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Insider trading versus medical professionalism

Lawmakers in the USA are calling for federal investigations of allegations that medical researchers are sharing confidential clinical trial data with investment analysts, who then use that information to beat the market.

In an investigative report published last month, reporters for The Seattle Times identified 26 cases in which doctors allegedly leaked information about unreleased drug-research findings to investment analysts. The confidential information would have allowed a select few investors to buy or sell stock days, and even months, before the research results were released to the public. The leaks, the paper said, may have violated not only confidentiality agreements the researchers signed with trial sponsors, but also insider trading laws. In a response to the paper’s report, Senator Charles Grassley, a Republican from Iowa and head of Senate Finance Committee, has called for an investigation by the US Department of Justice and the US Securities and Exchange Commission.

In recent years it has become common for US doctors to work as consultants to brokerages, hedge funds, and investment research groups. Some serve on the advisory boards of investment firms, but many sign up with “matchmaker” firms that link investment analysts with experts in a wide variety of fields. Doctors typically earn US$200–1000 an hour for their time. By one estimate, more than 75 000 US doctors have signed up to work as consultants, roughly one in ten, although the proportion is likely to be higher among academic researchers, whose expertise is more highly valued.

It is not surprising that investors would want to “pick the brains” of medical experts. Health care comprises roughly 15% of the US economy: there are fortunes to be made—and lost. Before investing, it makes sense to talk to doctors who have the scientific background and clinical experience to judge which new drugs and medical devices are likely to succeed and which are not. Doctors who serve as consultants say they do not provide confidential information but just pass on what is generally known in the field. And officials from “matchmaker” firms say they require experts who want to be consultants to promise they will not violate any confidentiality agreements they have already signed.

But researchers have access to a vast amount of confidential information: they have, of course, their own research, about which they are likely to have signed confidentiality agreements; but they also chat about ongoing research with colleagues at work and at conferences; they assess protocols from other research groups for granting agencies; and they participate in peer review of confidential manuscripts for journals. To let slip confidential information in a meeting with analysts would be very easy.

Indeed, one analyst boasted to The Seattle Times how easy it was to pry information out of researchers. This analyst claimed to have studied elicitation techniques used by police and intelligence interrogators. “We get them to talk about the weather, or the Mariners [the Seattle baseball team], then you pop in your one innocent question you want to know about”, he is reported to have said. “Then you switch back to whatever it was you were talking about before. When the doctor hangs up, he thinks he’s had a nice conversation about the weather or the Mariners.” In fact, simply refusing to answer a question can often give the answer the questioner is seeking.

Researchers who decide to be consultants to investment firms and investment analysts are clearly treading a fine line. Those that choose to be consultants must at the very least fully disclose their consultancies to their institutions and the sponsors of their research and when they present, discuss, or publish their data. Medical research institutions should also examine their regulations and decide whether they should allow such relationships and whether stricter regulation is necessary. At the very least, full disclosure should be required and mechanisms must be in place to determine if the relationships present a conflict of interest with a researcher’s scientific work.

We would hope that medical researchers consider carefully whether consulting for investment firms is in the best interests of science and medicine. Yes, it can be argued that helping investors make informed decisions helps bring funds to promising research. But as science and business appear to become more inextricably linked, the assertion that the primary goal of scientific research is to find the truth becomes less convincing in the eyes of the public. Researchers tempted to become consultants for investment firms should ask themselves whether the fees are worth that price; we suggest they are not. ■

The Lancet
The Global Fund is right to take a stand on Uganda

It is one thing to withdraw financial support from a failing health initiative; it is quite another to take a principled stand against misuse of funds when the project in question is revered for its achievements. Yet this is just what the Global Fund to Fight AIDS, Tuberculosis and Malaria has done this week, by suspending all five of its grants to Uganda.

Uganda’s record on AIDS has given it the reputation of a model African nation. Indeed, the country’s national AIDS control programme has previously been described by Global Fund literature as “exemplary” due to its sustained success in reducing the prevalence of HIV since 1992. But this success, it seems, is despite rather than because of Uganda’s government-level administration of the grants.

A review of one of Uganda’s five Global Fund grants, done by PriceWaterhouseCoopers, the local fund agent, revealed evidence of serious mismanagement by a unit of the Ministry of Health, which had responsibility for overseeing implementation of the Global Fund grants for the Ministry of Finance. There is no concrete evidence of corruption or fraud, but the Global Fund last week requested that this ministry unit be disbanded, and they demanded that the Finance Ministry devise an alternative implementation plan by the end of October.

Suspension of grant money is not an unprecedented step: last month, the Fund terminated money to Burma and last year Ukraine had its awards suspended in circumstances similar to those in Uganda. But the decision comes at an awkward time for the Fund. Only a few weeks ago, a renewal of Uganda’s HIV/AIDS grant was approved, a milestone that makes the current suspension slightly embarrassing. And, perhaps more importantly, this week international donors are due to meet in London for the third conference of the Fund’s new Voluntary Replenishment Mechanism—a system set up this year to improve the predictability of its cash flow.

News of Uganda’s problems is unlikely to escape mention at the London meeting. But as funders discuss cash commitments for 2006 and 2007, they should be mindful of the GF’s impressive achievements—helping support 220 000 people on AIDS drugs, treating 600 000 individuals for tuberculosis, and supplying medicines for 1·1 million people with malaria—as well as its difficulties.

A real headache for policy-makers

“Imagine, your eye is pushed out of its socket and your right eyelid is beginning to swell shut. You start squinting and your eye is tearing, you are convinced there was blood pouring out. A red-hot knife is crushed into your head, excrutiating, horrible, horrible pain”. This is how a patient who suffers from cluster headaches describes her condition in a Seminar published this week. Cluster headache, one of the most debilitating types of headache, is thankfully relatively rare with a prevalence of less than 1%. However, virtually everyone, whether rich or poor, will experience a debilitating headache during their lifetime.

Far less is known about the epidemiology of headache in low-income countries, where resources are understandably targeted towards fighting killers such as AIDS, tuberculosis, and malaria. The Global Campaign to Reduce the Burden of Headache, an alliance of non-governmental organisations and WHO that was formally launched in March, 2004, has started to gather information, by region and by country, on how healthcare resources are allocated to headache disorders. The Campaign has also funded research projects to fill in the gaps in the evidence base. It expects the resulting data to show that headache disorders are in the top ten causes of disability worldwide.

The leaders of the Campaign intend to use these data to raise awareness of the importance of headache to local governments, and to encourage them to tackle headache with practical local solutions. This will not be an easy task, since the barriers to care are considerable in resource-poor settings. Education is the key to success: headache disorders can be managed effectively if doctors know how to diagnose them correctly and if patients are taught to understand what triggers an attack. Importantly, the high prevalence of headache disorders means that even a small amount of progress will help thousands of people to live fulfilling lives free from headache.
ISAT trial: coiling or clipping for intracranial aneurysms?

In today’s Lancet, the International Subarachnoid Aneurysm Trial (ISAT) collaborators report a follow-up to the first landmark ISAT report, a randomised trial comparing neurosurgical clipping with endovascular coiling in patients with ruptured intracranial aneurysms. The investigators report the results after 1 year for the primary outcome measures of death and disability, and the secondary outcomes, such as epilepsy, rebleeding from the treated aneurysm, and the findings on follow-up angiography. They report a relative risk reduction for dependency or death of 23.9% with an absolute risk reduction of 7.4% in patients undergoing coiling, and conclude that in patients with ruptured intracranial aneurysms suitable for either treatment, a policy of endovascular coiling was substantially more likely to result in independent survival at 1 year compared with neurosurgical clipping. In addition, they report that the risk of rebleeding is low with endovascular coiling but lower with clipping. The initial report generated a large amount of controversy because it was believed by many that this study provided evidence that coiling is superior to clipping in all patients with an aneurysmal subarachnoid haemorrhage, and by others that the study was flawed. However, to a certain extent, ISAT only confirms data that have already been shown in other studies, with some reservations and revelations. First, of the 9559 patients that were eligible for inclusion, 78% were excluded. 9% of the exclusions were for refusal to participate, and the remaining 69% were excluded from the study because the aneurysm could not be treated by either procedure. Almost all intracranial aneurysms can be treated by surgery and therefore 69% of the aneurysms were excluded because they probably had a configuration not suitable or ideal for coiling. This proportion could be interpreted as representing a selection or sample bias in ISAT because a larger number of posterior circulation aneurysms would have favoured coiling, and a larger number of middle cerebral artery aneurysms would have favoured surgery.

Nonetheless, ISAT is not comparing the outcome in all aneurysms, but rather sought to establish which treatment is safer in those patients whose aneurysm was suitable for either treatment. Therefore ISAT has shown that, in those patients with aneurysms 10 mm or less in size that have a favourable configuration to be coiled, coiling is associated with less morbidity than clipping. However, this finding cannot be translated into believing that coiling is safer than clipping in all cerebral aneurysms. For example, most middle cerebral artery aneurysms are currently better treated with clipping, and aneurysms that do not have a configuration suitable for coiling, such as those with a small dome-to-neck ratio or having branches coming out of the aneurysm, will have a significantly worse outcome with coiling compared with clipping.

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The major concern that I have with ISAT is that, although the investigators report a relative risk reduction for dependency or death of 24% with coiling compared with clipping, I believe this is not the true extent of the difference. First, patients allocated to neurosurgery had a 50% or higher rebleed rate before treatment and these patients were included in the safety evaluation, which biases the results in favour of coiling.

Second, do these safety data apply to all neurosurgeons and all neurointerventionalists? The answer is probably no. The surgical results of the surgeons in the study were not what would be expected from neurovascular surgeons. The postclipping aneurysm remnants and the surgical mortality were higher than in other published series, and 3-5% of the patients underwent either wrapping, partial clipping, or no clipping, despite the fact that 93% of aneurysms were 10 mm or less in size. Most neurovascular surgeons would either clip these or use bypass techniques to secure the aneurysm. These surgical results can probably be accounted for by the surgeons’ experience and absence of intraoperative angiography. In ISAT, the neurosurgeons were generalists from Europe (for 95% of the patients), and published data indicate that for neurosurgeons and interventionalists, procedure volumes and experience directly affect outcome.9,10

By contrast with the European neurosurgeons, neurointerventional medicine is a highly specialised subspecialty. A comparison of the safety outcome in an aneurysm treated by a neurovascular surgeon and a neurointerventionalist is not answered by this study. Furthermore, the preservation of the parent vessel and its branches is vital in preventing a stroke and optimising outcome in patients undergoing treatment of their aneurysm. This preservation is best verified angiographically at the time of the procedure and in the surgical group no patients had intraoperative angiography compared with the endovascular group, in which angiography is an integral part of the treatment. This difference clearly creates a bias for success in the endovascular group regardless of whether it is standard practice or not to do angiography with surgical clipping in Europe. Visual estimation of aneurysm occlusion, as was described in ISAT, is often proved inaccurate and is not used in centres of excellence where intraoperative doppler and intraoperative angiography are often standard practice.11 Therefore the differences in safety data would probably have been less with the use of experienced neurovascular surgeons and intraoperative angiography.

When deciding what treatment option is best for a patient, the safety of a procedure is important. However, efficacy and durability are equally important, particularly in young and healthy patients, and the same argument applies in the management of a cerebral aneurysm. Therefore, in a ruptured aneurysm, the treatment must exclude the aneurysm from the circulation and change the natural history by preventing rebleeds both in the short and long term. ISAT and other studies12,13 have shown the superiority of clipping compared with coiling in achieving both of these goals, despite the discrepancy of operators’ experience and lack of intraoperative angiography in the surgical group in ISAT. Complete angiographic occlusion was found in 66%, subtotal occlusion in 26%, and 8% had incomplete occlusion with coiling. versus 82% complete occlusion, 12% subtotal occlusion, and 6% incomplete occlusion with clipping. These endovascular results are better than most reported series and probably represent a combination of factors that includes selection of aneurysms that were ideal for coiling and expertise of the endovascular surgeons. However, early and late rebleeds were much higher with coiling after treatment. Moreover, the early 11 rebleeds allocated to the neurosurgical group might have been treated with coiling because of crossover. After 1 year, eight of the nine patients that rebled underwent coiling compared with one patient in the surgical group that never received either intraoperative or postoperative angiography. Particularly concerning are the rebleeds in two patients who had complete angiographic occlusion with coiling.

Therefore ISAT has only validated endovascular coiling as another viable option in the management of patients with subarachnoid haemorrhage. Each patient and their aneurysm is different and the decision has to be made about what is in the best interest for each patient. None of the treatment options are superior, but rather each has strengths and weaknesses that can be used to decide what is best for each patient. Some patients should be clipped and some should be coiled. The ultimate decision is complex, including many variables to ensure the most appropriate care. These variables the surgeon’s or interventionalist’s experience, the patient’s factors, and aneurysm factors. Patient’s factors include age, clinical grade after the haemorrhage, and expected longevity. Aneurysm factors include aneurysm size, location, dome-to-
neck ratio, and presence of calcification. For example, it might be more appropriate for an elderly patient or a poorer-grade patient with a limited life expectancy to receive no specific treatment or a treatment that is safer than one that provided decades of cure. Similarly, a young patient might forego a safer treatment for one that is more permanent. Therefore management of a patient with a cerebral aneurysm will now be enhanced because physicians will have a validated additional tool in their armamentarium.

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I declare that I have no conflict of interest.


Humiliation instead of care?

Qualitative studies appear increasingly often in medical journals, showing their capacity for progress of knowledge beyond measures and numbers.1 Most qualitative medical studies are presented descriptively. Although such approaches can reveal hitherto underestimated accounts of people’s lives and health, their explanatory power might be limited. Analysis beyond storytelling is necessary to provide new understanding when change is called for.

In today’s Lancet, Lucy Smith and colleagues present an example of applied methodological advances in their meta-ethnography study about symptom and help-seeking experiences in cancer patients.2 Ethnography is the systematic description of behaviours and beliefs of a culture, usually based on anthropological fieldwork. Meta-ethnography is a related strategy, in which findings from several qualitative studies are pooled and re-interpreted.3 Once relevant studies have been identified and checked for scientific quality, interpretations across studies are translated into one another. Synthesis can be drawn from reciprocal translations of studies that are directly similar, refutational translation of studies opposing each other, or from logic translation of studies showing a line of argument, making coherence explicit.3 Meta-ethnography is not the same as meta-analysis, in which data from randomised trials or observational studies are compiled to increase the power of outcomes.4 In meta-ethnography, the diversity of findings is used to identify patterns that were not apparent in first-order analysis. The aim is not to test hypotheses by significance or consensus.

Smith and colleagues pooled findings from 32 qualitative studies about cancer patients’ experiences. Fear of cancer and of embarrassment were identified as barriers to seeking help. Patients explained that they did not contact their doctor when symptoms appeared, because they were worried about being labelled as “hypochondriacs” or “time-wasters”. Synthesis and re-interpretation also revealed that gender affected whether patients sought help or not, as well as seeking support from friends and family.
Comment

To me, as a clinician, patients’ fear of embarrassment is the principal finding of Smith and colleagues’ study. New questions of a more fundamental character arise: why do patients fear the verdict of the doctor? How do they learn to see their helper as a judge of dignity? What are the medical consequences of shame and blame? Where are the opportunities for explanation and change?

When cancer patients report their fear of humiliation in the medical encounter, it is no longer a question about some good guys and some bad guys, but a matter of behaviours and beliefs in the medical culture. Smith and colleagues offer a description of the unfortunate state of affairs. However, the findings are not pursued further in a theoretical analysis, in which causes and consequences could have been explored. A call for change requires a more specific understanding of the structural forces at play in the interface between knowledge and power.

A widely held biomedical assumption is that disease manifests itself as objective findings, which can be observed by the doctor. Patients have learned that the medical gaze and the voice of medicine have given the doctor the power to decide which of their symptoms are valid and relevant. Patients with complaints perceived by the doctor as trivial run the risk of being turned down. Women with chronic pain tell about consultations in which they are met with scepticism and lack of comprehension, feel rejected, ignored, and belittled, blamed for their condition, or assigned psychological explanation models.

Smith and colleagues show that the fear of embarrassment is not restricted to patients with medically unexplained disorders. The authors bring forward an alarming message about lack of trust. The findings indicate that patients do not trust their doctors to believe their symptoms of pain and suffering. Instead, disempowering interactions of shame and humiliation are expected.

For most people—doctors included—it is painful to realise that one’s behaviour can contribute to disempowerment of other people. But oppressive behaviour is hardly ever acted out deliberately. This behaviour emerges in health care as a cultural manifestation of how society’s general patterns of power are reproduced and sometimes produced by medicine. In the politics of medical knowledge, the notion of objectivity rules. From this foundation, doctors are allowed to dismiss subjective matters, such as pain, suffering, and trust, is needed in medicine to prevent further fear of embarrassment in patients.

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Comment

Reaching the unreached with measles vaccination

In today’s Lancet, Mac Otten and colleagues show the dramatic success achieved in the acceleration of efforts to reduce measles mortality in Africa between 2000 and 2003. The authors describe a decline in reported measles cases of 91% and estimate that the number of absolute deaths averted in 2003 was around 90 000. In other terms, that measles-specific mortality was reduced by 20% for Africa as a whole. The authors also conclude that initial supplemental immunisation campaigns targeting children aged 9 months to 14 years are more effective in reducing measles mortality than those targeting children aged 9 months to 5 years.

Furthermore, in conjunction with continued routine immunisation, follow-up campaigns sustain and strengthen the gains made in measles mortality reduction. The results represent a significant achievement for the 19 governments involved and for the innovative partnership, known as the Measles Initiative, that has provided funding and technical assistance.

In 2001, the joint UNICEF and WHO global plan for measles mortality reduction was released and included four major strategies: improved routine immunisation, a second opportunity for measles vaccination (usually through supplemental immunisation campaigns), optimum measles case-management, and enhanced measles surveillance. The target was a 50% reduction in annual measles deaths by 2005 compared with 1999 levels—to less than 440 000. This target will be achieved on time and a more ambitious target of a 90% reduction by 2010 will be set. Further substantial progress in Africa needs focused efforts on the few large countries, including Nigeria and the Democratic Republic of the Congo, which account for most of the remaining burden of measles disease.

The Lancet child survival series estimated that measles causes 1–9% of the 10·8 million deaths in children aged under 5 years every year. Of the preventable causes of deaths listed in The Lancet series, measles is perhaps the disease for which we have the most cost-effective and most readily available intervention. Studies in South Africa and Zambia, and recent work in emergencies in Afghanistan, confirm these cost estimates. The cost of delivering measles vaccine in a campaign was about US$0·60–1·00 a child, with overall cost savings by averting disease and deaths. In addition to the benefit on measles-specific mortality, several researchers have suggested that the benefits of measles vaccination might extend well beyond that attributable to the protective effect of the vaccine against the measles virus alone. This effect might be because of a non-specific immune boost; further research is needed to confirm whether the mortality benefit of measles vaccination is substantially greater than assumed previously and to investigate the specific mechanisms of these beneficial effects.

