news.

International trade agreements determine what can be done in terms of production and importation of medicines, so it is important for less-developed countries to understand fully the implications of these agreements. Equally, western governments need to receive a more balanced input of information when formulating trade policies that have public-health consequences.

Nongovernmental organisations can be more flexible than WHO and have an important part to play in defending the rights of less-developed countries at local and international level. Médecins Sans Frontières has been active as part of the Thai Non-Governmental Organisation Coalition on AIDS in bringing trade issues to public attention. Similarly, the AIDS Treatment Action Campaign has done much work in defending South Africa from US trade pressure. However, it remains to be seen whether WHO and nongovernmental organisations will be able to prevent western trade pressure from forcing less-developed countries to forego rights to produce and import medicines that are prohibitively expensive in today’s market.

References


Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement

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Summary

Background The Quality of Reporting of Meta-analyses (QUOROM) conference was convened to address standards for improving the quality of reporting of meta-analyses of clinical randomised controlled trials (RCTs).

Methods The QUOROM group consisted of 30 clinical epidemiologists, clinicians, statisticians, editors, and researchers. In conference, the group was asked to identify items they thought should be included in a checklist of standards. Whenever possible, checklist items were guided by research evidence suggesting that failure to adhere to the item proposed could lead to biased results. A modified Delphi technique was used in assessing candidate items.

Findings The conference resulted in the QUOROM statement, a checklist, and a flow diagram. The checklist describes our preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. It is organised into 21 headings and subheadings regarding searches, selection, validity assessment, data abstraction, study characteristics, and quantitative data synthesis, and in the results with “trial flow,” study characteristics, and quantitative data synthesis; research documentation was identified for eight of the 18 items. The flow diagram provides information about both the numbers of RCTs identified, included, and excluded and the reasons for exclusion of trials.

Interpretation We hope this report will generate further thought about ways to improve the quality of reports of meta-analyses of RCTs and that interested readers, reviewers, researchers, and editors will use the QUOROM statement and generate ideas for its improvement.

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See Commentary page ????????

Introduction

Health-care providers and other decision-makers now have, among their information resources, a form of clinical report called the meta-analysis,1,4 a review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method.3 The number of published meta-analyses has increased substantially in the past decade. These integrative articles can be helpful for clinical decisions, and they may also serve as the policy foundation for evidence-based practice, guidelines, economic evaluations, and future research agendas. The value of meta-analysis is evident in the work of the international Cochrane Collaboration,6,7 the primary purpose of which is to generate and disseminate high-quality systematic reviews of health-care interventions.

Like any research enterprise, particularly one that is observational, the meta-analysis of evidence can be flawed. Accordingly, the process by which meta-analyses are carried out has undergone scrutiny. A 1987 survey of 86 English-language meta-analyses6 assessed each publication on 23 items from six content areas judged important in the conduct and reporting of a meta-analysis of randomised trials: study design, combinability, control of bias, statistical analysis, sensitivity analysis, and problems of applicability. The survey results showed that only 24 (28%) of the 86 meta-analyses reported that all six content areas had been addressed. The updated survey, which included more recently published meta-analyses, showed little improvement in the rigour with which they were reported.8 Several publications have described the science of reviewing research,1 differences among narrative reviews, systematic reviews, and meta-analyses,2 and how to carry out,3,4,12 critically appraise,13–15 and apply3 meta-analyses in practice. The increase in the number of meta-analyses published has highlighted such issues as discordant meta-analyses on the same topic6 and discordant meta-analyses and randomised-trial results on the same question.10

An important consideration in interpretation and use of meta-analyses is to ascertain that the investigators who did the meta-analysis not only report explicitly the methods they used to analyse the articles they reviewed, but also report the methods used in the research articles they analysed. The meta-analytical review methods used may not be provided when a paper is initially submitted: even when they are, other factors such as page limitations, peer review, and editorial decisions may change the content and format of the report before publication.

Several investigators have suggested guidelines for reporting of meta-analyses.11,12 However, a consensus across disciplines has not developed. After the initiative to
improve the quality of reporting of randomised controlled trials (RCTs),20-22 we organised the Quality of Reporting of Meta-analyses (QUOROM) conference to address these issues as they relate to meta-analyses of RCTs. This report summaries the proceedings of that conference. The issues discussed might also be useful for reporting of systematic reviews (ie, meta-analysis, as defined above, without statistical aggregation), particularly of RCTs.

Methods

The QUOROM steering committee began with a comprehensive review of publications on the conduct and reporting of meta-analyses. The databases searched included MEDLINE and the Cochrane Library,23 which consists of the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, the YORK Database of Abstracts of Reviews of Effectiveness, and the Cochrane Review Methodology Database. We examined reference lists of the retrieved articles and individual personal files. Articles of potential relevance were retrieved and critically appraised by the QUOROM steering committee. The committee generated a draft agenda for the conference, which included six domains requiring discussion and debate. The content areas were slightly modified during preliminary discussions at the conference and were reported as: the search for the evidence; decision-making on which evidence to include; description of the characteristics of primary studies; quantitative data synthesis; reliability and issues related to internal validity (or quality); and clinical implications related to external validity (or generalisability).