The challenge remains to achieve and sustain measles mortality reduction in all countries, which will require greater efforts to improve implementation of all four parts of the strategy. Emphasis should be on improving routine immunisation, conducting safe and effective supplemental immunisation campaigns, and using measles supplemental immunisation campaigns to strengthen the cold chain and surveillance, as well as to increase demand for routine measles vaccination and clinical services. Higher routine coverage will allow follow-up campaigns to be less frequent. Quality will remain central to success; poor supervision and training might amplify the risk for adverse events, which can harm children and damage community confidence in immunisation for years to come. Measles control programmes and, immunisation programmes more generally, must be strengthened in the context of broader strengthening of health systems. Such pro-
Skin construct or biological bandage?

In today's Lancet, Judith Hohlfeld and colleagues1 describe the use of cultured fetal skin fibroblasts embedded within sheets of insoluble collagen to treat burns in young children. Benefits claimed for this procedure include rapid healing with cosmetically satisfactory results (ie, lack of scarring) and the avoidance of autografting. The success of the procedure is ascribed at least in part to the biological activities of growth factors secreted by the donor fibroblasts that are transiently present in the wounds.

Within the burn-treatment community there is much interest in "skin substitutes" to cover, especially, large wounds. Because of improvements in resuscitation, infection control, nutritional support, and surgical aspects of wound management, even 95% burns of the body surface area are now survivable by children 50% of the time.2 With this enhanced survivability come short-term and long-term complications: the increased demand for material to cover the wounds (to control pain, reduce fluid loss, and deter infection) and the increased risk of hypertrophic scarring. This last issue has been characterised as "the single most important unresolved problem in burn care".3 While autologous split-thickness skin grafts are likely to be the treatment of choice in large second-degree and third-degree burns for some time to come, the lack of suitable donor tissue in the most severely injured patients fuels the demand for alternative temporary or permanent wound coverings. Those coverings currently available commercially or in development range from the acellular composite synthetic and if combined with other interventions, will represent a major contribution to achieving Millennium Development Goal 4.

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We declare that we have no conflict of interest.


Comment

Programmes need to receive adequate attention in sector-wide and poverty-reduction strategies, and need to be incorporated into national plans and budgets so that reliance on external donor funding gradually decreases.

In May, 2005, WHO and UNICEF released a global strategic framework for immunisation, the Global Immunization Vision and Strategy.1 The framework highlights the importance of immunisations for achieving Millennium Development Goal 4: reducing under-5 mortality by two-thirds by 2015. It emphasises measles mortality reduction and reiterates that the supplemental immunisation campaigns’ platform should be used to deliver other child survival interventions, which might include insecticide-treated bednets, vitamin A and iron/folate supplementation, and anthelmintic drugs. The framework also emphasises equity in immunisation programmes, reaching the most vulnerable and marginalised—the unreached. In the future, new vaccines, such as rotavirus and pneumococcal vaccines, will be added to the menu of available interventions to combat under-5 mortality through campaigns and routine immunisation services.

With sustained support for the strategies elaborated and reaffirmed in the Global Immunization Vision and Strategy, most deaths from measles globally can be prevented by the end of the decade, thus virtually removing a major infectious disease scourge affecting children in developing countries. This success, especially
natural materials (eg, Biobrane® and Integra®) to the completely natural (xenograft, allograft, and cultured autologous cells, alone or with a "dermal equivalent"®).

Each of these materials has its proponents and its advantages and each has found application in burn care. Unfortunately none is ideal in all situations. Problems include poor mechanical integrity, immune rejection, inconsistent vascularisation, and failure to integrate. Re-operation and replacement of the construct with autograft is often the only recourse. Even what is arguably the most promising skin substitute—a xenogeneic collagen/glycosaminoglycan dermal equivalent populated with the patient’s fibroblasts and covered with his/her keratinocytes—may be less than ideal in practice. Certainly, a well-equipped laboratory and highly trained support staff are needed to harvest uninjured tissue from the patient (tissue that might be in short supply), to separate and expand the populations of keratinocytes and fibroblasts, and to culture these cells with the dermal equivalent. These procedures can take several weeks and the cost of sufficient material to cover a large-area burn can be prohibitive.

Ostensibly, the use in skin substitutes of fetal human fibroblasts derived from an individual donor, as described by Hohlfeld and colleagues, has many potential benefits. These cells, screened and certified free of known pathogens, are available at short notice and in large numbers (we are told that sufficient are on hand to populate several million 9 × 12 cm sheets of collagen). They grow and divide rapidly, and apparently lack the cell-surface antigens that might otherwise trigger an immune response. None of the eight young burn patients in Hohlfeld’s study required an autograft, although all were considered by the authors to be candidates for this procedure had they not been treated as described, and none developed hypertrophic scar. Nevertheless, it remains to be seen how this construct would fare on the more extensive full-thickness wounds with which the burn surgeon must often contend.

Is this then the end of the search for an ideal skin substitute? We would argue that it is not, and that the medical device described by Hohlfeld and colleagues, which is applied repeatedly and is rapidly degraded in vivo, should properly be considered a “biological bandage”. This comment is not intended to devalue the contribution of the work that, in pioneering the use of banked fetal fibroblasts in skin reconstruction, could be considerable. Rather we wish to point out the undiminished need for a true skin substitute: one that is available “off the shelf”, is mechanically robust, provides an immediate barrier to moisture loss and infection, and becomes integrated into the host tissue, either permanently or for as long as necessary to prevent hypertrophic scarring. We can look forward over the next few years to more exciting developments in this field, probably driven by the advances in stem-cell research that hold the ultimate promise of reconstructing in vitro the complex organ that is skin.

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Did BSE in the UK originate from the Indian subcontinent?

In today’s Lancet, Alan and Nancy Colchester1 put forward a scientific hypothesis that bovine spongiform encephalopathy (BSE), which has affected mostly the UK and to a lesser extent European dairy cattle, is the result of feeding vegetarian animals with an imported carnivorous diet. They further hypothesise that imported meat-bone meal from the Indian subcontinent was contaminated with human carcasses infected with Creutzfeldt-Jakob disease (CJD).

BSE has occurred in imported and indigenous cattle of several countries other than the UK.2,3 The origin of such cases has been attributed directly or indirectly to the export of infected cattle or infected meat-bone meal from countries with BSE. The incidence of the epidemic in most European countries where efficient surveillance or monitoring systems are in place implies indigenous exposure rather than direct linkage with imported cattle feed. Epidemiological studies in the UK have revealed a greater risk of developing the disease in the offspring of clinical cases of BSE (although risk perception has been downgraded recently on the basis of estimates and extrapolations).4

The probable spread of disease to human beings manifested as variant CJD has been proposed to be due to molecular similarities of the disease-related isof orm of abnormal prion protease-resistant protein (PrPsc) from human patients and certain animal species with naturally acquired or experimentally transmitted BSE. The biological behaviour of transmissible spongiform encephalopathy strains during their transit from one species to another and their adaptive behaviour when passed into secondary species from the primary source is still to be elucidated. It is appropriate and important to address all sources of meat-bone meal imported to the UK, from the Indian subcontinent and other countries, which could have contributed to the so-called human disease being transmitted to cattle by contaminated cattle feed. This broad analysis is vital for a better understanding of the evolution of this disease.

The Colchesters assume the prevalence of sporadic CJD to be uniform worldwide. However, one should also consider the role of geographic variations and genetic polymorphisms (panel). To date, India has had 85 recorded cases of sporadic CJD reported over the past 37 years.5,6 In India, all clinical and pathological specimens (biopsies and autopsies) are referred to the CJD Registry at the National Institute of Mental Health and Neurosciences, Bangalore, India. When the diagnosis is suspected, relatives are persuaded to undertake deep burial or cremation, respecting religious sentiments. Most Hindus do not eat beef, except for a few specific communities in India. Histopathologically verified CJD has been observed in vegetarians, suggesting that their disease belongs to a sporadic variant of CJD unrelated to dietary habits.

By the Colchesters’ extrapolation, 150 deaths in India are related to CJD. In most of the hospital-related deaths, the bodies are not taken to Varanasi, the holy city on the

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[Image: River Ganges at Varanasi]
banks of the Ganges in North India, but cremated or buried in community burial grounds. Even in Varanasi, most Hindus do not put half-burnt bodies into the river. The Colchesters have drawn heavily from pictures on the internet and other sources. A human body put into the river undergoes substantial putrefaction, unlike fallen cattle. No study has been done to establish whether or not putrefied human cadaver brain and spinal cord tissue from the Ganges contains CJD, and experimental transmission from this human source into animals has not been attempted. Successful transmission by feeding animals with this purportedly infective tissue seems unjustified, especially as pooling with other animal protein would have occurred in the meat-bone meal exported to the UK, and could conceivably result in an enormous and unspecified dilution that would greatly reduce infectivity. One approach would be to characterise the PrP* (the disease-causing protein) strain from the brains of CJD cases in India and show homology with PrP* in the afflicted British cows. If the bodies found in the Ganges were found to have CJD, there should have been a major epidemic in north India.

So far not a single case of BSE or scrapie has been reported from India, except for one case of scrapie from the Himalayan foothills in a sheep, which was probably imported. In India, the prevalence of CJD spreads far beyond the banks of the Ganges. Scientists must proceed cautiously when hypothesising about a disease that has such wide geographic, cultural, and religious implications. We agree that the idea proposed by the Colchesters needs to be probed further. Facts to support or refute their hypothesis now need to be gathered with urgency and great care.

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Panel: A few ground realities

- 85 cases of CJD have been recorded over past 37 years (1968–2005) (definite 40, probable 45 cases, according to Master’s criteria). 85 cases in population of 1 billion (0.085/million) is less than 0.5–1.0 in a million population worldwide. The CJD registry was established at National Institute of Mental Health and Neurosciences in 1988. Nationwide survey was done with predetermined comprehensive questionnaire (32% of cases aged 55–65 years; 25% of cases aged 35–45 years). Ten of 25 cases where dietary history was available were vegetarians.
- The Registry confirmed cases by immunohistochemistry on brain tissues from suspected cases of CJD. No case of iatrogenic CJD or variant CJD has been reported from India.
- No case of BSE has been recorded from India. Five Regional Disease Diagnostic Laboratories in India did surveillance for Ministry of Agriculture, Department of Animal Husbandry Dairy ing, New Delhi, from 2001 to 2004. Cattle and buffaloes from slaughter houses and fallen animals (ailing cattle with neurological deficits and dead are screened, and have been found negative for BSE). No case of scrapie has been identified from India (except for one anecdotal case).
- Indian meat exported to international markets is declared safe by Organization Internationale Des Epizooties on Animal and Animal Product Trade. It is difficult to obtain official information about export and import practices and magnitude during 1960–80 from India.


The changing face of NICE: the same but different

The National Institute for Health and Clinical Excellence became a reality on April 1, 2005, when the functions of the Health Development Agency transferred into the National Institute for Clinical Excellence. The combined organisation—which will still be known as NICE—will continue to provide clinical guidance; but it will also be
Comment

Panel: Priority public-health topics

Public-health interventions
Assessment of four commonly used methods to increase physical activity: brief interventions in primary care, pedometers, exercise-referral schemes, and community-based exercise programmes for walking and cycling. Assessment of interventions (including screening) to reduce transmission of Chlamydia spp and other sexually transmitted infections and to reduce the rate of under-18 conceptions, especially in vulnerable and at-risk groups. Assessment of brief interventions and referral for smoking cessation in primary care (including pharmacy, dental services, and general practitioner surgeries) and other settings, with particular reference to pregnant smokers and disadvantaged groups, and tailoring and targeting of interventions.

Public-health programmes
Guidance on optimal provision of smoking cessation services including provision of nicotine replacement therapy, for primary care, pharmacies, local authorities, and workplaces with particular reference to manual groups, pregnant smokers, and hard-to-reach communities. Guidance for midwives, health visitors, pharmacists, and other primary-care services to improve nutrition of pregnant or breastfeeding mothers and children in low-income households. Most appropriate means of generic and specific interventions to support attitude and behaviour change at population and community levels.

Table: Clinical guidance produced or in development in first 6 years of the NICE

<table>
<thead>
<tr>
<th>Subject area</th>
<th>Completed guidance</th>
<th></th>
<th>Guidance in progress</th>
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<tbody>
<tr>
<td></td>
<td>Appraisals</td>
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<td>Cancer</td>
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<td>35</td>
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<td>32</td>
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<td>35</td>
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<td>19</td>
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<tr>
<td>Infections</td>
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<td>6</td>
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<td>19</td>
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</tr>
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<td>8</td>
</tr>
<tr>
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<td>5</td>
</tr>
<tr>
<td>Obstetrics and gynaecology</td>
<td>3</td>
<td>5</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Others</td>
<td>11</td>
<td>3</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>37</td>
<td>113</td>
<td>235</td>
</tr>
</tbody>
</table>

arm’s-length bodies published by the Department of Health in July, 2004. However, its real genesis can be found in the two reports commissioned by the Treasury in 2000 and 2004. In the first report, the notion of a population fully engaged in seeking to improve its health was proposed; and in the second report, although exploring how this could be achieved, Wanless considered that there was no reason why the cost-effectiveness of prevention interventions should not be assessed in the same way as disease-management strategies. The analysis would allow commissioners of services (usually primary-care trusts) to compare the relative merits of prevention and treatment strategies; and would allow commissioners to develop a business case for purchasing a balanced portfolio of interventions. There is the expectation that advocates for health promotion and disease prevention could compete on a level playing field with the traditional strengths of the acute sector for resources. Perhaps, for the first time in its history, there is a real opportunity to achieve the initial aims of the architects of the National Health Service: that of making it a health—as well as a sickness—service.

Building on its previous experience, NICE has been restructured to create three new centres: Centre for Technology Evaluation, Centre for Clinical Practice, and Centre for Public Health Excellence.

Continuing its trademark approach of scientific rigour, transparency, and inclusiveness, NICE is currently consulting on its proposed approach to assessing the cost-effectiveness of public-health interventions, and programmes. The Department of Health has already published the first public-health work commission

 responsible for developing public-health guidance that promotes good health and prevents ill-health. Like its clinical guidance, NICE’s public guidance will take account of the evidence on cost-effectiveness and effectiveness. NICE’s new responsibilities mean that, for the first time, there is the opportunity to assess the comparative value of multiple approaches to improving specific health issues, so that patients, professionals, the public, and government can make informed choices.

The expansion of this sometimes controversial organisation occurs as the result of a review of the so-called
The challenges facing NICE are perhaps even greater than those it faced when it started in 1999. Then, its stakeholders were confined to the pharmaceutical and devices industries, patients, clinical professionals, and the Department of Health. NICE now has a wide and even more heterogeneous audience that includes the food, alcohol, and tobacco industries, the general public, public-health professionals, local government, and government departments, such as Transport, Education, and Skills. With its simpler remit, NICE managed most of the time to weave a fine course through the maze of competing interests. To achieve this momentum in its new guise, NICE will need to apply all its experience—and more—to address the concerns of its new stakeholders.

Ironically, the most sceptical of NICE’s new group of stakeholders might be public-health practitioners themselves. Despite a proud tradition, stretching over two centuries, public health has been through a storm in recent years. The absence of a universally agreed framework and a set of bioethical principles have often resulted in a sterile debate between protagonists on the extremes of a range of factors used to define the public-health approach. The tensions have included controversies about the medical versus the non-medical models of public-health practice, individual versus societal responsibilities for maintaining health, the respective roles and responsibilities of the National Health Service and local government, and the voluntary versus legislative approach to health promotion.

The premise that public health is everyone’s responsibility has often meant that no one has taken responsibility for its implementation in a complex and fragmented environment. It is unlikely that NICE can heal all these wounds at once. Nor should it try. NICE originally started as a means of helping clinical professionals and patients make informed decisions, and commissioners at a collective level. NICE should now agree its status with central and local government, explicit about the audience for NICE’s new guidance, and monitoring its implementation will all be crucial. The creation of a single organisation, to monitor both health and social services, should facilitate this.

There are, though, also many features that make the future look promising. Most importantly, NICE is not starting from scratch. In particular the Institute can build on the work of the Health Development Agency with its extensive collation and syntheses of evidence on what works in public health. In its first 6 years, the Institute developed a wide range of guidance documents covering most areas of clinical practice (table) and it is expected that the first public-health guidance will be issued by the end of this year.

NICE also has the opportunity to ensure that public health can re-emerge as an integral component of clinical practice, at the same time ensuring that public-health practice, based on sound evidence, infuses through lifestyle decisions by individuals and those responsible for the environment in which they live. However, in bringing together the prevention and treatment of disease, the essential factor will be to make sure that the public are presented with information that allows them to make informed decisions, without creating a public obsessed with disease and death.

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Small Latin, even less Greek

An item in the programme for this year’s meeting of the Classical Association of England and Wales caught the eye—a talk on “Sex and vegetables in the Hippocratic gynaecological treatise, and the Attic comedies”. This item is classicists looking at medicine but there is no lack of interest in the reverse, physicians inquiring into the origins of their discipline. The revered figures of medicine’s distant past, including Greeks and Romans, did not always write sense but with any discipline a little knowledge of the history gives useful perspective. It is a pity, though, that an equally important legacy of people who wrote when Athens or Rome dominated Mediterranean civilisations has been neglected—the vocabulary of medicine.

The surgeon—if not a caricature then surely the last of his breed—who urged more retractive effort on a junior trainee by muttering “Qui autem perseveraverit usque in finem, hic salvus erit” would in these unenlightened times face a disciplinary tribunal. Today, dead languages are frowned upon; even that bastion of obscurity, the legal profession, is exhorted to drop Latin. Medical school courses are far too congested to accommodate such teaching. Anyway, does it really matter that students do not know that mental/dementia and dyslexia/lexicon need not be the exclusive preserve of the humourless pedant. All the same, some basic knowledge of these lost tongues does seem to be required. The success of the Minimus programme for Latin is faintly encouraging, but from the little I can recall of its alphabet, accents, and verb irregularities, I would not hold out much hope for the other one.

The intention of 18th-century reformers was to introduce, into chemistry for example, terminology that would transcend language barriers but without dismantling them and would do away with eponyms. Out went Glauber’s, Epsom salts, and dephlogisticated muriatic acid (chlorine), but those same reformers today would have no difficulty with the French using ARN instead of RNA. Linnaeus (an MD) and others were working around the same time on terms for plants and animals that would also be universal, the differences being that taxonomies are untouched by living languages and the Latin can be forced to accommodate possessive eponyms. As academics turned to scientific inquiry in place of Aristotelian musings, physicians, not least among the scientists, had to invent new words, thousands of them, and for the most part turned to romanised Greek. They still do.

In the same year (1969) that Hogben’s entertaining book was telling us that there ought not to be a “c” in motorcade and that the “r” in positron was redundant—both lost battles I imagine—the dispute about fetus/foetus was settled, elegantly and wittily. Etymology need not be the exclusive preserve of the humourless pedant. All the same, some basic knowledge of these lost tongues does seem to be required. The success of the Minimus programme for Latin is faintly encouraging, but from the little I can recall of its alphabet, accents, and verb irregularities, I would not hold out much hope for the other one.

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A month after unprecedented rains lashed the teeming metropolis of Mumbai, killing more than 1000 and paralysing India’s commercial and entertainment capital, policy-makers are, at long last, making the link between drains and disaster.

Waking up after the Mumbai deluge, the government of Maharashtra, of which Mumbai is the capital, has put forward a Rs12000 million (around US$279 million) proposal to strengthen the city’s drainage and sewer network, under the proposed National Urban Renewal Mission scheme.

Last week, the State government also banned plastic bags, blaming them for choking the city’s drains and contributing to the spread of water-borne diseases, which have already claimed more than 300 lives.

While the spotlight on plastic bags is welcome, it does not bring out the underlying problems that turned torrential rains into a public-health disaster. For health experts interviewed by The Lancet, the high rates of disease that followed last month’s floods came as no surprise.

“Mumbai had always in the past asked for more and more loans for water. But never a rupee for sewerage, which demonstrates the mindset: uncontrolled urbanisation and no thought to infrastructure in a city hemmed in on three sides by the sea. The sewer lines, which run parallel to water lines that are never full 24/7, tend to leak into the latter”, says Darryl D’Monte, a Mumbai environmentalist and member of the newly created Concerned Citizens Commission on the floods. The Commission begins daily hearings this week all over Mumbai’s affected suburbs.

Indeed, sanitation, a neglected issue during normal times, is a key factor behind the post-flood disease outbreaks in India’s richest and dirtiest city. The city’s large concentration of slums with poor infrastructure and high population density exacerbated the problem: nearly 7 million of Mumbai’s 13 million and more inhabitants live in homes with no connection to the city’s sewerage system.

Steady migration to the city from the impoverished countryside has increased Mumbai’s slum population, but, as elsewhere in the region, infrastructure has not kept pace.

“The city’s population has boomed but the drains are where they were 100 years ago. On top of that, maintenance of existing drains is shabby and there is overload due to unregulated construction activities. Municipal authorities are supposed clean drains before the rains set in. Every year water-borne diseases break out during the monsoons but no-one pays heed. The drains are not cleaned properly. This time, the intensity of the rains just made things much worse: the already clogged drains got choked further with garbage and plastic bags and rats were out everywhere, as was their excreta”, says Alok Khanna, who visited Mumbai as part of a Red Cross fact-finding mission in the aftermath of the floods.

Now, although the media is rapidly losing interest in the floods, post-flood diseases continue to be reported. The largest numbers of patients have been registered for complaints of gastroenteritis and fever. Cases of jaundice, malaria, dengue, cholera, and leptospirosis are also being reported, according to WHO, which dispatched emergency medical relief teams and is providing financial support for stepping up sanitation and disease surveillance. Local medical and para-medical personnel have fanned out across the flood-affected areas to help implement prevention and control measures to stem the spread of infections.

However, merely increasing the sanitation budget will not ensure the desired public-health outcomes. The micro picture, especially at the implementation level, has to be kept in mind, emphasise WHO officials AK Sengupta and Sampath Krishnan.

“Many municipalities in India today outsource the actual de-silting of drains. Typically, the waste that is cleared out is kept alongside the drains because it would add to the costs to transport them long distances. When it rains heavily, all that waste goes back into the drains.”

Public-health engineers are supposed to oversee the cleaning operations even if the actual work is done by private parties. But in practice, this often does not happen.

If the deaths, disease, and huge financial losses suffered by one of Asia’s most dynamic cities in the wake of the unprecedented floods can succeed in sustaining the spotlight on the cities sewers and sanitation, Mumbai will be sounder in health.

Patralekha Chatterjee
Court takes over California’s prison health system

A US federal judge has ordered the takeover of California’s mammoth prison health-care system, describing the provision of medical care in the State’s prisons as showing “incompetence and at times outright depravity”. Laurie Udesky investigates the causes of California’s prison problems.

In announcing his decision to put California’s prison health-care system under the control of a court-appointed receiver, US District Court Judge Thelton Henderson said he was “driven in large measure by the stunning testimony that was uncontroversed that a prisoner in one of California’s 32 prisons dies on average every 6 or 7 days as a result of malpractice, negligence, or some other deficiency in the State’s medical care delivery system.”

The decision, issued June 30, is the culmination of a class-action lawsuit, filed 4 years ago. In response to the suit, California officials had promised to overhaul the prison health system, but the court found that the State failed miserably to effect reforms.

During the case, court medical investigators documented numerous cases of intentional cruelty, negligence, and squalid health facilities in many of California’s Department of Corrections and Rehabilitation prisons, which house more than 162 000 inmates. The investigators estimated that more than 64 prisoners died each year as the result of problems in the prison health system.

The court-appointed experts found that the prison health system is plagued with incompetent doctors. As one witness for the State admitted, Judge Henderson noted, “The State hired anyone with a license and pulse and a pair of shoes.”

Prisoners, the investigators found, often had to wait months for medical appointments and record keeping in disarray. The California Department of Corrections and Rehabilitation did not contest the findings.

In one case, a prisoner seeking care repeatedly for abdominal and chest pains was called a “faker” by a triage nurse and his doctor’s appointment cancelled, according to court documents. When the prisoner finally saw the doctor several weeks later, he angrily complained about his recurring pains. The doctor, however, refused to treat him, writing in his chart that the prisoner “could not come to clinic with a list of diagnoses”. The prisoner died of heart-related problems 2 weeks later.

The physician, who had 62 grievances filed by inmates against her, was quoted by court investigators as saying that most of the prisoners she examined had “no medical problems and were simply trying to take advantage of physicians.”

In another case involving a different doctor, a patient diagnosed with bacterial endocarditis never received medication or treatment from the doctor who diagnosed the problem. The doctor refused to provide emergency treatment a second time when the prisoner “had blue fingertips” and other signs of shock, despite pleas from nursing staff, according to court documents. Later that day, the prisoner died of cardiac arrest.

Prisoners with chronic problems often go months without proper treatment, says Corey Weinstein, a physician and medical consultant for the San Francisco-based human rights group Prison Focus, who has examined patients in 17 of the State’s 33 prisons. The California Department of Corrections, he says, is the “employer of last resort” for out-of-work physicians.

Court investigators estimated that the quality of care provided by 20–50% of prison physicians was poor, an proportion that the doctor’s bargaining unit, the Oakland-based Union of American Physicians and Dentists (UAPD), calls “exaggerated”.

According to Judge Henderson, the UAPD had “resisted efforts to improve the quality of member physicians”, and “to remove those who are incompetent or unwilling to meet professional standards”. Steve Fama of the San Francisco-based Prison Law Office, who brought the lawsuit, said that the UAPD had been “obstructionist”, resisting evaluation of doctors “at every turn”.

“That’s totally untrue”, insists UAPD spokesperson Gary Robinson. He says that the UAPD, which represents state employed and private practice physicians and dentists, opposes the court-mandated evaluation process, calling it “irrelevant” to what prison doctors do. “It was a test developed for impaired physicians, doctors with serious alcohol or drug abuse problems, or doctors who are potentially incompetent.”

Instead of being tested, Robinson says, UAPD prefers an evaluation in which experts would come to the prisons, review charts and interview doctors and patients. If necessary, explains Robinson, a physician could be “recom-
mended for more training or education or fired”. Nonetheless, the group’s doctors are complying with the court-ordered evaluations.

There is, however, little disagreement about the conditions of the workplace. The actual physical environments in which medical staff works seem more akin to an outpost in a beleaguered developing country than in one of the richest nations in the world.

“In some of the facilities there is standing water, no exam tables, no hand washing equipment”, says the lead attorney for the prisoners, Donald Specter, of the Prison Law Office.

According to court investigators, in San Quentin State Prison, which millions of tourists see from afar as they travel by ferry from San Francisco across San Francisco Bay, “the majority of medical clinics in housing units were dirty and showed no evidence of ever being cleaned”.

California Correctional Department’s health service has an annual budget of a US$1.1 billion, so why is it ailing? A major problem, wrote court investigators, is that health-care staff are under the authority of security staff. As a result, it is up to the guards to ensure prisoners can get to their medical appointments, something that is often not done.

Chuck Alexander, vice president of the California Correctional Peace Officers Association (CCPOA) blames the problem on understaffing. “If I’m working in a housing unit and I am alone and have 30 000 inmates, I have more to do than be at the beck and call of the medical staff.”

Kristin Hibbard, a clinical psychologist and neuropsychologist who treated mentally ill and head injured prisoners at five California state prisons, sees it differently. “Some patients didn’t show up for appointments, she investigated and found that inmates never received notices. “I’d go in the office at Salinas Valley State Prison that the correctional officers use and there’d be appointment slips in the garbage”, she explains.

Hibbard says that when she reported this and other allegations of wrongdoing to a federal monitor, “the associate warden told me that I shouldn’t have snitched on the guards and he proceeded to berate me”. Soon afterward Hibbard was fired.

Hibbard says hostility towards health workers was common among prison officials and guards, who, she says, “called us and anyone in health care ‘Thug Huggers’.”

This attitude toward criminal offenders is reflected in other aspects of California, a state considered a trendsetter for the rest of the country.

Since 1980, California’s prison population has rocketed from 24 500 to more than 162 000 today. Nearly a third of the prisoners are black adult men, even though this group makes up only 6% of the State’s population. To house the growing number of prisoners, the state has built 21 new prisons over the past 25 years. Today, travelling along California’s Interstate 5 from Oregon to the Mexican border, you can barely drive an hour without passing one of them. The state prisons’ US$7 billion price tag accounts for 6·3% of the State’s total budget, more than half of the amount set aside for higher education.

Not surprisingly, the California Department of Corrections is one of the State’s major employers. The CCPOA has grown from 2500 members in 1978 to more than 28 000 today. The prison guard lobby has helped keep the prison industry booming—and increasingly punitive. CCPOA was a major supporter of the 1994 “three strikes you’re out law”, which sends anyone who has committed a third offence after previously committing two serious or violent crimes to prison for 25 years to life, even if the third crime was for petty theft such as shoplifting.

Abysmal prison health services are not unique to California, says Robert Cohen, an internist who was director of New York City’s Rikers Island Prison medical services from 1982 to 1986. He is now a court-appointed monitor of prison health systems in Connecticut, Mississippi, Ohio, and Michigan. “There are very many deficiencies. Patients with serious illnesses such as cancers often have significant delays in access to care”, says Cohen, who believes the courts are the only means to force states to improve the health care of prisoners.

Cohen thinks that in order for there to be true reform in the country’s prison health systems, there has to be a major overhaul of how the USA provides health care. “As long as many people don’t have access to the medical care that they need, there is going to be resentment that prisoners get care.”

Laurie Udesky

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Laurie Udesky
Avian influenza remains a cause for concern

Health officials in Europe remain alert for possible cases of avian influenza following the disease’s arrival in Russia and Central Asia. Warnings from WHO about inadequate pandemic preparedness have heightened fears, despite news that the recent outbreak is under control. Ben Aris reports.

An avian influenza outbreak that swept through Siberia and into Central Asia during the past few weeks looks like it has now been brought under control, but health officials are remaining on the alert as migratory birds could yet spread the disease to western Europe.

Russia began slaughtering a hundred thousand chickens after the first case of the H5N1 avian flu was discovered in Novosibirsk, in Siberia, in July. The same influenza strain swept Southeast Asia in 2003, killing more than 60 people in Cambodia, Indonesia, Thailand, and Vietnam.

Some 11 000 birds died from the disease before the Russian cull began and roadblocks were thrown up around affected areas. Incidences of avian influenza were found in 35 towns and villages in seven regions, according to the Agricultural ministry, stretching across thousands of kilometres of tundra.

Last Wednesday, Russia’s top epidemiologist, Gennady Onishchenko said the spread of the infection was already in retreat. No human infections have been reported since the outbreak began. "Yesterday [Aug 24] we lifted quarantine in seven villages, and today in five more. All poultry farms were closed there, and all sick birds destroyed", Onishchenko told news agencies.

However, the same day, Kazakhstan’s chief veterinary doctor confirmed reports that avian influenza had been found in seven villages close to the Russian border.

“H5N1 was confirmed in all seven settlements where bird deaths have been noted. It is necessary to show maximum vigilance”, the chief veterinarian, Asylbek Kozhumuratov, was quoted by the Gazeta.kz news Internet site as saying.

Kazakh authorities immediately imposed a quarantine in the affected Pavlodar region and began a mass cull of birds. One farm worker was hospitalised with suspected infection, but later given a clean bill of health.

More than 140 million chickens were slaughtered in Southeast Asia to contain the previous outbreak at an estimated cost of US $12 billion, but Russia has got off lightly, bringing the disease under control after culling a little more than 120 000 birds.

The infection hit small commercial farms hardest, which saw their entire stock of chickens slaughtered by health authorities. However, the total culled represents only one tenth of 1% of Russia’s total chicken stock.

For once Russia’s massive expanse had an advantage: the long distances between cities in the taiga mean transport routes are few and easily checked.

Despite its poor reputation, Russia boasts a centralised and efficient veterinary service, one of the few things the Soviets did well. By the end of last week Onishchenko said meat from poultry plants in the infected regions was safe to eat.

As Russians are picky about their food (if not their diet) and have a strong bias for “natural” food, Russian farms tend to have higher hygiene standards than legally required, say agricultural experts.

Domestic demand for chicken was relatively unaffected, partly because chicken remains the cheapest meat on the market. With 17·8% of Russia’s 142 million-strong population living on or below the poverty line many cannot afford alternative meat. Poverty is especially high in rural areas in the Asian part of Russia where the outbreak was located.

As the danger subsides western European countries are playing safe. Two weeks ago, Dutch authorities ordered its poultry farmers to keep birds indoors in case migratory birds form Russian brought the disease with them.

The German government also dispatched a team to Russia to monitor the situation and to prepare a plan in case the disease crossed into Germany.

A European rapid alert system was developed after the Asian outbreak and authorities are standing by to roll out a mass cull of western European birds if necessary. The EU banned the import of live birds from Russian and Kazakhstan on August 12.

However, the EU executive commission downplayed the dangers of avian flu arriving in western Europe this week and said there was no evidence the disease had even reached the European part of Russia, bounded by the Ural mountains.

Nevertheless the EU is putting plans to stockpile antiviral medications into place. WHO warned last week that existing global stocks of drugs are not sufficient and manufacturing capacity could not be increased fast enough to counter a pandemic should the disease spread rapidly in western Europe.

Ben Aris
On July 28, 2005, a moving memorial service was held at Westminster Abbey, London, UK, for the former British prime minister Lord Callaghan (Jim Callaghan) and his wife Audrey. Their son-in-law, professor Michael Adler, spoke of Callaghan's outrage at the Nazi atrocities carried out against the Jews before and during World War II. He had met, in the immediate aftermath of the war, a refugee journalist, Alfred Wiener, who had amassed a huge collection of material about Nazi anti-Semitic persecution, and argued that it needed to be stored as evidence of what had transpired. Much was used at the Nuremberg trials, and Callaghan later successfully chaired the appeal for the Wiener Library in London, to ensure it a permanent home.

However, even to this day, much evidence lies in the minds of survivors of the most barbaric medical experiments in the concentration camps. “Survivors of medical atrocities are able to confront history and point to the inadequacies of care and compensation”, according to Paul Weindling in the introduction to his masterly volume, Nazi Medicine and the Nuremberg Trials. Although most victims were murdered in the name of perverted science, those who survive can make sure that what took place is fully recorded, as can the historians of medicine who work in this area, such as Robert J Lifton, Paul Weindling, Edward Pellegrino, and now Naomi Baumslag, with her new book, Murderous Medicine: Nazi Doctors, Human Experimentation, and Typhus.

Baumslag explores in impressive detail how typhus was characterised by Nazis as the Jewish plague. Those who suffered from it were killed in huge numbers or isolated in unsanitary conditions, with inadequate food and medicine. In the concentration camps, typhus was allowed to flourish and prisoners were deliberately infected with the disease to test typhus vaccines. The way typhus was used to kill Jews, Slavs, and gypsies epitomises Nazi medicine’s deliberate disregard of those who took part in research, classing them as subhuman. Such thinking was wholly in accordance with Nazi ideology, but in total contradiction of medical ethics. There are accounts from survivors that even suggest some doctors’ positive delight in killing and maiming, and a desire to experiment on some of the victims to prepare for genocide. Weindling is particularly effective in nailing down the views of the postwar German medical establishment. He describes as a monster Eugen Haagen, who did experiments with a typhus vaccine that caused damage and frequent death to prisoners at Natzweiler concentration camp. Haagen’s lack of concern for his research subjects was legendary. Yet Haagen, arrested and released by the Americans and then by the French, argued that he should have received the Nobel prize (he had developed a yellow fever vaccine before the war), and that his “guineapigs”, including the hundreds transported from Auschwitz to Natzweiler for his research, served legitimate scientific ends.

Haagen’s belief that anything was legitimate if it advanced scientific knowledge was all part of his and others’ blindness to their own immoral behaviour and wilful disregard for human life. The simple fact remains that doctors were easily recruited, including from the highest echelons of German academic medicine, to carry out unspeakable trials and to injure, maim, sterilise, and kill other human beings. When it came to the Nuremberg trials, physicians argued that it was not their fault, since they had received their orders from on high, and that treating them as war criminals would be disastrous for the reputation of medical research and science, especially as what they had done was in fact useful. Nor were other countries immune from morally questionable behaviour.

One telling example is that of Janet Vaughan, a haematologist who led the Medical Research Council’s (MRC) team at Belsen in the immediate aftermath of the war, and whose work Weindling describes in an earlier book, Epidemics and Genocide in Eastern Europe (2000). The MRC wanted to experiment with Amigen, an American enzyme product, and with an “intravenous hydrolysate”. Vaughan recorded that the research terrified patients, who believed they were about to receive a fatal injection. “When we went up to our patients with a stomach tube they would curl themselves up and say ‘nicht crematorium’.” She soon realised that what these survivors needed was proper care and nursing. With hindsight, this is blindingly obvious. The research soon ceased, but one still cannot help wondering why the research personnel did not spend their time more humanely. Weindling notes that the camp became a sort of experimental station for nutritionists studying starvation and the US Typhus Commission, which did chemotherapeutic and clinical studies in the US liberated camps. Meanwhile, the Allies were concerned that the Nuremberg Trials should not undermine public confidence in medical science. Lord Moran, sent by Clem Attlee to look at German
human medical experiments, argued that the state, not the individual, was the main culprit of this unethical research. Kenneth Mellanby, a medical entomologist who persuaded the British Medical Journal to designate him as its official correspondent at Nuremberg, argued that “the victims were dead; if their sufferings could in any way add to medical knowledge and help others, surely this would be something that they themselves would have preferred” (Human Guinea Pigs, 1945). How could he know?