In planning the QUOROM conference, the steering committee identified clinical epidemiologists, clinicians, statisticians, and researchers who conduct meta-analysis as well as editors from the UK and North America who are interested in meta-analysis. These 30 individuals were invited to a conference in Chicago on Oct 2-3, 1996. Participants were surveyed before the meeting to elicit their views on current reporting standards of meta-analyses and whether these needed improvement. In addition, they were sent relevant citations for review and were asked to indicate in which of the six groups they wished to participate.

The conference included small-group and plenary sessions. Each small group had a facilitator who was a member of the steering committee and was responsible for ensuring the discussions of as many as possible of the issues relevant to their specific remit. Each small group also had a recorder, who was responsible for documenting the main points and the consensus on each issue discussed during that session; the recorder presented the group’s consensus during the plenary sessions. During the plenary sessions, an elected scribe from each small group was responsible for recording the principal points relevant to that group’s charge that arose during the plenary discussion.

The participants in each small group were asked to identify items that they thought should be included in a checklist of standards that would be useful for investigators, editors, and peer reviewers. We asked that, whenever possible, items included in the checklist be guided by research evidence that suggested that a failure to adhere to the particular checklist item proposed could lead to biased results. For example, a substantial lack of sensitivity and specificity of MEDLINE searches is evident. Therefore, the checklist suggests that investigators explicitly describe all search strategies used to locate articles for inclusion in a meta-analysis. In considering whether candidate items were essential, each subgroup used a modified Delphi technique23 that was replicated in the plenary sessions.

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<td>Abstract</td>
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<td>Methods</td>
<td>Quantitative data synthesis</td>
<td>The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias**</td>
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<td>Results</td>
<td>Trial flow</td>
<td>Provide a meta-analysis profile summarising trial flow (see figure)</td>
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<td>Results</td>
<td>Study characteristics</td>
<td>Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)</td>
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<td>Results</td>
<td>Quantitative data synthesis</td>
<td>Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2×2 tables of counts, means and SDs, proportions)</td>
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<td>Discussion</td>
<td>Summary key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda</td>
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Quality of reporting of meta-analyses
Results
The conference resulted in the QUOROM statement: a checklist (table) and a flow diagram (figure). The checklist of standards for reporting of meta-analyses describes our preferred way to present the abstract, introduction, methods, results, and discussion sections of a report of a meta-analysis. The checklist is organised into 21 headings and subheadings to encourage authors to provide readers with information on searches, selection, validity assessment, data abstraction, study characteristics, quantitative data synthesis, and trial flow. Authors are asked to provide a flow diagram (figure) providing information about the number of RCTs identified, included, and excluded and the reasons for excluding them.

Pretesting
After development of the checklist and flow diagram, two members of the steering committee (DM, DJC) undertook pretesting with epidemiology graduate students studying meta-analysis. Residents in general internal medicine, participants at a Canadian Cochrane Center workshop, and faculty members of departments of medicine and of epidemiology and biostatistics. One group of candidates for a master's degree in epidemiology used the checklist and flow diagram to report their meta-analyses as if their work were being submitted for publication. Feedback from these four groups was positive, most users stating that the checklist and flow diagram would be likely to improve reporting standards. Modifications of the checklist (eg, inclusion of a statement about major findings) and changes to the flow diagram (eg, more detail) were incorporated.

Discussion
In developing the checklist, we identified supporting scientific evidence for only eight of 18 items to guide the reporting of meta-analyses of RCTs. Some of this evidence is indirect. For example, we ask authors to use a structured abstract format. The supporting evidence for this item was collected by examining abstracts of original reports of individual studies and may not pertain specifically to the reporting of meta-analyses. However, the QUOROM group judged this a reasonable approach by analogy with other types of research reports and pending further evidence about the merits of structured abstracts for meta-analyses.

We have asked authors to be explicit in reporting the criteria used when assessing the "quality" of trials included in meta-analyses and the outcome of the quality assessment. There is direct and compelling evidence to support recommendations about reporting on the quality of RCTs included in a meta-analysis. A meta-analytic database of 255 obstetric RCTs provided evidence that trials with inadequate reporting of allocation concealment (ie, keeping the intervention assignments hidden from all participants in the trial until the point of allocation) overestimated the intervention effect by 30% compared with trials in which this information was adequately reported. Similar results for several disease categories and methods of quality assessment have been reported. These findings suggest that inclusion of reports of low-quality RCTs in meta-analyses is likely to alter the summary measures of the intervention effect.