Yet scientists continued to do terrible things in the name of research, although on nothing like such a scale. In 1966, Henry Beecher, professor of anaesthesiology at Harvard, published “Ethics and Clinical Research” in The New England Journal of Medicine, and drew attention to 22 examples of unethical clinical research in which patients’ lives had been put at risk. These trials included the Tuskegee syphilis experiments and other studies in which prisoners and those who were not free to choose or give consent were experimented upon to their detriment. Soon after Beecher’s paper, Maurice Pappworth’s Human Guinea Pigs: Experimentation on Man (1967) was published. Pappworth’s contention that research which put patients at risk was not uncommon in the UK made him unpopular in medical circles; he did not get his Fellowship of the Royal College of Physicians until shortly before he died. This work by Beecher and Pappworth came out in the wake of a series of revelations about Nazi medical war crimes. But unethical trials have taken place since then.

Today, concern is expressed about research on children and those with mental illness or dementia and the extent to which they can—or should—give consent. Can advanced directives be used to allow researchers to conduct studies when the person is unable to give consent at the time it is needed? Despite the fact that nothing so terrible occurs now as it did in Nazi Germany, lessons still remain to be learned and inwardly digested—of seeking informed consent, telling the patient what emerges from a study, and seeing the patient as a partner in a trial, not a subject to be used. With all our ethical guidelines and research ethics committees, good as they are, we still have a long way to go.

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In brief

Book  Orgasm and evolution

Underlying biases exist throughout science, but surely nowhere in as extreme a form as in research into female sexuality. The assumptions in this area boil down to two: female orgasm must be “for” something, and this purpose must be linked to reproductive sex. Elisabeth Lloyd neatly dissects the history of these biases and their results in The Case of the Female Orgasm.

Adaptive evolutionary accounts propose that female orgasm either improves reproductive success directly (the gruesome-sounding upsuck theory of uterine contractions moving sperm more efficiently), or indirectly (by promoting pair bonding—better in bed being correlated with better father material). Lloyd prefers the theory that since the penis and clitoris arise from the same undifferentiated embryological organ, women get the erectile and nervous tissue necessary for orgasm as a by-product of the selection pressure for the male-sperm delivery system.

As she reviews and finds wanting 21 explanations for female orgasm, Lloyd uncovers fascinating biases. Some adaptationists argue that the by-product account is flawed because, well, it rules out the adaptive explanation. And her analysis of sexology literature shows that only 25% of women always orgasm with intercourse; this suggests it isn’t an especially highly selected trait. Links between orgasm and reproductive success are unproven—in fact, primate research indicates that orgasm is more highly correlated with female-female sexual encounters than with mating. Lloyd could not find any studies on orgasm in lesbian sex, so I did a brief (unscientifically sound) e-mail survey. Of the ten women I asked, five had had sex with women as well as men—four of five rated the frequency of achieving orgasm as higher with women, the remaining woman rated it the same.

Aside from methodology, one of the biggest problems in sexology research is a failure to define the basics—what is meant by an orgasm? Faced with explaining why heterosexual sex just doesn’t do it as well as female-female sex for macaques, researchers suggested that the macaques were just having “subtle, imperceptible” orgasms. Their evidence? Human research that showed female orgasms were common in heterosexual sex, but just much weaker than those that resulted from masturbation or direct clitoral stimulation. Call it my bias, but of all the debate on what constitutes a female orgasm—breath holding, uterine contractions, round-mouthed frowning stare (macaques, not women), clutch reaction (both)—in human studies you could start with a basic premise: if she didn’t notice it, it didn’t happen.

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Ten most wanted
June, 2005

1 The metabolic syndrome (Seminar, April 16)

2 Addison’s disease (Eponym, June 11)

3 Type 2 diabetes (Seminar, April 9)

4 Systemic adjuvant therapies for breast cancer (Article, May 14)

5 Depression in the elderly (Seminar, June 4)

6 Heart failure (Seminar, May 28)

7 Transient ischaemic attack (Article, June 18)

8 Breast cancer (Seminar, May 14)

9 CB, and obesity (Article, April 16)

10 Health in the EU (Editorial, June 4)
Clarence Dennis
Co-inventor of a heart-lung machine.
Born June 16, 1909, in St Paul, MN, USA; he died of complications of dementia in St Paul on July 11, 2005, aged 96 years.

Clarence Dennis did the first open-heart surgery using a multiple screen blood oxygenator that he had developed—later known as a heart-lung machine—in April, 1951, at the University of Minnesota, Minneapolis, MN, USA. "The behaviour of the oxygenator was most gratifying", Dennis would later say in an interview with W Gerald Rainer, former president of The Society of Thoracic Surgeons. However, Dennis would recall, "when the right heart was opened in order to try to make the necessary repair, it was found that this patient had a much more complicated lesion which neither [another surgeon] nor I recognised while the child was alive. The child, therefore, was lost on the table." That, combined with a second failed surgery caused by a technician’s error a month later set Dennis back and made it possible for John Gibbon, a surgeon at Jefferson University, Philadelphia, PA, with whom Dennis had been sharing notes on the device, to do the first successful such surgery in 1953. Dennis, who moved to the State University of New York Downstate Medical Center in Brooklyn shortly after his 1951 attempts, would be successful in 1955.

Although Gibbon got the credit for the first successful surgery, the development of a pump oxygenator that could maintain the artificial cardiac arrest that was necessary to operate on the heart "revolutionised cardiac surgery", said Michael Zenilman, who is Clarence and Mary Dennis Professor and Chairman at the Department of Surgery at Downstate Medical Center. Such surgery would not have been possible without Dennis' work, "Before that, you could not operate on the heart because it was a beating organ".

Martin Kaplitt, a cardiovascular surgeon who trained at Downstate under Dennis, called him "one of the greatest men in American surgery". "Whether it was performing a closed anastomosis of the bowel with ‘Dennis clamps’ or performing a coronary gas endarterectomy on a patient in cardiogenic shock while on cardiopulmonary bypass, the guidance, equanimity, and encouragement provided by Dr Dennis always led to either success or at least a great advance in surgical knowledge." Michael Mastrangelo, who trained with Dennis as a thoracic surgery resident at Downstate, said Dennis was "a meticulous and most gentle surgeon". Gus Tanaka, one of his first interns at Downstate, remembered his kindness. After Tanaka was diagnosed with a tuberculous pulmonary effusion, a week after being selected for the internship, rather than advising him to seek another career path, as Tanaka feared, "the kindly Dr Dennis came to my bedside and assured me that I would not be dropped from the programme", and outlined a programme that would assure Tanaka a better chance of getting a decent night’s rest.

Dennis chaired Downstate’s Department of Surgery until 1972, when he went to work at the National Heart and Lung Institute in Bethesda, MD. In 1975, he was appointed to the faculty of State University of New York Stony Brook, where he would remain until his retirement in 1988, when he moved back to St Paul. In 1991, he became director of the University of Minnesota’s Cancer Detection Center, which had been founded by Owen Wangensteen, who had, in the 1930s, first assigned Dennis to creating a pump oxygenator. The center closed in 1996, at which point Dennis retired for a second time.

Dennis loved to tinker in machine shops and his own garage, which is where one of the first ventricular assist devices was developed. One of his first inventions was an atraumatic clamp, now known as the Dennis clamp, "that holds the intestine while you’re sewing it up", said David Rothenberger, who worked with him in Minnesota. After Dennis developed macular degeneration, he put together a video player that made it possible for him to see slides during grand rounds, according to John Najarian, of the University of Minnesota. "He had this contraption on his head that would look at the slides and then put them on a television screen that was in front of his eyes, about the size of a 3-by-4 card, and he would see everything in that fashion.” His last patent was for a bread slicer in 1999.

His first wife, Eleanor Smith, predeceased him; their marriage ended in divorce. Dennis is survived by his wife, Mary; a daughter, Jane Wigertz; three sons, Richard, James, and David; two stepchildren, Katherine Franda and Gregory Mott; a brother, Lyman Clark Dennis; and a sister, Clara Louise Jameson.

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Safety of influenza vaccines in children

Since publishing our systematic review of the effects of influenza vaccines in healthy children (Feb 26, p 773),1 we have completed our review of the published and unpublished safety evidence for these vaccines.7

We found only one safety study of inactivated vaccine in 35 children aged 12–28 months done nearly 30 years ago with an influenza B vaccine;3 all other safety studies of inactivated vaccine we found were in children aged 3 years or more. Three studies reported safety data of live vaccine in children aged 22 months or younger (combined denominator 827).4,5 Seven further studies included children younger than 2 years.5,6 Only one trial of live vaccine had serious adverse events as an outcome (measured up to 3 months after vaccine administration).7 The lack of reported trial safety data for inactivated vaccines in younger children is particularly surprising given that this vaccine is now recommended for healthy children aged 6 months and older in USA and Canada.1

We wrote to 15 first or corresponding authors or research group leaders of the 31 studies (30 randomised controlled trials [RCTs] and one cohort study) included in our review to enquire about any unpublished data. Some authors had published more than one study, and email addresses for two authors of four studies (one RCT and three cohort studies) could not be found. We received 12 replies (80% response rate), accounting for 27 (87%) of the studies included in our review.

One retrieved paper, by Bergen and colleagues,8,9 reported that more than 2500 medical adverse events that occurred in vaccine recipients and more than 1300 in placebo recipients, but fewer than half—ie, only those that were significantly associated with increased or decreased risk in vaccine recipients—were specified by diagnosis (table). We wrote to the corresponding author, Steven Black, asking for the data on the non-significant events to include in our meta-analysis. Black responded saying that he had the data we requested but would require clearance from the vaccine manufacturer, MedImmune, to send it. He later responded that MedImmune did not want to share the data.

We requested a contact at MedImmune and wrote to Robert Walker explaining the need to include non-significant outcomes in the meta-analysis of a systematic review. Walker declined to let us have the data. Walker was contacted once again at a later date after two authors of other studies on live vaccine safety (Belshie and Gruber) informed us that all safety data from their studies2,4,7,15–18 was controlled by MedImmune. Walker responded in the same manner to this new request, stating that “MedImmune does not provide study data to outside parties”.

Although so far we have found no evidence to suggest a serious harmful effect of any of the vaccines in our review, we are concerned by our findings of limited clinical trial evidence for inactivated vaccines. In addition, the withholding of safety data for live attenuated vaccines makes it impossible to present a complete evidence base of their safety. Although a frequent practice, lack of reporting of non-significant outcomes raises the real possibility that our review may present a biased picture.15,16 Heterogeneity of outcome definition and reporting are additional problems in vaccine trials.19

An incomplete or fragmented evidence base could hinder identification of rare and serious adverse events. Given their rarity, these may not be identifiable from single studies but may require a complete data set, as was the case for intussusception and rotavirus vaccines.21 We believe all unpublished trial safety data should be readily accessible to both the regulatory bodies and the scientific community on request. Our evidence gives rise to a concern that lack of access to unreported data prevents published safety data being put into context and hinders full and independent review. This cannot be good for public confidence in these vaccines.

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Table: Comparison of total medical adverse events recorded and total medical adverse events (by diagnosis) reported in study by Bergen et al2

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<tr>
<th>Vaccine group</th>
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<td>Combined settings</td>
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*Hospital admissions <24 h in duration were not necessarily reported as serious adverse events.

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All other authors have no conflict of interest.
Effects of ICL670 (deferasirox) on cardiac iron concentrations

On the basis of 1-year clinical trial results, the pharmaceutical company Novartis announced that submission for global registration of ICL670 is anticipated in the first half of 2005. ICL670 has an orphan drug status in the USA and European Union, and fast-track status by the US Food and Drug Administration. However, although deferoxamine was used for comparison in the trial, the efficacy and safety profile of ICL670 is not yet clear because no information is given on the effects of ICL670 on cardiac iron concentrations and cardiac function. Such information is crucial for the safety of patients, since cardiomyopathy from excess cardiac iron is the major cause of death in thalassaemia patients. 1–3 Progressive improvement of heart function associated with a reduction in cardiac iron, as monitored by MRI T2, was seen in thalassaemia patients treated with intravenous deferoxamine during a 1-year study.4

Despite the fact that a reduction in liver iron and serum ferritin concentrations was reported in many patients treated with the higher doses of 20 and 30 mg/kg per day of ICL670 used in the 1-year trial, such a finding does not mean that cardiac iron concentrations are similarly reduced. 1–3 These doses are ineffective in achieving negative iron balance in most patients, suggesting that only some of the iron mobilised by ICL670 from the liver is excreted in the faeces, while the remainder could be redistributed to the heart and other organs.5

The transfer of iron to the liver and erythrocytes by ICL670 has been shown in normal animals.6 Iron loading of the heart by ICL670 is also suspected because of its lipophilicity, long half-life in plasma (12–16 h), and the transfer of iron from its iron complex to transferrin.6–8

Although in the 1-year trial, the overall inferiority of ICL670 to deferoxamine was admitted by Novartis, the extent of inferiority cannot be validated unless information is provided on the compliance of the group of patients treated with subcutaneous deferoxamine 5 days per week. The most common toxic side-effects reported in the 1-year trial and previous studies were gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain), transaminitis, skin rash, and increase in creatinine concentrations.9–11 The latter was reported to be dose-dependent, but rarely progressed to renal insufficiency or required the discontinuation of ICL670.1 No statistics on this and other toxic effects involving the 300 patients were available for the 1-year trial or the 800 patients who have so far taken ICL670.1 Similarly, no information is provided on the toxic effects of the metabolites of ICL670.

Pending further studies on efficacy and toxicity, ICL670 could have a significant role in the treatment of transfusional iron overload, perhaps not as a monotherapy but in combination with other chelating drugs. It is hoped that the low dose of ICL670 will increase the prospects of compliance and reduced treatment costs for thalassaemia patients in developing countries who cannot use deferoxamine or deferiprone.

I declare that I have no conflict of interest.

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3 Kolagou A, Fessas Ch, Papatryphonas A, Economides Ch, Kontoghiorghes GJ. Prophylactic use of deferoxamine (L1) and magnetic resonance imaging T2* or T2 for preventing heart disease in thalassaemia Br J Haematol 2004; 127: 360–61.


Thyroid cancer after neck irradiation during childhood

Thyroid cancer as a result of head and neck irradiation in childhood is well described in Alice Sigurdson and colleagues’ study (June 11, p 2014) and in the accompanying Comment (p 1986). I would like to take this opportunity to...
remind physicians of other long-term consequences of this treatment.

I was given nine separate radiation treatments for a strawberry naevus on the front of my neck between the ages of 4 and 15 months, starting in 1955. I have the original records and know that the total dose was equivalent to about 10 Gy. I developed thyroid cancer and discovered my primary hyperparathyroidism aged 41 years, and breast cancer aged 44 years. Although the follow-up period in Sigurdson and colleagues’ study was 30 years, I developed my cancers 40 years after exposure. Annual surveillance for thyroid cancer is recommended for patients like me, but clinicians should also be aware of the association between irradiation of the head and neck and primary hyperparathyroidism,3,4 and consideration should be given to monitoring calcium concentrations as part of routine follow-up. In addition, early breast cancer screening may be appropriate in some of these patients, as recommended for childhood survivors of Hodgkin’s disease.5

I declare that I have no conflict of interest.

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In Alice Sigurdson’s study of primary thyroid cancer after a first tumour in childhood,1 the 72 patients who developed pathologically confirmed thyroid cancer were identified from a mailed questionnaire. It is not clear whether these patients were identified by palpation or ultrasonography. In our experience, thyroid function tests and palpation are not sufficient to detect all carcinomas.

In 2002, we described 143 childhood survivors of cancer—65 with direct exposure and 78 with scatter radiation exposure of the thyroid.2 Two of 19 palpable thyroids and four of 46 impalpable thyroids from the direct group and nine of 22 palpable and three of 56 impalpable thyroids from the scatter radiation group had cancer. Six had a microcarcinoma (<1 cm) and two had lymph-node involvement. All had abnormal results on ultrasonography.

We can report as follow-up that a further 10 patients were diagnosed with thyroid cancer during 1998–2005. All of these had normal palpation but were picked up by ultrasound. One patient had extensive disease requiring six courses of iodine-131. This patient had had a dose of 3500 cGy to the neck area.

The evidence to date suggests that long-term survival for patients with radiation-induced thyroid cancer is excellent.3 It could therefore be argued that there might be no increased mortality risk if detection is delayed. Nevertheless, we would strongly suggest that normal palpation should not be viewed as an adequate exclusion of thyroid carcinoma. This message should be promulgated to primary-care physicians, who may have direct responsibility for long-term surveillance in these patients.

We declare that we have no conflict of interest.

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Long-term outcomes after transient ischaemic attack

I van Wijk and colleagues (June 18, p 2098)1 report that, for a cohort of patients with transient ischaemic attack (TIA) and minor stroke, the risk of a vascular event declined over the next 3 years but rose thereafter. The reasons for this trend are speculative, but may indicate progression of the degree of stenosis of large arteries (eg, the carotid artery) after an initial period of plaque stabilisation. These results could have implications for the management of carotid artery stenosis after TIA or stroke.

If carotid doppler identifies a critical stenosis immediately after a TIA or minor stroke, carotid endarterectomy may be indicated. For other patients with carotid stenosis of lesser severity, there is potential, over the years, for progression to a critical stenosis that is amenable to surgery. Another trial supports the benefit of surgery for these patients who have, essentially, an asymptomatic critical carotid stenosis.2

One strategy to improve outcome after TIA or minor stroke might be to do a carotid doppler periodically after the event (eg, annually) for selected patients with non-critical stenosis. Consideration could be given for carotid endarterectomy should the need arise. However, further trials are required to determine the benefits of the use of carotid doppler in this manner, and hopefully the results will lead to a reduction in the high rate of vascular events in the years after TIA or minor stroke as reported in this study.

We declare that we have no conflict of interest.

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I van Wijk and colleagues\(^1\) assess the long-term risk of death and vascular events in patients with transient ischaemic attack or minor stroke of arterial origin. However, among the predictors factors of future events, they have not considered the baseline concentrations of C-reactive protein (CRP). This marker of systemic inflammation has been shown to be higher in patients with symptomatic carotid artery disease than in those with asymptomatic disease,\(^2\) suggesting that systemic inflammatory status could be a marker for patients with an exaggerated inflammatory response that might accelerate atheroma progression and facilitate plaque instability.

Since an increased concentration of CRP after a first ischaemic neurological event seems to be associated with a worse prognosis,\(^3,4\) C-reactive protein could be added to conventional risk factors in the secondary prevention of cerebrovascular events.\(^5\)

We declare that we have no conflict of interest.

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Furthermore, a recommendation for routine use of prophylaxis should only be made after comparison with all alternative management approaches—a task that was outside the limited objective of the review. An alternative approach to the prevention of post-transplant cytomegalovirus disease is pre-emptive therapy (ie, administration of antiviral drugs once active surveillance has detected evidence of cytomegalovirus infection by PCR or antigenaemia laboratory assays). The use of a pre-emptive approach is supported by the findings of a randomised placebo-controlled trial.\(^6\)

The incidence of late disease in transplant recipients, coupled with evidence of antiviral resistance with prolonged use of ganciclovir,\(^7\) urges caution in the use of prophylaxis. The strategy of pre-emptive therapy is an effective way of preventing cytomegalovirus disease and may not be so susceptible to these disadvantages. We believe, therefore, that the decision as to how to prevent cytomegalovirus disease in solid organ transplant recipients is currently best made locally at each transplant centre.

**Antiviral treatment after solid organ transplantation**

We were interested to read the comprehensive systematic review by E M Hodson and colleagues (June 18, p 2105)\(^1\) but are concerned over the interpretation of the results. Specifically, the statements: “prophylaxis with antiviral medications reduces the risk of cytomegalovirus disease and associated mortality in recipients of solid-organ transplants” and “this approach should be used routinely in cytomegalovirus-positive recipients and in cytomegalovirus-negative recipients of organs positive for the virus” are not fully supported by the data presented.

Limaye and colleagues\(^2\) have shown that, although antiviral prophylaxis prevented cytomegalovirus disease in recipients of liver transplants during the prophylaxis period, a significant number of patients developed late disease once antivirals were stopped. In the study by Paya and colleagues,\(^3\) in which patients were randomised to receive 100 days of prophylaxis with oral ganciclovir three times a day or once daily valganciclovir, a quarter of the patients who developed cytomegalovirus disease in the valganciclovir group did so 6–12 months after transplantation. Late-onset disease has also been independently associated with post-transplant mortality.\(^4\) Because studies with follow-up phases as short as 3 months are included in the systematic review, one cannot draw conclusions about the risk of cytomegalovirus disease or associated mortality for the whole period that patients are known to be at risk.

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Authors’ reply
B Caplin and colleagues are concerned that cytomegalovirus prophylaxis for 6–12 weeks after transplantation does not prevent disease occurring during the complete period of risk. This point is self-evident, but has only become relevant because antiviral prophylaxis has increased the number of survivors at risk of late cytomegalovirus disease compared with patients not on routine prophylaxis. As we show in table 3 of the original paper, the effects of antiviral prophylaxis are no different 3–6 months after transplantation and 9–12 months after transplantation. There are significant reductions in cytomegalovirus disease and all-cause mortality extending to 12 months after transplantation, and we could find no evidence for a waning or “rebound” effect which would be expected if there was an excess risk of late cytomegalovirus in the treated group. Indeed, given the expected survival bias in the treated group, estimates for cytomegalovirus disease are likely to be an underestimate of the true benefit of prophylaxis. Caplin and colleagues cite only two studies, which highlights the potential pitfalls of selective data reporting compared with formal systematic reviews. However, as we emphasised in our paper, we agree that additional trials are needed to determine the optimum duration of antiviral medications to prevent cytomegalovirus disease after transplantation.

Caplin and colleagues also suggest that routine antiviral prophylaxis should be compared with other strategies such as pre-emptive therapy before superiority can be claimed. We agree and have recently completed a systematic review. There are striking differences in the quantity, quality, and results of randomised controlled data on pre-emptive therapy compared with prophylaxis. For antiviral prophylaxis, there are 19 published trials involving 1981 patients. By contrast, only six trials (288 patients) have compared pre-emptive therapy with placebo or no treatment, and only three trials (151 patients) have compared the two strategies. Pre-emptive treatment reduced the risk of cytomegalovirus disease but not mortality. Also, around 20% of patients developed cytomegalovirus disease after screening and before randomisation and were excluded from the trials, so the true benefit of the pre-emptive strategy is likely to be less than that reported by the trials. A direct comparison of pre-emptive therapy with prophylaxis was uninformative due to lack of power.

We agree that ganciclovir resistance should prompt caution in the long-term use of the drug. However, we tested this hypothesis by using year of study and duration of treatment as explanatory covariates and found no empirical evidence of resistance.

Caplin and colleagues finish with an intriguing sentence: “We believe, therefore, that the decision as to how to prevent cytomegalovirus disease in solid organ transplant recipients is currently best made locally at each transplant centre”. We would agree if they had shown that the benefit-harm trade-off for routine antiviral prophylaxis and for pre-emptive therapy varied significantly by centre through case-mix differences in absolute risks of cytomegalovirus disease or adverse effects. As researchers, it is not our role to decide local practice but simply to inform clinicians, patients, and policymakers. On the basis of our data, we would suggest that routine prophylaxis (except in donor-negative or recipient-negative patients) or participation in randomised controlled trials of pre-emptive therapy versus prophylaxis or of different durations of therapy should be local practice.

EMH, ACW, GFMS, and JCC are supported through financial support to the Cochrane renal group.

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Intelligence and socioeconomic inequalities in health

David Batty and Ian Deary raise an interesting point in their Correspondence (May 21, p 1765)1 based on our paper about educational inequalities in cause-specific mortality.2 They state that researchers should examine the possibility that education is a proxy for intelligence in its association with mortality. We agree that the role of intelligence in the association between socioeconomic position and health should be assessed because it may help us to explain part of the association.

We saw that the association between education and mortality was present in men and women, in all age-groups, and all countries.2 This finding means that, besides country-specific explanations for inequalities in mortality, we also need to look for generic explanations, and intelligence may be one. However, after examining the findings of several pieces of research, we believe that it is still premature to accept that this is the case.
Correspondence

Inter-relations between childhood intelligence quotient (IQ), socioeconomic status, and mortality are highly complex (figure), and research in this area is still scarce. Nonetheless, current research can already give us clues about the relative importance of different parts of this model. For instance, some existing studies have found that childhood IQ is not related to cardiovascular disease, coronary heart disease, or stroke after age 65 years; childhood IQ is not related to mortality in women; and adjustment for measures of adult socioeconomic position (including education) substantially attenuates the association between cognitive ability and mortality. However, we should not abandon investigation of the role of intelligence in socioeconomic inequalities in health. We would be particularly interested in studies that are able to assess a possible interplay between intelligence and education. In our view, education provides people with the skills to function in society: literacy, principles of social communication, knowledge of where to find accessible information, acceptance of scientific knowledge as meaningful, and much else. Intelligence on the other hand may indicate just how many of these skills a person is able to acquire, retain, and develop. If this notion is found to be true, then the interplay between intelligence and education in their effect on health may contribute in part to our understanding of inequalities in health, and open up new opportunities for tailoring health promotion towards the needs of disadvantaged groups.

We declare that we have no conflict of interest.

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Department of Error

National Prospective Tonsillectomy Audit. Tonsillectomy technique as a risk factor for postoperative haemorrhage. Lancet 2004; 364: 697–702. In this Article (Aug 21), the “Return to theatre” data in Table 2 should be as shown below. The corresponding fifth paragraph of the Results should read: “4 patients (1%) had a haemorrhage of sufficient severity to require return to the operating theatre (table 2). Coblation was the only technique that had an increased return to theatre rate compared with the cold steel group.”

<table>
<thead>
<tr>
<th>Haemorrhage</th>
<th>Return to theatre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of events</td>
</tr>
<tr>
<td>Cold steel</td>
<td>1327 (11·2)</td>
</tr>
<tr>
<td>Cold steel + bipolar diathermy</td>
<td>613 (5·2)</td>
</tr>
<tr>
<td>Cold steel + bipolar diathermy</td>
<td>3831 (32·5)</td>
</tr>
<tr>
<td>Monopolar diathermy forceps</td>
<td>198 (1·7)</td>
</tr>
<tr>
<td>Bipolar diathermy forceps</td>
<td>3773 (32·0)</td>
</tr>
<tr>
<td>Bipolar diathermy scissors</td>
<td>893 (7·6)</td>
</tr>
<tr>
<td>Coblation</td>
<td>684 (5·8)</td>
</tr>
<tr>
<td>Other</td>
<td>477 (4·4)</td>
</tr>
<tr>
<td>Total</td>
<td>13 796</td>
</tr>
</tbody>
</table>

*, Relative risk with cold steel as the baseline category. †y test.

Table 2: Rates of tonsillar haemorrhage and return to theatre with tonsillar haemorrhage (primary and secondary combined) by surgical technique.

808 www.thelancet.com Vol 366 September 3, 2005
International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion

Andrew J Molyneux, Richard S C Kerr, Ly-Mee Yu, Mike Clarke, Mary Sneade, Julia A Yarnold, Peter Sandercock, for the International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group

Summary

Background Two types of treatment are being used for patients with ruptured intracranial aneurysms: endovascular detachable-coil treatment or craniotomy and clipping. We undertook a randomised, multicentre trial to compare these treatments in patients who were suitable for either treatment because the relative safety and efficacy of these approaches had not been established. Here we present clinical outcomes 1 year after treatment.

Methods 2143 patients with ruptured intracranial aneurysms, who were admitted to 42 neurosurgical centres, mainly in the UK and Europe, took part in the trial. They were randomly assigned to neurosurgical clipping (n=1070) or endovascular coiling (n=1073). The primary outcome was death or dependence at 1 year (defined by a modified Rankin scale of 3–6). Secondary outcomes included rebleeding from the treated aneurysm and risk of seizures. Long-term follow up continues. Analysis was in accordance with the randomised treatment.

Findings We report the 1-year outcomes for 1063 of 1073 patients allocated to endovascular treatment, and 1055 of 1070 patients allocated to neurosurgical treatment. 250 (23·5%) of 1063 patients allocated to endovascular treatment were dead or dependent at 1 year, compared with 326 (30·9%) of 1055 patients allocated to neurosurgery, an absolute risk reduction of 7·4% (95% CI 3·6–11·2, p=0·001). The early survival advantage was maintained for up to 7 years and was significant (log rank p=0·03). The risk of epilepsy was substantially lower in patients allocated to endovascular treatment, but the risk of late rebleeding was higher.

Interpretation In patients with ruptured intracranial aneurysms suitable for both treatments, endovascular coiling is more likely to result in independent survival at 1 year than neurosurgical clipping; the survival benefit continues for at least 7 years. The risk of late rebleeding is low, but is more common after endovascular coiling than after neurosurgical clipping.

Introduction

The International Subarachnoid Aneurysm Trial (ISAT), a randomised trial comparing neurosurgical clipping with endovascular coiling in patients with ruptured intracranial aneurysms, closed recruitment after an interim analysis showed a benefit of endovascular treatment on the primary outcome: death or dependency at 1 year. Our first report of the interim results used the outcome data available at the time of that analysis. These data were incomplete because 1-year follow-up was available for only 1594 of the 2143 patients enrolled. However, the difference between the two treatments was significant: endovascular coiling was associated with an absolute reduction in the risk of death or dependence at 1 year of 6·9% (a relative risk reduction of 22·6%, p<0·001) compared with neurosurgical clipping. The 1-year data are now complete and we report here the primary outcome at 1 year for all patients combined and subdivided by the prespecified subgroups. We also report results for secondary outcomes: epilepsy, rebleeding from the treated aneurysm, deaths during medium-term follow-up (with survival curves to 7 years), and the findings on follow-up angiography. Patients were eligible for enrolment into ISAT if the responsible neurosurgeon and neuroradiologist were uncertain about the best treatment. If there was insufficient uncertainty, the patient could not be randomised.

Methods

Patients

The trial protocol and methods, including the randomisation and minimisation criteria, recruiting centres, patient demographics and aneurysm characteristics, have already been published. Eligible patients had subarachnoid haemorrhage due to intracranial aneurysm, suitable for either endovascular or neurosurgical treatment. These subgroups were prespecified: World Federation of Neurosurgical Societies (WFNS) grade at randomisation, age groups by decade (<40, 40–49, 50–59, 60–69, ≥70 years), amount of...
blood on CT scan (Fisher grade), and the site and lumen size of the aneurysm. All centres obtained local ethics or institutional review board consent before enrolling patients. Able patients provided written informed consent. However, some ethics committees allowed assent from relatives to enable patients who could not give their own written consent to be enrolled in the trial.

Procedures
Randomisation procedures have been published elsewhere.\textsuperscript{1} The primary objective was to determine whether a policy of endovascular treatment compared with neurosurgical treatment reduced the proportion of patients dead or dependent at 1 year. ISAT also set out to assess any differences between endovascular treatment and neurosurgery in: rebleeding from the treated aneurysm; quality of life at 1 year (assessed with euroqol [EQ5D] measure); epilepsy; cost-effectiveness; and, neuropsychological outcomes in a substudy done in eight centres in the UK, which will be published separately.\textsuperscript{2,3} Blinded assessment of definite or suspected rebleeding and intracranial haemorrhage was not possible because clips, coils, and evidence of a craniotomy are readily seen on CT scans. RSCK and AJM (a neurosurgeon and a neuroradiologist, respectively) independently judged all reported instances of definite or suspected rebleeding and intracranial haemorrhage. These were reported to the ISAT office by the investigators or by means of death certificate and of notifications on the hospital readmission reports. The timing of rebleeding was categorised as: before a first procedure, after a first procedure and within 30 days of the subarachnoid haemorrhage, between 30 days and 1 year, and after 1 year. Any disagreement over categorisation was resolved by discussion.

Details of seizures were collected on a separate case record form. There was detailed review of the case record form, the case notes, and, where necessary, information was directly obtained from the patient. Data were extracted from the case records by centre clinicians and coordinators, including: history of epilepsy, anticonvulsant drugs taken or prescribed after seizures, the number and type of seizures, and, if the patient was assigned to endovascular treatment, whether any other neurosurgical procedure (craniotomy or ventricular shunting) was done. The timing of the seizures was defined as: before treatment, after treatment and before initial discharge, after initial discharge to 1 year, and after 1 year. Seizures occurring with the first haemorrhage were not included, those associated with rebleeding were included.

Angiographic follow-up was requested in all patients who had endovascular coiling, because it is standard practice; it was typically done 6 months after treatment, but occasionally was done earlier and, depending on the findings, repeated later. Follow-up was nearly always done by intra-arterial angiography during the period of the trial. Some centres used magnetic-resonance angiography (MRA) because image quality became satisfactory towards the end of the trial. Angiographic follow-up after neurosurgical clipping was not mandatory because this would have been a change in standard clinical practice in many centres. When angiography was done, data on angiographic occlusion were recorded on the case-record forms at discharge, 2 months, 1 year, and thereafter on the annual case record form. At the time of treatment, the investigator assessed (visually during neurosurgery or from the final angiogram for patients who had endovascular coiling) the percentage of occlusion of the aneurysm. On subsequent angiography the investigator was asked to estimate the degree of occlusion within one of three categories: complete aneurysm occlusion, neck remnant or subtotal occlusion, or incomplete occlusion, indicating substantial aneurysm refilling. This method of categorisation has been described previously.\textsuperscript{4}

RSCK and AJM assessed survival and long-term outcome by reviewing the certified causes of death, and the case record forms, the clinical records, and post-mortem details, when available. Follow-up data were sought at 1 year and annually thereafter by mailing a postal questionnaire to known surviving patients; the last mail-out for the data reported here was done in November, 2004. Long-term survival data for UK patients is obtained from the Office of National Statistics, so that all deaths of UK patients are reported directly to the ISAT office. This allows us to assume reliably that patients for whom we do not have a death notification are alive, even if they do not return their annual postal questionnaire. Similar mortality data are being collected by all centres in Canada, Sweden, Denmark, and Finland, and several centres in France and Germany. We wish to continue follow-up as long as possible in this cohort of patients, which includes more than 90% of the people who took part in ISAT. The dataset for these analyses was finalised on Nov 30, 2004.

### Table 1: Technical outcome of first procedure *

<table>
<thead>
<tr>
<th>Neurosurgical procedure</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not attempted</td>
<td>15 (1·4%)</td>
</tr>
<tr>
<td>Completed</td>
<td>1014 (92·6%)</td>
</tr>
<tr>
<td>Failed to catheterise target aneurysm</td>
<td>29 (2·6%)</td>
</tr>
<tr>
<td>Aneurysm catheterised but anatomy unsuitable</td>
<td>37 (3·4%)</td>
</tr>
<tr>
<td>Not attempted</td>
<td>15 (1·4%)</td>
</tr>
<tr>
<td>Total</td>
<td>1095 (100%)</td>
</tr>
</tbody>
</table>

*The results relate to the first procedure done, not the random treatment assignment.*
Statistical methods

Data handling and statistical analyses have been described previously. The Kaplan-Meier method was used to analyse time to death, with the log-rank test used to compare mortality between the treatment groups. A statistical test of interaction was done to assess whether the treatment effect was consistent across the prespecified subgroups. Relative risks describe the direction and magnitude of the treatment effect, and relative risk reduction and absolute risk reduction are presented to aid interpretation.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN49866681. The protocol for this study was peer-reviewed and accepted by The Lancet: a summary of the protocol was published on the journal’s website, and the journal then made a commitment to peer-review the primary clinical manuscript.

Role of the funding source

The trial was designed, completed, and analysed independent of the sponsors. The principal investigators (RSCK and AJM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Baseline characteristics of the enrolled patients were similar between the treatment groups and have been detailed. 88% of patients were in good clinical grade (WFNS 1 or 2) at the time of enrolment, 95% of the aneurysms were in the anterior cerebral circulation, and 90% were smaller than 10 mm. The mean follow-up is now 4 years, with 6542 patient years of follow-up available after 1 year.