We also ask authors to be explicit in reporting assessment of publication bias, and we recommend that the discussion should include comments about whether the results obtained may have been influenced by such bias. Publication bias derives from the selective publishing of studies with statistically significant or directionally positive results, and it can lead to inflated estimates of efficacy in meta-analyses. For example, trials of single alkylating agents versus multiple-agent cytotoxic chemotherapy in the treatment of ovarian cancer have been analysed. Published trials yielded significant results in favour of the multiple-agent therapy, but that finding was not supported when the results of all trials—both those published and those registered but not published—were analysed.

The statement asks authors to be explicit about the publication status of reports included in a meta-analysis. Only about a third of published meta-analyses report the inclusion of unpublished data. Although one study found that there were no substantial differences in the dimensions of study quality between published and unpublished clinical research, another suggested that intervention effects reported in journals were 33% greater than those reported in doctoral dissertations. The role of the "grey literature" (difficult to locate or retrieve) was examined in 39 meta-analyses that included 467 RCTs, 102 of which were grey literature. Meta-analyses limited to published trials, compared with those that included both published and grey literature, overestimated the treatment effect by an average of 12%. There is still debate between editors and investigators about the importance of including unpublished data in a meta-analysis.

We have asked authors to be explicit in reporting whether they have used any restrictions on language of publication. Roughly a third of published meta-analyses have some language restrictions as part of the eligibility criteria for including individual trials. The reason for such restrictions is not clear, since there is no evidence to support differences in study quality, and there is evidence that language restrictions may result in a biased summary.

Progress through the stages of a meta-analysis for RCTs

"..."
The reports of 127 RCTs written in English, compared with those reported in four other languages, showed little or no difference in several important methodological features.46 Similar results have been reported elsewhere.47 The role of language restrictions has been studied in 211 RCTs included in 18 meta-analyses in which trials published in languages other than English were included in the quantitative summary.48 Language-restricted meta-analyses overestimated the treatment effect by only 2% on average compared with language-inclusive meta-analyses. However, the language-inclusive meta-analyses were more precise.49

Reports of RCTs with statistically positive results are more likely than those with negative results to be published in English.50 Likewise, there is emerging evidence to suggest that reports of RCTs from certain countries mostly have statistically positive results.51

We used several methods to generate the checklist and flow diagram: a systematic review of the reporting of meta-analyses; focus groups of the steering committee; and a modified Delphi approach during the conference. Although we did not involve certain users of meta-analyses (policy-makers or patients), we formally pretested this document with representatives of several constituencies who would use the recommendations and made modifications accordingly.

The QUOROM group also discussed the format of a meta-analysis report, how best to assess the impact of the QUOROM statement, and how best to disseminate it. The format we recommend includes 15 subheadings that reflect the sequential stages in the conduct of the meta-analysis within the text of the report of a meta-analysis. The checklist included in the statement can also be used during the planning, performing, and reporting of a meta-analysis and during peer review of the report after its submission to a journal.

We delayed publication of the QUOROM statement until its impact on the editorial process had been assessed. We organised an RCT involving eight medical journals to assess the impact of use of QUOROM criteria on journal peer review. Accrual is now complete and we will report the trial results elsewhere.

After about 5 weeks of electronic posting we had received five comments from investigators, whom we thank for their thoughtful consideration of the statement. Several issues, in particular in relation to terminology, cannot be addressed in the statement at present. The QUOROM group is agreed on the importance of making changes to the checklist in the light of documented evidence and must resist changes based on opinion or anecdotal evidence unless there is a compelling rationale for doing otherwise. Nonetheless, the issues raised have been noted for consideration and discussion in future.

Several queries addressed the distinction between the meta-analysis and systematic review. As we indicate in the introduction, and throughout the statement, the QUOROM group agreed to observe the distinction as defined by the Potsdam consultation on meta-analysis.4

We were also asked to clarify the checklist item asking investigators to interpret their results in light of the totality of evidence. Increasingly, several meta-analyses on the same topic are reported.51–53 If other similar reports are available, authors should discuss their results as they relate to such evidence.

For the QUOROM statement to continue to be useful, it must remain evidence based and up to date. Members of the QUOROM group need to survey the literature continually to help inform themselves about emerging evidence on reporting of meta-analyses. They in turn need to be collated and presented annually for two purposes. The first is decisions on which checklist items to keep, delete, or add; these decisions can be made similarly to the selection of the original items. The second purpose is that an up to date summary on the reporting of meta-analyses can be prepared. These efforts are being coordinated through a website. This approach is similar to the CONSORT initiative.