Table 2: Clinical outcome at 2 months and 1 year

<table>
<thead>
<tr>
<th>2 month outcome</th>
<th>1 year outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular n=1065</td>
<td>Neurosurgery n=1063</td>
</tr>
<tr>
<td>Endovascular n=1063</td>
<td>Neurosurgery n=1055</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified Rankin Scale</th>
<th>Endovascular</th>
<th>Neurosurgery</th>
<th>Test of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 No symptoms</td>
<td>293 (19.1%)</td>
<td>144 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>1 Minor symptoms</td>
<td>310 (29.1%)</td>
<td>273 (25.7%)</td>
<td></td>
</tr>
<tr>
<td>2 Some restriction in lifestyle</td>
<td>274 (25.7%)</td>
<td>254 (23.8%)</td>
<td></td>
</tr>
<tr>
<td>0-2 inclusive</td>
<td>787 (73.9%)</td>
<td>671 (63.1%)</td>
<td></td>
</tr>
<tr>
<td>3 Significant restriction in lifestyle</td>
<td>107 (10.1%)</td>
<td>189 (17.8%)</td>
<td></td>
</tr>
<tr>
<td>4 Partially dependent</td>
<td>34 (3.2%)</td>
<td>46 (4.3%)</td>
<td></td>
</tr>
<tr>
<td>5 Fully dependent</td>
<td>62 (5.8%)</td>
<td>73 (6.9%)</td>
<td></td>
</tr>
<tr>
<td>6 Dead</td>
<td>75 (7.0%)</td>
<td>84 (7.9%)</td>
<td></td>
</tr>
<tr>
<td>(3-6 inclusive)</td>
<td>278 (26.1%)</td>
<td>392 (36.9%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Clinical outcome at 2 months and 1 year

<table>
<thead>
<tr>
<th>Risk ratio (95% CI)</th>
<th>Number of events</th>
<th>Test of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endovascular</td>
<td>Neurosurgery</td>
<td>p=0.04</td>
</tr>
<tr>
<td>0.91 (0.59, 1.33)</td>
<td>34/186</td>
<td></td>
</tr>
<tr>
<td>0.83 (0.61, 1.14)</td>
<td>35/174</td>
<td></td>
</tr>
<tr>
<td>0.60 (0.47, 0.78)</td>
<td>71/352</td>
<td></td>
</tr>
<tr>
<td>0.73 (0.55, 0.98)</td>
<td>54/198</td>
<td></td>
</tr>
<tr>
<td>1.15 (0.82, 1.61)</td>
<td>34/61</td>
<td></td>
</tr>
<tr>
<td>0.71 (0.61, 0.83)</td>
<td>208/999</td>
<td></td>
</tr>
<tr>
<td>1.11 (0.84, 1.46)</td>
<td>42/64</td>
<td></td>
</tr>
<tr>
<td>0.61 (0.39, 0.94)</td>
<td>28/245</td>
<td></td>
</tr>
<tr>
<td>0.79 (0.58, 0.92)</td>
<td>222/818</td>
<td></td>
</tr>
<tr>
<td>0.76 (0.61, 0.93)</td>
<td>117/549</td>
<td></td>
</tr>
<tr>
<td>0.71 (0.57, 0.89)</td>
<td>101/431</td>
<td></td>
</tr>
<tr>
<td>0.96 (0.65, 1.42)</td>
<td>32/83</td>
<td></td>
</tr>
<tr>
<td>0.89 (0.73, 1.09)</td>
<td>131/533</td>
<td></td>
</tr>
<tr>
<td>1.04 (0.71, 1.55)</td>
<td>46/162</td>
<td></td>
</tr>
<tr>
<td>0.56 (0.41, 0.72)</td>
<td>69/344</td>
<td></td>
</tr>
<tr>
<td>0.38 (0.14, 1.00)</td>
<td>4/24</td>
<td></td>
</tr>
<tr>
<td>0.76 (0.66, 0.87)</td>
<td>250/1063</td>
<td></td>
</tr>
</tbody>
</table>
1073 and 1070 patients were randomised to endovascular coiling or neurosurgical clipping, respectively. Of the 1073 patients allocated endovascular treatment, seven died before the procedure, and nine underwent clipping as the first procedure. Of the 1070 patients allocated to neurosurgery, 19 died before the first procedure, 39 had coiling as the first procedure, and seven were treated conservatively, and the information is missing for two. Table 1 shows the technical outcome of the first procedure done.

The mRS values at 2 months are missing for eight of the 1073 patients in the endovascular group and seven of the 1070 in the neurosurgery group. At 1 year, eight (0.4%) patients (three endovascular, five neurosurgical) had been lost to follow up, 25 (1%) patients were known to be alive but had missing Rankin data: 10 endovascular and 15 neurosurgical.

278 (26.1%) of 1065 patients allocated endovascular treatment were known to be dead or dependent at 2 months compared with 392 (36.9%) of 1063 allocated neurosurgery (relative risk=0.71, 0.62–0.80; p<0.0001; table 2). 250 (23.5%) of 1063 patients allocated to endovascular treatment were known to be dead or dependent at 1 year compared with 326 (30.9%) of 1055 patients allocated to neurosurgery (0.76, 0.66–0.87); this corresponds to a relative risk reduction at 1 year of 23.9% (12.4–33.9), and an absolute risk reduction of 7.4% (3.6–11.2) in favour of coiling (p=0.0001). Case fatality rates at 1 year were 8.0% (6.4–9.8) and 9.9% (8.2–11.9) among patients allocated endovascular and neurosurgical treatment, respectively.

Figure 1 shows subgroup analyses for death or dependency at 1 year. The treatment effect was heterogeneous and difficult to interpret within these subgroups: age, WFNS grade at baseline, and aneurysm location. For example, of the patients studied, only a small number were older than 70 years or younger than 40 years, and there was no consistent trend for age. Similarly, the number of patients with poor clinical grade (WFNS 4–6) who were randomised was small (<4% of the total).

The advantage of endovascular over neurosurgical treatment varies widely with aneurysm location, but endovascular treatment seems beneficial for all sites. The smallest subgroups were the greatest outliers and also the most subject to chance effects.

Deaths occurring within the first 7 years along with the numbers at risk in each year are shown in figure 2. There were more deaths among patients allocated to neurosurgery than to endovascular treatment (log-rank p=0.03), which seemed to be consistent over time. The causes of deaths after 2 months (and up to 8 years) are shown in table 3, subdivided to show deaths after the first year separately.

Table 4 shows the findings from the first follow-up angiography. Of 988 patients alive at 1 year after endovascular allocation, angiographic follow-up

---

Table 3: Causes of death

<table>
<thead>
<tr>
<th></th>
<th>2–12 months</th>
<th></th>
<th>After 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endovascular</td>
<td>Neurosurgery</td>
<td>Endovascular</td>
</tr>
<tr>
<td>Complication of severe dependent survival (eg, chest or other infections)</td>
<td>7</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Treated aneurysm rebleeding</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Probable or definite bleed from another aneurysm</td>
<td>0</td>
<td>0</td>
<td>3*</td>
</tr>
<tr>
<td>Other intracranial haemorrhage</td>
<td>0</td>
<td>0</td>
<td>1†</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Cancer</td>
<td>0</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Suicide</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections not related to dependent survival</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Other causes (eg, trauma, perforated ulcer, pulmonary embolus, neurodegenerative)</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>21</td>
<td>33</td>
</tr>
</tbody>
</table>

*Includes all reported deaths up to November 2004. †See text for details. ‡Confirmed at autopsy as primary intracerebral haemorrhage.
information was available on 881 (89% of surviving patients). Most angiograms (690 of 881) were done between 2 months and 1 year. 28 were done before discharge, 80 before 2 months, 58 from 1 to 2 years, and 25 after 2 years. MRA was used as an alternative to intra-arterial angiography in 47 patients in the endovascular group. In the neurosurgical group, 450 angiograms were done in 965 potentially eligible patients (47%). 142 were done before discharge, 61 before 2 months, 58 from 1 to 12 months, and 48 from 1 to 5 years.

After endovascular coiling, 66% of follow-up angiograms showed complete angiographic occlusion, 26% showed subtotal occlusion or a neck remnant, and 8% showed incomplete occlusion with aneurysm refilling. We have included all angiograms done during the first year as well as those done later when they were the first that a patient had had. Analyses of angiographic data after the first angiogram will be covered in a future paper. In the 450 patients in the neurosurgical group who had follow-up angiograms, 82% were completely occluded, 12% had a neck remnant, and 6% were incompletely occluded. This group of neurosurgical patients is probably a selected population because angiography is not routinely done in all centres and was not required by the protocol. In the UK, post-clipping angiography is more likely to be done if there is doubt about whether the aneurysm has been occluded satisfactorily.

We have previously reported part of the data available on rebleeding. These data were mostly for rebleeds during the first year in patients with follow-up to that time point. Rebleeds and patient follow-up beyond that time were few.

Here we report complete data on rebleeding within the first year in almost all patients and additional data beyond 1 year. After the first year there are 3258 patient years of follow-up for the endovascular group and 3107 patient years of follow-up for the neurosurgical group, with a mean follow-up of 4 years. All rebleeding events due to the target aneurysm are shown in table 5 and figure 3. Nine patients (seven allocated endovascular and two allocated neurosurgery) had confirmed rebleeding from the target aneurysm after 1 year (webtable). Rebleeding from another aneurysm was either definite or probable in three patients. A man aged 54 years with a ruptured middle-cerebral aneurysm was randomised to endovascular treatment and had successful coiling. On follow-up angiography he was found to have a new pericallosal aneurysm. This patient died after a further haemorrhage that happened 15 months after his original presentation. Autopsy confirmed haemorrhage from the pericallosal aneurysm. A woman aged 52 years who was randomised to neurosurgery had clipping of a posterior communicating artery aneurysm. She developed a second posterior-communicating aneurysm on the opposite side, which ruptured in year 3, had further clipping, and survived with mRS 1 at follow-up. A woman aged 61 years with a ruptured anterior-cerebral aneurysm who was allocated endovascular treatment had successful coiling. 2 years later her posterior communicating artery aneurysm ruptured and at follow-up her mRS was 4.

![Screenshot of a graph showing cumulative rebleeding risk from target aneurysm](https://example.com/cropped-graph.png)
Two patients died after a further haemorrhage thought to be from another aneurysm: one patient has been previously described, the second patient was a woman aged 69 years who was allocated endovascular treatment and had coiling of a posterior-communicating aneurysm and a good outcome (mRS 1). She is known to have had four further aneurysms and to have died suddenly in year 4; the certified cause of death was intracranial haemorrhage but no CT or autopsy was done.

One patient died of a primary intracerebral haemorrhage (confirmed at autopsy) at age 76 years, 4 years after coiling of a middle cerebral aneurysm.

In summary, among the eight cases of rebleeding from the treated aneurysm after coiling (including one crossover from the neurosurgery group) three patients were independent at follow-up and five were dead or dependent.

Craniotomy or ventricular drainage is known to carry a small risk of later seizures. Table 6 shows the incidence of seizures at various time periods after randomisation in ISAT, by allocated treatment. There was a highly significant reduction in seizures in the endovascular group compared with the neurosurgery group after the first procedure (relative risk 0·52, 0·37–0·74). A separate paper will examine and describe the epilepsy results in more detail.

Discussion
The final 1-year results presented in this paper reinforce our preliminary findings. Endovascular coiling, compared with neurosurgical clipping, for ruptured intracranial aneurysms that were anatomically suitable for either procedure leads to a significant reduction in the relative risk of death or dependency of 23·9% (12·4–33·9). This equates to an absolute risk reduction of 7·4% (3·6–11·2), which is equivalent to 74 patients avoiding death or dependency at 1 year for every 1000 patients treated.

After publication of the preliminary results of ISAT, there was much controversy and discussion in the worldwide neurosurgical community. Several position statements were issued by groups in neurosurgery and related specialties, including the American Association of Neurological Surgeons, the American Society Neuroradiology (ASNR) and American Society of Therapeutic and Interventional Neuroradiology (ASITN), and the respective German and Japanese societies. These statements drew attention to the many questions that the early results did not answer, in particular the durability and long-term efficacy of coil treatment at preventing rerupture, applicability of the results, and possible challenges in the use of ISAT results to inform the treatment of all patients with subarachnoid haemorrhage. Criticisms mostly related to the proportion of eligible patients who were enrolled, which varied widely between centres, and the expertise of the neurosurgeons who treated patients in ISAT, particularly those in the UK.

We have responded to these criticisms previously but it is worth restating some key points. One of the main successes of ISAT is that it overcame the problems of enrolling patients into randomised trials by recruiting those for whom the best treatment was unclear. This uncertainty clearly also existed during the recruitment period into ISAT in the wider community of clinicians treating patients with subarachnoid haemorrhage. In such circumstances of collective and individual uncertainty, it is ethically justifiable to offer randomisation to the patient (and in fact, when a suitable trial exists it could be deemed unethical not to offer randomisation to such patients). The uncertainties about treatment varied among centres and individual surgeons and interventionists within centres. Thus it was inevitable that enrolment rates for different centres would vary. This variation is a strength of ISAT and justifies large pragmatic trials, not a shortcoming or “fault”, because it accommodates the breadth of professional opinion.

Contrary to widespread opinion, observational data cannot objectively and reliably show that one neurosurgeon’s results are substantially better than another’s for aneurysm clipping. The shortcomings of such data include the small annual volume of cases of aneurysm surgery for an individual neurosurgeon, the objectivity of the collection of outcome data, and the varied case-mix of the treated population (eg, patients’ age, clinical grade, location of the aneurysm, timing of presentation, and surgery after the subarachnoid haemorrhage). Comparisons of observational data also ignore the reality of subarachnoid haemorrhage management—and, that most patients with aneurysms are treated at the neurosurgical unit to which they are first admitted or transferred. Transfer of very sick patients to distant units is hazardous owing to clinical risks during transfer and delay in treatment. Comparisons with other randomised trials are also problematic. We expect that comparisons will be made between ISAT and the Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST). In that randomised trial, 1001 patients who had surgery for aneurysm in 30 centres were enrolled. The trial found that 85% of patients had good outcomes (Glasgow outcome score of 1 or 2) at 3 months with 6% mortality, which initially

<table>
<thead>
<tr>
<th></th>
<th>Endovascular n=1073</th>
<th>Neurosurgery n=1070</th>
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</thead>
<tbody>
<tr>
<td>Before first treatment</td>
<td>3 (3)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>After procedure to</td>
<td>16 (2)</td>
<td>33 (3)</td>
</tr>
<tr>
<td>before discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge to 1 year</td>
<td>27 (1)</td>
<td>44</td>
</tr>
<tr>
<td>After 1 year</td>
<td>14 (1)</td>
<td>24</td>
</tr>
</tbody>
</table>

Figures in parentheses indicate seizures associated with re-bleeding. *Onset of first seizure not associated with first subarachnoid haemorrhage.

Table 6: Seizure occurrence by treatment allocation
seems better than ISAT. However, there is an important difference between ISAT and IHAST: in IHAST, randomisation took place in the anaesthetic room immediately before surgery and therefore included a group of patients who had already passed through a period of high risk. If we exclude deaths due to rebleeding before treatment in ISAT, then the mortality at 2 months would be very similar to IHAST: death of 65 (6.1%) of 1063 patients in the neurosurgery group and 68 (6.3%) of 1065 patients in the endovascular group.

After the preliminary results of ISAT were published, practice in the UK and several other countries changed substantially as objectively shown by the National Audit of subarachnoid haemorrhage, Royal College of Surgeons Clinical Effectiveness Unit, (Lindsay K, Langham J, personal communication). However, there are still wide variations in the availability and use of endovascular treatment among countries and within countries. Access to endovascular treatment has been hampered by a lack of trained endovascular operators or adequate neuroangiographic equipment, the cost of coils and other consumables associated with endovascular treatment compared with those for surgery (and the source of payment for these), and logistical barriers (eg, the availability of anaesthesia in neuroradiology departments).

In the subgroup analyses, the relative effects of treatment were heterogeneous by age, WFNS grade, and aneurysm location. However there is no robust evidence that neurosurgical treatment has advantages over endovascular treatment for these subgroups of patients. For example, although there was heterogeneity by age, there was no trend for treatment effect and age. Although the point estimate might suggest that there is less advantage for coiling than clipping in patients older than 70 years and with poor WFNS grade, the estimates of effect are very imprecise because of the relatively small number of such patients in the trial. During ISAT, many patients older than 70 years were not randomised because individual investigators expected that elderly patients would fare worse with surgery. Data from the International Study of Unruptured Intracranial Aneurysms (ISUIA) supported this view.11 The ISUIA data showed significantly higher morbidity at 1 year among patients older than 50 years who had neurosurgery for an unruptured intracranial aneurysm, with incremental worsening of outcome in each decade after 50.

Dividing the data from any trial into subgroups makes it likely that the results in some subgroups will become non-significant simply because of the reduction in the amount of data and the increased imprecision of the result. Thus, although the effect of the treatments on patients with anterior-cerebral-artery aneurysm was not significant for the primary outcome measure, one of the treatments could still be more beneficial than the other. In addition, for patients with aneurysm of the anterior cerebral artery, there is a greater expectation that they will have cognitive impairment, other deficits of memory and executive functioning, and subtle personality changes, because the surgical techniques used to access the area of the anterior communicating artery might require resection or retraction of frontal lobe structures, such as the gyrus rectus and frontal gyri. A case-matched study of MRI changes and cognitive outcomes after clipping and coiling showed local damage or encephalomalacia exclusively after neurosurgery and more small infarcts in the vascular territory of the aneurysm in the surgical group, with no difference in the incidence of large infarcts.12 There was also a trend towards poorer cognitive outcome in the surgical group, which was significant on four neuropsychological tests. An ISAT substudy is assessing the neuropsychological effects of the treatments and will be important in detecting subtle deficits that can affect social functioning and return to work.4

In summary, the subgroup analyses show no good evidence that the benefit from endovascular treatment does not apply across all the sub-groups.

A crucial issue for endovascular techniques is the uncertainty about the long-term durability of aneurysm occlusion with coils and whether it protects from further aneurysm rupture. ISAT gives the most reliable evidence to date to answer this question. Overall, there was no significant difference in the frequency of rebleeds between the groups. The angiographic outcomes of coil occlusion are not as good as those for surgery either in this study or in the other published large series with follow-up angiography.11-13 However, the reported risk of rebleeding from the coiled aneurysm after 1 year is low despite several thousand patient years of follow-up. The rebleed rate is 0.2% per patient year with follow-up from 1 to 8 years with a mean of 4 years. Data from Finland have shown that the risk of further haemorrhage continues for up to 30 years after subarachnoid haemorrhage14 and highlight the importance of the continued follow-up of the ISAT patients.

Patients who have an aneurysmal subarachnoid haemorrhage have a small risk of aneurysm recurrence and new aneurysm formation. The Dutch ASTRA group reported follow-up CT angiography on 610 patients 1–15 years after surgical clipping of a ruptured aneurysm and found an incidence of 16% of new aneurysms.15 In 24 patients, aneurysms were present at the site of the previous clipping and in three of these, the postoperative angiogram had shown complete aneurysm occlusion. Thus, patients with aneurysmal subarachnoid haemorrhage are at some risk of further subarachnoid haemorrhage. Ronkainen and colleagues16 reported that patients with a good outcome after subarachnoid haemorrhage who were followed up for up to 21 years (mean 7.5 years) had a standardised mortality rate that was twice that of a matched population. Therefore, it is
unreliable to extrapolate the ISAT results beyond the 7 years for which robust evidence is currently available. Ongoing assessment and follow-up will allow the continued monitoring of this issue for inclusion in future ISAT analyses. The angiographic findings for ISAT reported here are slightly better than those in two other large observational studies: the frequency of incomplete treatment at follow-up angiography was 8% and probably reflects two factors that distinguish the ISAT series. First, most (90%) of the aneurysms treated in ISAT were less than 10 mm in diameter and occlusion results are known to be substantially better in patients with aneurysms of this size than in patients with large and giant aneurysms. Second, the ISAT results are more recent than those of the other studies and reflect improvements in the coils available and operator experience.