In summary, our choice of items to include in a meta-analysis report was based on evidence whenever possible, which implies the need to include items that can systematically influence estimates of treatment effects. Currently, we lack a detailed understanding of all the factors leading to bias in the result of a meta-analysis. Clearly, research is required to help improve the quality of reporting of meta-analyses. Such evidence may also act as a catalyst for improving the methods by which meta-analyses are conducted.

The QUOROM checklist and flow diagram are available on The Lancet’s website [www.thelancet.com]. We hope that this document will generate further interest in the field of meta-analysis and that, like the CONSORT initiative, the QUOROM statement will become available in different languages and locations as it is disseminated. We invite interested readers, reviewers, researchers, and editors to use the QUOROM statement and generate ideas for improvement.

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References
Has the Turner Prize made its bed?

The 1999 Turner Prize Exhibition

Rage and outrage, symptoms increasingly enacted in our daily lives, may be due to PMT—premillennial tension, that is, the pressure to have and say it all before the chimes strike out midnight on December 31. In this, the art world is no exception; the Turner Prize shortlist and exhibition has covered enough steaming column inches to put it back on its perennially disputed pedestal as the most prestigious and pilloried visual-arts award in the U.K. Last year, the penultimate millennial year, the Turner Prize exhibition lost some of its notoriety because, elephant dung aside, the usual moan about the death of painting couldn't be applied, and what is more, the painter won, despite a competitive multimedia atmosphere that was otherwise integral and stimulating.

This year, in a display that should be a reflection of at least some of the parts of a century that has seen the rise and demise of celluloid in favour of digitalisation, is it odd then that film constitutes a significant component of each of the shortlisted entries? The exhibition does, however, pick through the wider artistic legacy of the 20th century, if only by reference. Themes and metaphors recur and link much of the work, and in the words of Tracey Emin, the most controversial of the exhibitors, the show probably does go a long way to reflecting "the state of the nation's psyche at the moment".

Emin's multimedia display runs from film to embroidery to neon sculptures to installations, including of course the inciteful My Bed. That Tracey Emin's work does have a basis and a tradition is not, nor should be, disputed, even though some of her ideas may not be original. Soiled nappy liners (Mary Kelly), beds and mattresses (John and Yoko, Rauschenberg), and embroidery (social protest art in The Subversive Stitch) have all been previously exhibited. Nonetheless, she is entitled to her version. The bed symbolises the life cycle of our civilisation; traditionally it is where we are born, procreate, and die, where we have fun and where we are sick. Emin's My Bed is an unmade bed, the sheets of which are emblazoned with the secrets and excretions of daily life. Bedside detritus includes the paraphernalia of menstruation, contraception in its many forms, and indulgence. The only thing missing is thePacket of Prozac, or is it? Tracey's experience has become a personal crusade, as opposed to a collective one, with no talk-show host to direct and no self-selected audience. She is therefore more exposed and vulnerable, and therein lies both her appeal and her detraction, full frontal emotion. Her films that are on show verbalise the state of My Bed in an articulate, if somewhat self-absorbed way, and so her work, while valid, is no more than a commentary on the century's twin obsessions of real life drama and public confession.

Speaking of twins, Jane and Louise Wilson, who also live and work together, allegedly prefer no mention of their twindom. This may be because their work alludes to it all the time, with mirror images and doubles a consistent motif. They are film-, video-, and photography-based artists, and their exhibits are about the psychology of space and architecture. Having shared space since conception, this is not surprising. Most of their exhibition is taken up by Las Vegas, Graveyard Time. Filmed in casinos in Las Vegas early in the morning (graveyard time) and at the Hoover Dam that supplies the city's water, split projection mirror images of the empty casinos are spliced and projected onto the two walls of a corner so as to merge in a nystagmus-inducing kaleidoscope, with the empty corridors and turbine rooms of the dam doing the same in the opposite corner. The sounds of the automated cogs of the dam machinery play alongside the sounds of cards being dealt and the roulette ball nervously skittering around the wheel. It is a wonderful, albeit dispassionate, parody of control and fate.

Speaking of betting, the odds-on favourite Steve McQueen, exhibits two films and a slide installation of merging stills. Deadpan, a take on a famous Buster Keaton stunt, is superb; its visual boundaries are black and white and clean-cut, echoing the taut control necessary for successful slapstick. Prey, a tape recorder playing out the rhythm of a tap dancer, nestles in the grass only to be lifted away in a flight of fancy by a white balloon, and to fade into the distance and merge with the white sky, until it can barely be seen or heard. Mesmerised and tantalised by the white screen, we wait to see if the balloon will burst. Luckily, the fantasy is parachuted to safety and the cycle begins again. Heaven, earth, and mortality. Both films are technically
50th anniversary of Ridley's pioneering procedure

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It is unusual for a major medical advance to be traced back to just one individual. If we think diabetes, we think Banting and Best, not one or the other. However, there is no question that we owe to one individual, Harold Ridley, late of St Thomas's and Moorfields Hospitals in London, UK, the discovery of the artificial lens inserted after the removal of a cataract. This procedure has to be one of the most important developments this century in terms of improving the quality of life of many patients. The 50th anniversary of Ridley's pseudo-phakic procedure is November 29.