We have not yet analysed angiographic findings beyond the first follow-up angiogram but such analyses will allow comparison with those of Raymond and colleagues who did angiography 1–3 years after coiling and reported deterioration in the angiographic occlusion. In two cases in ISAT, a coiled aneurysm that was completely occluded on 6-month follow-up angiography reruptured, and there were also several reports of late aneurysm recurrence after complete occlusion. Such late recurrence was also observed in the ASTRA study after surgical clipping. Follow-up imaging, particularly non-invasive MRA might be justified as a routine procedure, particularly for young patients. Even though many patients had subtotal occlusion or neck remnant of the aneurysm at follow-up angiography after coiling, the risk of delayed rerupture seems to be low, at least in the medium term. Patients who have complete aneurysm occlusion on a follow-up angiogram in the first year can therefore be advised that the risk of rerupture is very low. In patients with subtotal occlusion or neck remnant, the risk seems to be low. Thus, any recommendation to retreat the aneurysm needs to be weighed carefully against the risks of further treatment, particularly in older patients.

In patients who had neurosurgical treatment, the likelihood of late rebleeding is extremely low; this event has occurred in only one patient in ISAT, who had a middle cerebral aneurysm after 6 years. This patient had not had follow-up angiography but the very low rate of rebleeds after clipping raises the question of whether patients who have had neurosurgical clipping should have follow-up intra-arterial angiography as routine, unless there are uncertainties at the time of surgery.

All patients enrolled in ISAT in the UK are now noted for data cleaning, editing, table preparation, and checking. The cumulative mortality curve to 7 years shows slightly more deaths in the neurosurgical group. The effect of rebleeding on death or dependent survival over this period seems small. These findings provide reassurance that late events, in particular late aneurysm rebleeding leading to death or dependency, are uncommon in both treatment groups and are unlikely to reverse the early benefit of endovascular treatment.

The ISAT data now give a reliable estimate of the risk of seizures occurring after allocation to craniotomy and clipping compared with endovascular coiling. The risk of seizures is significantly lower with coiling than with neurosurgery. This finding has important practical implications when seizures occur late after discharge, especially in those for whom the ability to drive is important. The ISAT data on seizures are unique in their scale and reliability and will also provide driving authorities with evidence to formulate advice and policy on whether, and for how long, patients should not drive after subarachnoid haemorrhage and its treatment.

The complete 1-year data from ISAT confirm and reinforce our preliminary findings. Endovascular coil treatment of ruptured intracranial aneurysms, when a patient is in good clinical grade and the aneurysm anatomy is suitable for endovascular treatment, is more likely than neurosurgical treatment to lead to independent survival at 1 year.

Because of a very small risk of late rerupture 1 year after coiling, follow-up to monitor aneurysm reopening might be appropriate.

Continued follow-up of patients in ISAT will give a unique data set of the long-term outcome of subarachnoid haemorrhage and will give even more robust evidence for patients and neuroscience clinicians who advise them.

These new analyses support the conclusion reached in the position statement of the ASNR and the ASITN: “The study data allow us to conclude that for patients with SAH [subarachnoid haemorrhage] and aneurysm anatomy indicating a high likelihood of success by endovascular techniques patients should be offered that option”. The new analyses also address their caveat that “this must be tempered by the limited data for long-term durability after 1 year”, by providing these data. The updated results confirm that the changes in practice seen on the basis of the preliminary findings should have led to substantial reductions in death and dependency for patients with subarachnoid haemorrhage.

Contributors
Primary authorship was the responsibility of A J Molyneux and R S C Kerr. P Sanderson and M Clarke provided direct input into the writing, editing and decisions on content, and advice on clinical trial and sub-group analysis interpretation. L-M Yu was responsible for all statistical aspects and analysis. J A Yarold and M Sneade were responsible for data cleaning, editing, table preparation, and checking.
Conflict of interest statement
AJM has a consulting and advisory agreement with Micrus Inc, a manufacturer of detachable platinum coils, with stock interest in the company. He has a minor stockholding in Micro Therapeutics Inc and receives salary support from the Medical Research Council. RSCK, AJM, and JAY have received support for travel to meetings from Boston Scientific. No other conflicts of interest by investigators or authors have been notified to the coordinating centre.

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References
Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial


Summary

Background Most women receiving systemic therapy for breast cancer experience hot flashes. We undertook a randomised, double-blind, placebo-controlled, multi-institutional trial to assess the efficacy of gabapentin in controlling hot flashes in women with breast cancer.

Methods 420 women with breast cancer who were having two or more hot flashes per day were randomly assigned placebo, gabapentin 300 mg/day, or gabapentin 900 mg/day by mouth in three divided doses for 8 weeks. Each patient kept a 1-week, self-report diary on the frequency, severity, and duration of hot flashes before the start of the study and during weeks 4 and 8 of treatment. Analyses were by intention to treat.

Findings Evaluable data were available on 371 participants at 4 weeks (119 placebo, 123 gabapentin 300 mg, and 129 gabapentin 900 mg) and 347 at 8 weeks (113 placebo, 114 gabapentin 300 mg, and 120 gabapentin 900 mg). The percentage decreases in hot-flash severity score between baseline and weeks 4 and 8, respectively, were: 21% (95% CI 12 to 30) and 15% (1 to 29) in the placebo group; 33% (23 to 43) and 31% (16 to 46) in the group assigned gabapentin 300 mg; and 49% (42 to 56) and 46% (34 to 58) in the group assigned gabapentin 900 mg. The differences between the groups were significant (p = 0.0001 at 4 weeks and p = 0.007 at 8 weeks by ANCOVA for overall treatment effect, adjusted for baseline values); only the higher dose of gabapentin was associated with significant decreases in hot-flash frequency and severity.

Interpretation Gabapentin is effective in the control of hot flashes at a dose of 900 mg/day, but not at a dose of 300 mg/day. This drug should be considered for treatment of hot flashes in women with breast cancer.

Introduction

Most women going through the menopause experience hot flashes, a symptom complex that includes a collection of vasomotor symptoms such as a sudden feeling of warmth and redness that begins in the chest and spreads to the neck and the face, accompanied by sweating, palpitations, and anxiety. Hot flashes are also among the most commonly reported symptoms in women receiving systemic therapy for breast cancer, adversely affecting quality of life.

The pathophysiology of hot flashes is not entirely clear, but a working model has emerged, which hypothesises that physiological concentrations of oestrogen and progesterone maintain the concentrations of endorphin in the hypothalamus. At menopause, endorphin concentrations decrease with falling oestrogen and progesterone levels, which results in a lowering of the set point in the thermoregulatory nucleus. This process leads to an increased hypothalamic release of norepinephrine and serotonin and leads to a lowering of core body temperature. Treatment with oestrogen and progesterone can ameliorate these symptoms, but there is controversy about their use in women with breast cancer. A trial of hormone replacement therapy in women with breast cancer was terminated early because of the finding that the treatment increased the risk of recurrence.

Various non-hormonal agents have been tested. Clonidine, a centrally acting α-adrenergic agonist, was effective in a controlled trial with a transdermal patch and in a double-blind placebo-controlled trial given orally in women with breast cancer. Newer antidepressants, such as selective serotonin-reuptake inhibitors and inhibitors of serotonin and norepinephrine reuptake, are promising non-hormonal treatments for hot flashes. Randomised placebo-controlled trials have shown that venlafaxine, fluoxetine, and paroxetine are effective in control of hot flashes. Gabapentin is a GABA analogue used in the treatment of epilepsy, neurogenic pain, restless-leg syndrome, essential tremor, bipolar disorder, and migraine prophylaxis; it was first reported for its effects on hot flashes in five women and one man. A randomised double-blind, placebo-controlled trial has shown that gabapentin is effective in control of menopausal hot flashes, and a pilot study showed that it had promising effects in women with breast cancer.

On the basis of these observations, we undertook a double-blind, placebo-controlled trial of gabapentin to assess its efficacy in the treatment of hot flashes in women with breast cancer. The most commonly used dose of gabapentin is 900 mg per day. However, we decided to study a lower dose (300 mg per day) also; if this dose could control hot flashes, the patients would benefit overall. The 8-week study duration was selected on the basis of our previous study of clonidine, to provide internal consistency.
Methods

Patients

The patients were participants in a multicentre clinical trial at 18 geographically diverse member sites of the University of Rochester Community Clinical Oncology Program. Women aged 18 years or older who had breast cancer and were having an average of two or more hot flashes per day were eligible to take part in the study. Acceptable non-steroidal contraceptive measures were required. Patients currently receiving chemotherapy were not eligible, although endocrine therapies were allowed. Most of the patients were taking adjuvant tamoxifen. Patients taking venlafaxine, clonidine, or anticonvulsants were not eligible for the study, but use of other antidepressants including selective serotonin-reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors was allowed. The other reasons for exclusion were: pregnancy; breastfeeding; use of steroidal contraception; coronary insufficiency; recent history of myocardial infarction, symptomatic cardiac disease, peripheral or cerebrovascular disease, stroke, syncope, or symptomatic hypertension; hepatic dysfunction (aspartate aminotransferase concentration above twice the upper limit of normal, or bilirubin concentration above the upper limit of normal, as defined at each institution); renal dysfunction (serum creatinine concentration above 1·25 times the upper limit of normal); and known allergy to gabapentin. The Institutional Review Boards of the University of Rochester and each participating site approved the protocol. Written informed consent was obtained from each participant.

Design and procedures

Patients were randomly assigned placebo, gabapentin 100 mg, or gabapentin 300 mg, each to be taken by mouth three times a day, for 8 weeks. There was a 3-day titration period for all patients because the study was double-blind. The study drugs were supplied as capsules of similar appearance in bottles. Treatment assignment was done by use of a randomisation table created in SAS computer program (version 8) and was stratified by the Community Clinical Oncology Program site and by the duration of hot flashes (<9 months or ≥9 months). A block size of three was used to ensure that the treatment assignment was balanced after every three participants within each stratum.

The primary objective of the study was to compare the efficacy and the side-effect profile of gabapentin 300 mg/day or 900 mg/day with that of placebo.

Each participant kept a 1-week self-report diary on hot flashes, originally developed by the North Central Cancer Treatment Group,22 before the start of the study and during weeks 4 and 8 of treatment. All hot flashes were recorded, and symptoms were assigned a grade of 1 (mild), 2 (moderate), 3 (severe), or 4 (very severe). In addition, a single question assessed the average duration in minutes of all hot flashes experienced that day.

A patient-report symptom inventory, modified from a measure created at the M D Anderson Cancer Center, Houston, TX, USA,23 was used to monitor other symptoms. The symptom inventory is a series of uniscales in which the severity of each of ten symptoms (fatigue, pain, nausea, sleep disturbance, shortness of breath, memory, appetite, drowsiness, vomiting, and distress) is indicated by filling in the appropriate circle on an 11-point scale, from 0 (not present) to 10 (as bad as you can imagine). The checklist was completed by patients three times: at the end of the pretreatment (baseline) week, at week 4, and at week 8.

Statistical analysis

In our previous research on clonidine, the SD of the percentage change from baseline in hot-flash frequency was about 35%. A sample of 114 evaluable participants per group would give 80% power to detect a 15% difference between any pair of groups. To allow for up to 16% dropout by 8 weeks, we planned to enrol 136 participants per group.

The method of analysis was decided prospectively and incorporated the intention-to-treat principle: data are included in the treatment group to which the participant was assigned, irrespective of any subsequent changes to the treatment. The statistical package SAS for Windows,
Estimated effect of gabapentin

Table 2:

*Difference in change scores between gabapentin group and placebo group.

Demographic and baseline characteristics

Table 1:

Data are number of participants unless otherwise stated.

Table 1: Demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo 300 mg (n=137)</th>
<th>300 mg gabapentin (n=139)</th>
<th>900 mg gabapentin (n=144)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>54 (7)</td>
<td>55 (9)</td>
<td>55 (9)</td>
</tr>
<tr>
<td>White</td>
<td>131 (96%)</td>
<td>131 (94%)</td>
<td>138 (96%)</td>
</tr>
<tr>
<td>Married</td>
<td>99 (72%)</td>
<td>101 (73%)</td>
<td>111 (77%)</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently taking tamoxifen</td>
<td>103 (75%)</td>
<td>95 (68%)</td>
<td>100 (69%)</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td>12 (9%)</td>
<td>13 (9%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>9 (7%)</td>
<td>11 (8%)</td>
<td>12 (8%)</td>
</tr>
<tr>
<td><strong>Hot flashes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) number per day</td>
<td>8.8 (6.4)</td>
<td>8.5 (5.9)</td>
<td>8.7 (5.3)</td>
</tr>
<tr>
<td>Mean (SD) severity score</td>
<td>19.9 (17.9)</td>
<td>19.4 (19.6)</td>
<td>18.7 (13.7)</td>
</tr>
<tr>
<td>Mean (SD) duration, min</td>
<td>5.2 (6.4)</td>
<td>5.0 (4.9)</td>
<td>5.0 (4.3)</td>
</tr>
</tbody>
</table>

Data are number of participants unless otherwise stated.

Results

Between June, 2001, and July, 2003, 420 women with breast cancer were enrolled and randomly assigned placebo, gabapentin 300 mg/day, or gabapentin 900 mg/day by mouth in three divided doses, for 8 weeks (figure 1). The mean age of the participants was 55 years, and most were married (75%) and white (95%). Demographic, clinical, and hot-flash characteristics at baseline are given in table 1. The baseline hot-flash frequency ranged from 2 to 54 and the severity score from 2 to 191. Evaluable data were available for 371 (88%) of the 420 patients at week 4 and 347 (83%) at week 8. Diaries were obtained from all the patients, including those who discontinued the assigned treatment, unless the patient decided to withdraw from the study.

According to our preplanned analyses, we first examined between-group differences in changes in frequency, severity, and duration of hot flashes by a mixed-effects model. None of the interaction terms (time, age, and current use of tamoxifen) in these analyses was significant, so models including only main effects were used to describe our data. For hot-flash frequency, the estimated effect (the difference in the change scores between the gabapentin group and the placebo group at both week 4 and week 8) was –0.80 (95% CI –1.70 to 0.10) for the group assigned 300 mg gabapentin and –2.10 (–2.95 to –1.23) for the group assigned 900 mg gabapentin (table 2). For severity, the estimated effects were –1.79 (–4.38 to 0.80) for the 300 mg group and –4.88 (–7.23 to –2.53) for the 900 mg group. These findings show a clear benefit for the group assigned 900 mg gabapentin, but no evidence of benefit with 300 mg gabapentin in reducing hot-flash frequency and severity. Similar analyses provided no evidence of differences in the mean duration of hot flashes between the groups.

Similar analyses were done on the percentage change scores. Again, none of the interaction terms was significant, so models including only main effects were used. For hot-flash frequency, the estimated effects on percentage change scores were significant for both...
gabapentin groups (table 2). For severity, the difference in percentage change score was significant only for the 900 mg group.

After fitting each model, we did residual analyses to check for adequacy of the mixed-model assumptions, which include the normality of error terms, mean model, and covariance structures. Since there were only two repeated change scores for each individual, there was no need to check for correlation structure, so only the assumption of constant variance was checked. Since the residuals are correlated, we transformed the residuals by multiplying the residual vector from each participant by the inverse of the Cholesky decomposition of the estimated covariance matrix. The covariates and the predicted mean values were transformed in the same way. The Q-Q plot of the transformed residuals was used to check for outliers and normality assumptions of the error terms. The transformed-residual versus transformed-predicted mean values plot was used to check for the assumption of constant variance. The transformed-residual versus transformed-covariate plots were checked for adequacy of the mean models. Outliers were identified for models involving different outcomes, and models were refitted without them. The parameter estimates were changed slightly when the outliers were excluded; however, none of these sensitivity analyses changed our main conclusion. The residual plots show that our mean models are adequate.

In general, the distribution of the transformed residual for the models involving the change scores had some

### Table 3: Changes in hot-flash characteristics between baseline and week 4 or week 8

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change (95% CI) from baseline to week 4</th>
<th>p*</th>
<th>Change (95% CI) from baseline to week 8</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=119)</td>
<td>Gabapentin 300 mg (n=123)</td>
<td>Gabapentin 900 mg (n=129)</td>
<td>Placebo (n=113)</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>-1.98 (-2.79 to -1.17)</td>
<td>-2.64 (-3.47 to -1.81)</td>
<td>-4.00 (-4.83 to -3.17)</td>
<td>-2.25 (-3.33 to -1.17)</td>
</tr>
<tr>
<td>Percentage change</td>
<td>-18% (-25 to -11)</td>
<td>-28% (-36 to -20)</td>
<td>-41% (-48 to -34)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>-1.06 (-1.90 to -0.22)</td>
<td>-1.57 (-2.24 to -0.90)</td>
<td>-1.56 (-1.99 to -1.13)</td>
<td>0.206</td>
</tr>
<tr>
<td>Percentage change</td>
<td>9% (-16 to 34)</td>
<td>-19% (-27 to -11)</td>
<td>-22% (-31 to -13)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change</td>
<td>-5.45 (-8.06 to -2.84)</td>
<td>-7.50 (-10.4 to -4.56)</td>
<td>-9.97 (-12.0 to -7.93)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Percentage change</td>
<td>-21% (-30 to -12)</td>
<td>-33% (-43 to -23)</td>
<td>-49% (-56 to -42)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*From ANCOVA tests of the overall treatment effect adjusted for baseline values.
Table 4: Changes in symptoms between baseline and week 4 or week 8

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Change (95% CI) in symptoms from baseline to week 4</th>
<th>p*</th>
<th>Placebo (n=119)</th>
<th>Gabapentin 300 mg (n=123)</th>
<th>Gabapentin 900 mg (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite</td>
<td>-0.27 (-0.49 to -0.05)</td>
<td></td>
<td>-0.36 (-0.55 to -0.17)</td>
<td>0.05 (-0.14 to 0.24)</td>
<td>0.012 (-0.34 to 0.10)</td>
</tr>
<tr>
<td>Distress</td>
<td>-0.08 (-0.57 to 0.41)</td>
<td></td>
<td>-0.23 (-0.71 to -0.25)</td>
<td>-0.54 (-1.04 to -0.04)</td>
<td>0.239 (-0.85 to 0.19)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>-0.11 (-0.51 to 0.29)</td>
<td></td>
<td>-0.31 (-0.70 to 0.08)</td>
<td>-0.22 (-0.73 to 0.27)</td>
<td>0.552 (-1.02 to -0.06)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>-0.14 (-0.63 to 0.35)</td>
<td></td>
<td>-0.19 (-0.66 to 0.25)</td>
<td>-0.22 (-0.67 to 0.23)</td>
<td>0.452 (-1.11 to -0.19)</td>
</tr>
<tr>
<td>Nausea</td>
<td>-0.17 (-0.42 to 0.08)</td>
<td></td>
<td>-0.11 (-0.32 to 0.10)</td>
<td>0.08 (-0.34 to 0.30)</td>
<td>0.775 (-0.54 to 0.06)</td>
</tr>
<tr>
<td>Pain</td>
<td>0.20 (-0.23 to 0.63)</td>
<td></td>
<td>-0.30 (-0.69 to 0.09)</td>
<td>-0.09 (-0.47 to 0.29)</td>
<td>0.039 (-0.56 to 0.15)</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.33 (-0.73 to 0.07)</td>
<td></td>
<td>-0.38 (-0.70 to 0.06)</td>
<td>-0.31 (-0.62 to 0.00)</td>
<td>0.209 (-1.12 to -0.34)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>-0.07 (-0.43 to 0.29)</td>
<td></td>
<td>-0.22 (-0.50 to 0.06)</td>
<td>-0.22 (-0.59 to -0.07)</td>
<td>0.165 (-0.53 to 0.09)</td>
</tr>
<tr>
<td>Sleep</td>
<td>-0.83 (-1.35 to -0.31)</td>
<td></td>
<td>-1.02 (-1.55 to -0.49)</td>
<td>-1.27 (-1.74 to -0.80)</td>
<td>0.065 (-1.28 to -0.74)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-0.19 (-0.41 to 0.03)</td>
<td></td>
<td>-0.25 (-0.44 to 0.06)</td>
<td>0.12 (-0.09 to 0.33)</td>
<td>0.120 (-0.43 to 0.05)</td>
</tr>
</tbody>
</table>

A negative value denotes an improvement in the symptom. *From ANCOVA tests of the overall treatment effect adjusted for baseline values.