Cataract blindness is the most common remediable cause of blindness worldwide, and with populations getting older and older it will continue to be of increasing importance. Before Ridley's innovation, the routine operation was extracapsular extraction, which was devised by Jacques Daviel of Bernay, a small town in Brittany, in 1748. Before Daviel, cataracts were dislocated, or couched, into the posterior chamber by a needle inserted at the limbus in front of the iris, which engaged the cataract in the pupil and pushed it backwards, thus clearing the visual axis at the cost of numerous destructive complications. Both couching and Daviel's operation destroyed the focusing mechanism of the eye, thus making awkward inconvenient contact lenses necessary, or in most cases the even more uncomfortable cataract spectacles that were essential to restore the focus but magnified by a third.

Ridley brooded about the possibility of completing Daviel's operation with the aid of an artificial lens (or pseudo phakos) throughout his training. And although he was to some extent encouraged by his father, a consultant ophthalmic surgeon in Leicester, and by his great teacher A C Hudson (Huddy), they both said, "What a good idea but it is far too dangerous". Nevertheless, Ridley proceeded with this imaginative yet logical concept. I had the good fortune to be his resident at Moorfields at the time, 50 years ago, so I was privy to what he was doing and why he was doing it.

Ridley was well aware that such a bold innovation would constitute a challenge to the ophthalmic establishment, but I think even he was unprepared for the vicious nature of the onslaught to which he and his ideas were subjected. However, there is more than one way of going wrong, and is useful in developing countries.

Ridley’s operation restores a patient’s sight to what it was before they developed cataracts, and often the artificial lens used can be tailored to neutralise any refractive error that the patient had in addition to the cataract, so that they may well end up seeing better than they actually—into cameras. Not only do they take the photographs in tripped sequence but the various spin and rinse cycles of the washing machine process the film. Locomotion—Laundromat, a further reference to Muybridge and his landmark studies of human and animal locomotion, has the 12 pictures show the sequence of a horse riding through the laundromat. He uses other structures, such as train toilets, fridges, and wardrobes, as cameras reflecting the camera obscura. His work is funny, original, and technically innovative. In turning the camera back onto ourselves, he persuades us that we can have the last laugh. His exhibit is most deserving of the Prize to be announced on November 30, but ironically enough, Pippin believes that his Turner nomination is the end of the road—or is that millennium?—for him.

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Visionary views of the Amazon

Inner Visions: Artists of the Peruvian Amazon

Showing at The October Gallery, London, U.K.

Accompanied by the symposium "Amazon Visions: past, present, future"
on Nov 6, 1999.

T o an outsider, the Amazon basin evokes many images. Historically, the world's key area of tropical rainforest was considered an infernal jungle populated by primitives, which needed to be controlled so that its natural resources could be exploited. The view of today's commercial prospectors seems little changed, except that now science is the means to relieve the forest of its cornucopia of natural products, including gold, medicines, and even genes. To those of a more liberal persuasion, the region is the epitome of eco-disaster that, despite all efforts, continues to threaten people who lead simple lives in harmony with nature. For some decades, the liberals and the money men have fought to impose these opposing ideals with little regard for the vision that the Amazonian people have for their home. But according to Steve Nugent, visual anthropologist at Goldsmith's College, London, U.K., these popular images of Amazonia are nothing more than stereotypes, albeit detailed and informed ones, which obscure a clearer view of this complex region.

The indigents have other visions, however, that are slowly being brought to the fore in various guises, from scientific collaborations to exhibitions such as Inner Visions. Just as art is often used as a tool of expression by the main keepers of traditional knowledge—the shamans—so art can be a powerful medium for these disempowered people to communicate their worldview to the world at large. The October Gallery exhibition, part of a series showing art from shamanic societies, features work by four Peruvian artists who draw heavily on the shamanistic traditions of their culture to present an inner world that is at once alien and relevant to ours. The images are truly visionary, in the sense that they represent a view of nature that is accessed and understood only through shamanic rituals that include the ingestion of hallucinogenic plants.

On one level, the presented works by Pablo Amaringo, Francisco Montes Shuña, Yando Rios, and Elvis Luna provide an insight into the shamanic cosmos, in which the manifest world in all its glory is merely a small part of a wider, mostly unseen reality. But the art also reflects the intense eco-awareness of the shamanic ideal: since all things are inter-related and can be understood only in terms of these relationships, man's role should be to strive for harmony within rather than domination of the universe. Thus, the rich iconography of jungle animals and plants employed by all artists reflects both the manifest forms of primal jungle spirits and the rich biodiversity found in the region.

Shuña, a practising vegetalista (a healer-shaman who is guided in the use of plants by power plants) uses natural pigments on bark for his exquisitely simple illustrations of his plant-teachers in their physical and spiritual forms. On the other side of a translucent divide, Rios, one of Peru's best known contemporary artists and the son of a shaman, uses modern mixed media to produce striking images of spirit beings, surrounded by luminosity and filled with the animal wisdom of his home.

Amaringo's visions are more recognisable as psychedelic art with echoes of both other esoteric traditions and of what are now believed to be universal aspects of trance states, such as entoptic phenomena (see Lancet 1998; 351: 1295). His former shaman uses bright, sometimes luminous colours and geometric forms in his complex scenes that encompass subjects as diverse as extraterrestrials and shamanic healing. Amaringo now runs the USKO-AYAR Amazonian School of Painting, which he founded in 1988 as a tool for conservation. By encouraging his pupils to develop his skills of internal visualisation (an amazing ability to recreate plants or even whole jungle scenes from memory), he aims to increase awareness and respect for the Amazonian ecosystem among his students and their audiences. The exhibited jungle scenes by Luna, who studied at USKO-AYAR, are a testimony to the richness of colour and detail produced through this technique.

The art, however, is just the focus for the wider field of view that these men have of their home. To draw attention to the broader issues, Shuña and Amaringo participated alongside western experts in a 1-day symposium.
that explored the value of the visions depicted in the art and the wider visions that have shaped and continue to affect the region’s future.

Assuming that the international community does not continue to lie idle behind misguided stereotypes, what future vision should we have of Amazonia? Experts on the region, including Sir Ghillean Prance (former director, Royal Botanic Gardens, Kew, U.K.), and anthropologists Françoise Freedman and Luis Eduardo Luna, point to a view of the Amazon as a storehouse of knowledge with the inhabitants as caretakers. Formerly, freely given indigenous wisdom, such as the way to extract latex and synthetise rubber, was rewarded with exploitation, domination, pollution, and disease. But if Amaringo and Shuña can be considered representative of the peoples of the region, they remain keen to share this knowledge for the greater good through mature partnerships that reflect the shamanic vision of our interdependency.

On many levels, then, we can learn much from these supposed “noble savages”: useful plant lore, eco-awareness, skills almost lost from western societies such as eidetic memory, and even perhaps the ability to use psychoactive substances to expand consciousness and gain knowledge, without that drug use becoming de-ritualised and abusive. Which brings us back to the visions represented in the artwork. During shamanic, the shaman takes the drug—usually, though not always, an ayahuasca mixture—rather than the patient as is more customary elsewhere. Shuña told me that, through the use of power plants, he is guided to “see” the disease as a black spot on the sick person, and to determine what plant-based remedies would be appropriate.

Many westerners may find laughable the concept of accessing some greater knowledge through drug-induced visions. But decades of anthropological and ethnomedical research has failed to explain some great mysteries of Amazonian wisdom. Was it really just serendipity that led, for example, to the complex preparation of Psychotria viridis and Banisteriopsis caapi to make an ayahuasca mixture? Primitive people could not have known that the hallucinatory compound in P viridis (N,N-dimethyltryptamine) can be absorbed through the gut only if administered with monoamine-oxidase inhibitors, as are found in B caapi. For now, this question and many others remain a matter of academic debate. But as Amaringo points out, the Amazon “is a great library”. And further scientific exploration of this repository for the good of humanity is surely reason alone for the protection of the Amazon region and its inhabitants. It is time we started listening to the librarians.

Kelly Morris
The Lancet, London, UK

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**The Nobel Chronicles**

Three scientists shared the 1982 Nobel Prize in Physiology or Medicine “for their research concerning prostaglandins”.

Sune Bergström (figure, left) was born in Stockholm, Sweden, and studied medicine at the Karolinska Institute. After research experience in England and the USA, he rejoined the Karolinska Institute and did lipid research under Ulf von Euler, who had discovered “prostaglandin” from secretions of sheep prostate glands.

Bergström realised that the study of prostaglandin biochemistry posed formidable challenges because of the small quantities of matter involved. By the late 1950s, Ragnar Ryhage, a chemist, and Bengt Samuelsson (figure, centre), Bergström’s graduate student, had developed a new instrument that combined gas chromatography and a mass spectrometer, greatly aiding prostaglandin measurements. By 1962, Bergström, Samuelsson, and colleagues discovered that there were at least six compounds that made up the prostaglandin complex, and that arachadonic acid was their common precursor.

John Vane (figure, right) was born in Worcester-shire, U.K., and studied at Oxford University, earning his PhD in 1953. Vane credits Harold Burn for inspiring in him an interest in pharmacology. For brief periods, Vane worked at Yale University and at the University of London before joining the Wellcome Foundation as Director of Research in 1973. Vane’s first major contribution was in the field of bioassays. He developed such advanced laboratory methods as superfusion bioassay, with which up to six tissues could be studied simultaneously, and blood-bathed organ technique with which the biological properties of tiny amounts of chemical substances could be assessed.

Vane and colleagues discovered that during anaphylaxis in guineapigs three substances are released—prostaglandin $E_2$, $F_{alpha}$, and a hitherto unknown chemical, prostacyclin. Vane also discovered that aspirin blocked prostacyclin actions. One weekend in 1971, he formulated a brilliant hypothesis that the actions of aspirin were mediated by its inhibitory effect on prostaglandin. Within a week, he had proved it.

The ubiquitous nature of prostaglandins and the discovery of their physiological properties led to deciphering of the mysteries of such universally common symptoms as fever, pain, and inflammation. Prostaglandin research also led to the development of treatments for many disorders. Prostaglandins or their inhibitors are now used routinely in stopping premature uterine contractions during pregnancy, closure or maintenance of the patency of the ductus arteriosus in neonates, and prevention of coronary heart disease in adults.

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more than 14,000 people have registered for Autism '99, an international conference for academics, professional practitioners, people with autistic spectrum disorders, families, and care-givers. The conference is unique in that it is entirely web-based. Posted on the site are more than 100 scientific and personal papers, remarks (real audio) by Tony Blair, neurologist Oliver Sacks, and other luminaries, and archived discussion groups. And although the conference technically runs until the end of November, "it's a bit artificial to say it runs for a specific time period, because the site will look like it does now for quite some time," says technical director Mark Smith. That "look" is powerful, thanks to the Flash plug-in. Flash allows for haunting effects, smooth navigation, and pages that download reasonably fast (download the "offline" viewing zip from the Information Centre; it will run on your desktop). Users spend an average of 23 min on the site, says Smith; for most sites, an average visit lasts 3 min. This is partly because the design has a quasi-mesmerising effect, but also because the materials are well-written, accessible, and easily browsable.

I found the "In Our Own Words" papers most compelling. Here, for example, musician Ian Stewart reflects on the life and work of Andy Warhol; Temple Grandin, author and scientist, is concerned that intellectually gifted children with autism are not receiving a proper education because worry about their social lives leads to neglect of their intellectual lives. In addition to these personal perspectives, the papers area offers insights into autism research, diagnostic and assessment tools, psychological and social interventions, and policy issues.

But the web conference—a joint project of the National Autistic Society (http://www.oneworld.org/autism_uk), Shirley Foundation (a newly formed autism charity), and RMR Design Associates Ltd (http://www.mrmdesign.com)—is just the beginning, according to Smith. Web seminars will start in December, followed by the launch of Autism2000, a portal site that will host the materials from the current site, and also offer personalised content for people with autism and others, and a dedicated search engine for web autism sites.

"The internet is for many high functioning autistics what sign language is for the deaf," writes Martijn Dekker, who runs an e-mail support group. And the internet conference can help those of us without the disorder to better understand it.

"I t was an old-fashioned lynching, carried out with the help of county officials, that came to symbolise hardcore resistance to integration. Dead were three civil rights workers, Michael Schwerner, Andrew Goodman, and James Chaney, all shot in the dark of night on a lonely road in Neshoba County, Mississippi." So begins a riveting account by legal historian Douglas Linder (University of Mississippi-Kansas City Law School, USA) of the 1967 "Mississippi Burning" trial, complete with quotes from local papers, Ku Klux Klan (KKK) documents, maps, trial transcript excerpts, and images. There is something chilling about reading these materials in their original form, without massage or commentary. What to make of the KKK, for example, which proclaims "We are looking for, and enlisting ONLY: Sober, Intelligent, Courageous, Christian, American, White men." The Mississippi case is one of a dozen featured on a website that began as a teaching tool for Linder's university seminar. Others include the Scopes "monkey" trial, in which Clarence Darrow defended John Scopes, a high school teacher accused of violating a state law for teaching about evolution; the My Lai courts martial of William Calley, accused of brutally slaughtering civilians in Vietnam; and the trial of accused spies, Ethel and Julius Rosenberg.

After launching the site, "the large number of e-mails from outsiders convinced me that there was a broad interest in learning about historic trials," says Linder. He will begin adding famous world trials—eg, of Socrates, Jesus of Nazareth, Joan of Arc, Thomas Moore—to the website next year.

**More about autism**
- Autism Network International http://www.anl.ac/
- Autism Research Centre (ARC) http://www.psychiatry.cam.ac.uk/arc
- Center for the Study of Autism http://www.autism.org/
- internAUT http://spidernet.nl/~martijn_dekker/internaut/intro.spml
- OASIS (Online Asperger Syndrome Information and Support) http://www.udel.edu/bkirby/asperger/

**Net News**

Neurologists and the Internet, a review article in the November Archives of Neurology has a comprehensive table of neurology resources on the web, with URLs accurate as of Sept 20, 1999.
- Internet Policy Institute launches as a non-profit, non-partisan "independent think tank" dedicated to researching subjects from the role of the internet in privacy to the internet's impact on taxation and health care.
- http://www.internetpolicy.org
- NetCoalition.com—the public policy voice for leading internet companies—announces a "Privacy Education Campaign" for web users. The initiative includes public service announcements and other online promotions aimed at directing users to privacy resources and information.
- http://www.netcoalition.com
Older local developments have made me realise how sketchily health texts. Yes, there is mention of hair growth, scrotal and breast changes, and the adolescent growth spurt. There are, however, many other things that parents have to endure.

As is well known, male voices break. Almost overnight, I found my eldest son's cherubic tones had turned into a loud deep growl which would not disgrace a foghorn or a station announcement, and was about as comprehensible.

As for hair, it does of course start sprouting. Or rather it sprouts on legs and armpits, though not on the upper lip until later. In fact, the rate of facial hair growth in pubertal boys varies in inverse proportion to the time spent in front of the bathroom mirror.

A lot of time is spent in the bathroom around now, because this is when boys discover something that girls have long known about. It is water. Unfortunately boys are not all adept at using it. I know one lad who had not thought to remove his socks in the shower. His economy in the use of water was such that these did not even get damp while he washed.

And what socks! As parents know, little boys smell like rabbit hutches. Bigger boys are something else, and, thanks to the use of water was such that these did not even get damp while he washed. And what socks! As parents know, little boys smell like rabbit hutches. Bigger boys are something else, and, thanks to

Griffith Edwards

After qualification in medicine and undertaking postgraduate training in psychiatry, Griffith Edwards' career has centred on the study and treatment of addictions. He is editor-in-chief of Addiction and is a member of the WHO Advisory Panel on Alcohol and Drug Dependence.

Who was your most influential teacher, and why? Jo Osipoff, who in the 1940s brilliantly taught me mathematics and lent me Adam Bovary.

What event has had the most effect on your work, and why? In the early 1960s, Abraham Wikler altered my understanding of addiction science over lunch in the Maudsley canteen.

What would be your advice to a newly qualified doctor? Taste your own joys.

How do you relax? Iileness of several different hues.

What is your greatest regret? Envy of friends who have unfairly been dealt multiple creative talents that I don't possess.

What complementary or alternative therapies have you tried? Did they work? I have always seen orthodox medicine as a pretty good alternative.

Who is the greatest love of your life? She's a brilliant cook.


What is your favourite building? Nightingale—it enwraps me.

What socks! As parents know, little boys smell like rabbit hutches. Bigger boys are something else, and, thanks to conditioning.

A teenager's clumsiness is legendary. According to one piece of research I came across, this is because boys in particular grow so fast that their muscle power outstrips their brains. This explains why adolescent boys, on their many trips to raid the fridge, have the knack of tripping over perfectly smooth vinyl floors.

But all this is as nothing compared with the mental trauma of adolescence. “Physical growth does not hurt, though emotional growth can hurt like hell” wrote the distinguished paediatrician John Apley, who obviously knew what he was talking about. Sense-of-humour failure is characteristic of puberty. This is why if, as a parent, you refuse your teenager’s demands for a TV in the bedroom or a second computer, or you point out gently where the laundry basket is, he either throws things at you or threatens to kill himself.

At times like these, parents may suspect that the trials of puberty are their own fault, or else they wonder if their youngster is on drugs. The truth is that adolescents are already on drugs. They are hormones, the most potent mind-altering chemicals of all.

I recently came to the comforting conclusion that it is not just human beings who find adolescence painful. One family I know kept chicks, hand-rearing them as soon as they had emerged from their eggs. For weeks the imprinted chicks adoringly followed the humans around as if they were the parents—until the hormones kicked in. The chicks turned aggressive, pecking viciously at them for no apparent reason, and seemingly having forgotten all their earlier conditioning.

Similarly, your fluffy little kitten playing with a ball of wool will tomorrow become a leggy adolescent who wanders off snootily whenever he feels like it. He may well commit hare-kiri in the high street, or else he will survive and return home to spray everything in sight just to let you know it is his. After he has marked it, you will not want it any more. You may not want him either, at least not until he has had a trip to the vet to reduce his testosterone levels on a permanent basis.

My advice to human parents? Hide all your breakables, lay in some wine or spirits to relax you, and prepare for a siege lasting several years. It is not your fault, except perhaps for that lapse in contraception a dozen or more years back. Adolescence is like a rerun of toddlerhood, but writ large.

Carol Cooper