Discussion

The results of this randomised, double-blind placebo-controlled trial accord with those of our pilot study of menopausal women; there was a 46% reduction in the hot-flash severity score with gabapentin 900 mg/day, compared with a 54% reduction versus placebo reported in postmenopausal women treated with gabapentin 900 mg/day for 12 weeks. We analysed our data in two different ways, and in each approach we observed a significant effect on hot flashes with gabapentin 900 mg/day, whereas gabapentin 300 mg/day was no better than placebo for any comparison. An even higher dose of gabapentin might be more effective. Evidence in support of that idea comes from the study by Guttuso and colleagues, in which an open-label dose escalation was allowed after the 12-week study period. 75% of patients who elected to continue requested an increase of their dose beyond 900 mg/day (maximum allowable dose 2700 mg/day); among these patients there was a 67% reduction in the hot-flash severity score, which suggests a strong dose effect in the control of hot flashes.

Short-term (<4 weeks) side-effects were not assessed in this study, because the first symptom inventory was obtained during week 4 of the study. We examined the reasons given for withdrawing from the study owing to side-effects and found that somnolence or fatigue was given as the reason by one, three, and six patients in the placebo, gabapentin 300 mg, and gabapentin 900 mg groups, respectively; the overall numbers withdrawing because of side-effects were six, six, and ten. The opposite pattern was noted in patients who withdrew because the study treatment was not helpful (seven, five,
A subsequent study found that paroxetine was the most potent inhibitor of CYP2D6, followed by fluoxetine, sertraline, and citalopram. Venlafaxine was the least potent inhibitor of CYP2D6. Gabapentin is not a potent inhibitor of CYP2D6, followed by fluoxetine, sertraline, and citalopram. Venlafaxine was the least potent inhibitor of CYP2D6.

Recent studies have found that gabapentin and pregabalin are effective in the treatment of neuropathic pain. Gabapentin is believed to exert its effect on hot flashes by increasing the concentration of endoxifen, an active metabolite of tamoxifen, which is generated by N-demethylation of tamoxifen, a selective oestrogen-receptor modulator, and is converted to its active metabolites. The interaction of gabapentin with tamoxifen was investigated in a double-blind, placebo-controlled trial; 61% with venlafaxine at 75 mg or 150 mg; 62.2% and 64.6% with controlled-release paroxetine at 12.5 mg and 25.0 mg/day, respectively; and 50% with fluoxetine. Gabapentin 900 mg/day provides similar control of hot flashes in women with breast cancer. The side-effect profiles of these drugs differ. Oral clonidine was associated with sleeping difficulty, and transdermal clonidine was associated with dryness of mouth, constipation, drowsiness, and pruritus at the site of the patch. Side-effects of venlafaxine included dryness of mouth, decreased appetite, nausea, and constipation, and the most common side-effects of controlled-release paroxetine were headache, nausea, and insomnia. Without a randomised trial directly comparing not only the effect of hot flashes but also the side-effects of each of these drugs, the optimum non-hormonal drug for alleviation of hot flashes remains to be identified.

The selective serotonin-reuptake inhibitors are regarded as the most promising non-hormonal treatment for hot flashes in women with breast cancer, but a study by Stearns and colleagues has raised concern about the possible interaction between these agents and tamoxifen, a selective oestrogen-receptor modulator, because selective serotonin-reuptake inhibitors inhibit the cytochrome P450 enzymes that are important in converting tamoxifen to its active metabolites. The mechanism of action of gabapentin remains unknown. A 37-year-old patient with known hypothalamic dysfunction who took gabapentin for 6 months for control of his seizure disorder had an increase in the frequency of hypothermic episodes of 100 times. The frequency of these episodes returned to baseline once gabapentin was discontinued. Gabapentin inhibits neuronal calcium currents in vitro, and its binding site is known to be on the αβ subunit of voltage-gated calcium channels. This binding site was upregulated by 17 times selectively in rat dorsal root ganglion in response to peripheral-nerve injury. This process could be one of the mechanisms of action of gabapentin in the treatment of neuropathic pain. We speculate that similar upregulation of the gabapentin binding site could be involved in the hypothalamus as a result of oestrogen withdrawal, leading to increased activity of the neurotransmitters in the hypothalamus. Gabapentin might exert its effect on hot flashes by this mechanism.

Our study was designed to test the intervention for 8 weeks; therefore, we cannot comment on long-term use of gabapentin. However, gabapentin is used for long durations for various other symptoms and certainly could be considered for hot flashes also. We did not obtain data on immediate side-effects of gabapentin, but we did examine the reasons for withdrawing from the study. We might have underestimated the adverse effects of gabapentin, and the withdrawal rate of 12% at 4 weeks and 17% at 8 weeks might be due entirely to the side-effects of the treatment. However, the withdrawal rate was much the same in all three study groups and thus cannot be attributed to side-effects of gabapentin. We cannot think of any systematic bias that can explain these results, and we believe that random errors have been kept to a minimum by means of the randomised, double-blind, placebo-controlled design.

We believe gabapentin can be added to the list of non-hormonal agents for the control of hot flashes in women with breast cancer, and the effects of doses higher than 900 mg/day merit further study.

Conflict of interest statement
We declare that we have no conflict of interest.

Contributors
Kishan J Pandya was Study Chair, had the idea for and designed the study, and wrote the protocol in collaboration with Gary R Morrow for study design, statistics, and behavioural science, and Joseph A Roscoe, Jane T Hickok, and Hongwei Zhao for study design and statistics; all of these authors also assisted in the review of the report and suggested changes. Gary R Morrow also oversaw the approval of the protocol at the National Cancer Institute in his capacity as the Principal Investigator of the University of Rochester Community Clinical Oncology Program. Eduardo Pajon, Thomas J Sweeney, Tarit K Banerjee, and Jane T Hickok, and Hongwei Zhao for study design and statistics; all of these authors also assisted in the review of the report and suggested changes. Gary R Morrow also oversaw the approval of the protocol at the National Cancer Institute in his capacity as the Principal Investigator of the University of Rochester Community Clinical Oncology Program. Eduardo Pajon, Thomas J Sweeney, Tarit K Banerjee, and Hongwei Zhao for study design and statistics; all of these authors also assisted in the review of the report and suggested changes. Gary R Morrow also oversaw the approval of the protocol at the National Cancer Institute in his capacity as the Principal Investigator of the University of Rochester Community Clinical Oncology Program. Eduardo Pajon, Thomas J Sweeney, Tarit K Banerjee, and Hongwei Zhao for study design and statistics; all of these authors also assisted in the review of the report and suggested changes. Gary R Morrow also oversaw the approval of the protocol at the National Cancer Institute in his capacity as the Principal Investigator of the University of Rochester Community Clinical Oncology Program.
Acknowledgments
We thank Maarten Hofman, Jacque Lindke, Shonda Ranson, Jennifer Yates, and Barbara Hartzog of the University of Rochester Cancer Center for their technical and writing assistance in the preparation of this article.

References
Patients’ help-seeking experiences and delay in cancer presentation: a qualitative synthesis

Lucy K Smith, Catherine Pope, Johannes I Botha

Summary

Background The reduction of delay in cancer diagnosis has been targeted as a way to improve survival. We undertook a qualitative synthesis of international research evidence to provide insight into patients’ experiences of recognising symptoms of cancer and seeking help.

Methods We searched international publications (1985–2004) for delay in cancer diagnosis to identify the relevant qualitative research, and used meta-ethnography to identify the common themes across the studies. Our synthesis interpreted individual studies by identification of second-order constructs (interpretations offered by the original researchers) and third-order constructs (development of new interpretations beyond those offered in individual studies).

Findings We identified 32 papers (>775 patients and carers) reporting help-seeking experiences for at least 20 different types of cancer. The analysis showed strong similarities in patients with different cancer types. Key concepts were recognition and interpretation of symptoms, and fear of consultation. Fear manifested as a fear of embarrassment (the feeling that symptoms were trivial or that symptoms affected a sensitive body area), or a fear of cancer (pain, suffering, and death), or both. Such analyses allowed exploration of third-order constructs. The patient’s gender and the sanctoning of help-seeking were important factors in prompt consultation.

Interpretation Strategies to understand and reduce patients’ delay in cancer presentation can help symptom recognition but need to address patients’ anxieties. The effect of the patient’s sex in help-seeking also needs to be recognised, as does the important role of friends, family, and health-care professionals in the sanctioning of consultation. This meta-ethnography provides an international overview through the systematic synthesis of a diverse group of small-scale qualitative studies.

Introduction

The shortening of delays in diagnosis has been an important part of a national strategy by the UK government to reduce cancer morbidity and mortality. Many initiatives have focused on the reduction of organisational delays, which take place between a patient’s first presentation of possible symptoms to doctors and the subsequent diagnosis and treatment. Yet the gap between patients noticing symptoms and seeking medical assessment also contributes to overall delay. Systematic reviews of delay in cancer diagnosis have provided valuable evidence of the length of these periods and have helped to quantify patients’ awareness of cancer symptoms and risk factors for delay, emphasising the failure to recognise the severity of symptoms as a particular problem. To reduce this delay, presentation, mechanisms underlying these risk factors need to be established. Qualitative research has been recognised as a legitimate way to obtain knowledge that might not be accessible by other methods and to provide extensive data on how people interpret and act on their symptoms, but it is often criticised as being contextually specific and having little generalisability. Integration of findings from qualitative studies about cancer experiences has been suggested to develop effective health-care interventions. We undertook a qualitative synthesis of international research on cancer patients’ experiences of help-seeking and explored why patients delay in presenting to a health professional by comparing published data for patients with different types of cancer.

Methods

Identification of published work

To find qualitative research is difficult; qualitative research is not indexed as well as quantitative research (eg, qualitative is not a MEDLINE MeSH term), is widely distributed, and is often catalogued in databases that are not well-known to medical researchers. We used a combination of strategies: extensive searches of electronic medical, sociological, and psychological databases (MEDLINE, EMBASE, PubMed, BIDS, IBSS, PsycINFO, SCI, SSCI) using explicit criteria; hand searching of key journals; exploration of references listed in papers obtained; and the use of PubMed to identify related articles.

The study was restricted to papers published in peer-reviewed journals between Jan 1, 1985, and July 31, 2004, that reported qualitative research about cancer patients’ help-seeking experiences, from first onset of symptoms to first medical consultation. We excluded studies of screening services and public knowledge of cancer symptoms to concentrate on delay in symptomatic patients. We focused on patients with a diagnosis...
A term that encompasses several methods of data collection and analysis based on qualitative methods of data collection. Initially, we restricted the synthesis to UK studies to eliminate possible differences arising from health-system variation (eg, different mechanisms for patients contacting health professionals). We then expanded the synthesis to include all international papers published in English to explore international differences. Editorials and reviews were excluded, but unlike some previous syntheses we included multiple papers from studies if they provided additional data and interpretation. Qualitative synthesis is a relatively new technique and the issue of appraisal of data is contested because of the tensions between inclusiveness and quality. We opted for an inclusive strategy, and on the basis of previous experience we did not use a formal appraisal checklist such as the Critical Appraisal Skills Programme (CASP). We used Noblit and Hare’s approach to judge the value of papers with respect to their contribution to the synthesis.

**Analysis**

We used ethnography to synthesise the research. Meta-ethnography is an interpretative approach that has been successfully used previously to investigate themes in diabetes care and medicine taking. It entails the systematic identification of shared concepts and themes in published work. Ethnography A term that encompasses several methods of data collection and different analytical strategies, which typically involves lengthy participation in a setting. Distinguished by its emphasis on the reciprocal translation of studies into one another, in which researchers compare and contrast the findings of individual studies. A worked example of meta-ethnography can be found in the study by Britten and colleagues.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year of publication</th>
<th>Site of cancer</th>
<th>Country</th>
<th>Participants</th>
<th>Data collection method</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>2001</td>
<td>Multiple sites</td>
<td>Netherlands</td>
<td>23 patients</td>
<td>Home interviews</td>
</tr>
<tr>
<td>30</td>
<td>2001</td>
<td>Multiple sites</td>
<td>Hawaii, USA</td>
<td>45 male and female patients</td>
<td>Focus groups</td>
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<tr>
<td>31</td>
<td>2000</td>
<td>Male breast</td>
<td>UK</td>
<td>747 patients</td>
<td>Home interviews</td>
</tr>
<tr>
<td>32</td>
<td>2001</td>
<td>Breast</td>
<td>USA</td>
<td>13 female patients</td>
<td>Home interviews</td>
</tr>
<tr>
<td>33</td>
<td>2001</td>
<td>Breast</td>
<td>USA</td>
<td>13 female patients</td>
<td>Home interviews</td>
</tr>
<tr>
<td>34</td>
<td>1994</td>
<td>Breast</td>
<td>USA</td>
<td>26 female patients</td>
<td>Interviews</td>
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<tr>
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<td>2004</td>
<td>Four sites</td>
<td>UK</td>
<td>57 male patients</td>
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<tr>
<td>36</td>
<td>1999</td>
<td>Brain</td>
<td>Sweden</td>
<td>28 patients and spouses</td>
<td>Interviews</td>
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<tr>
<td>37</td>
<td>2000</td>
<td>Testicle</td>
<td>Sweden</td>
<td>21 male patients</td>
<td>Home interviews</td>
</tr>
<tr>
<td>38</td>
<td>1998</td>
<td>Three sites</td>
<td>Sweden</td>
<td>3 patients (two women, one man)</td>
<td>Home interviews</td>
</tr>
<tr>
<td>39</td>
<td>2003</td>
<td>Seven sites</td>
<td>Finland</td>
<td>86 male cancer patients</td>
<td>Interviews</td>
</tr>
<tr>
<td>40</td>
<td>2003</td>
<td>Breast</td>
<td>UK</td>
<td>27 male and female patients</td>
<td>Focus groups</td>
</tr>
<tr>
<td>41</td>
<td>1998</td>
<td>Breast</td>
<td>Canada</td>
<td>20 female patients</td>
<td>Home and clinic interviews</td>
</tr>
<tr>
<td>42</td>
<td>2002</td>
<td>Ovary</td>
<td>Canada</td>
<td>18 female patients</td>
<td>Telephone interviews</td>
</tr>
<tr>
<td>43</td>
<td>1994</td>
<td>Multiple sites</td>
<td>USA</td>
<td>46 male and female patients</td>
<td>Oral testimonies</td>
</tr>
<tr>
<td>44</td>
<td>2003</td>
<td>Breast</td>
<td>Hong Kong, China</td>
<td>17 female patients</td>
<td>Interviews</td>
</tr>
<tr>
<td>45</td>
<td>2001</td>
<td>Prostate</td>
<td>USA</td>
<td>Seven male patients and their wives</td>
<td>Focus groups</td>
</tr>
<tr>
<td>46</td>
<td>1957</td>
<td>Breast</td>
<td>UK</td>
<td>18 female patients</td>
<td>Hospital interviews</td>
</tr>
</tbody>
</table>

**Table: Summary information on selected papers**

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full role in the design and conduct of the study, analysis and interpretation of the data, and preparation, review, or approval of the manuscript.
access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 32 original papers that met our inclusion criteria based on focus groups, interviews, and oral testimonies with patients and carers providing data for more than 775 individuals, of whom at least 712 were patients with more than 20 different types of cancer (table). 23 papers focused on one type of cancer, most commonly breast (11), testicular (four), and colorectal (three). 20 papers were sex-specific, six focused on minority ethnic groups, and one focused on economically disadvantaged individuals. The earliest paper was published in 1994, although most had been published since 1999. They were published in general practice (six), social science (five), and oncology-related (21) journals, with four studies reported in multiple papers.

Although the publications reported studies of different types of patients with respect to cancer site and symptoms, clear similarities were recorded in the patients’ help-seeking experiences. The synthesis identified two second-order constructs (recognition and interpretation of symptoms, and fear; panel 1) and two third-order constructs (the patient’s gender and sanctioning; panel 2).

A main theme throughout the study was how patients recognised abnormalities, attributed body changes to illness, and assessed the seriousness of their condition.

…”It was a lump that just appeared overnight . . . straight away, I just knew it was cancer” (p 968).32

The status of patients with well-recognised specific symptoms (eg, a lump) changed from symptom awareness to serious illness attribution most promptly.32,35,57 Symptoms were often perceived to have developed suddenly,36 which led to panic. Illness recognition was also faster in patients with severe symptoms such as seizure.36

By comparison, patients with vague or non-specific initial symptoms frequently delayed attributing these signs to illness. They recognised changes in their bodies but sought alternative everyday explanations such as trauma, skin problems, indigestion, menopause, diarrhoea, old age, or piles.37,39,40,41 Symptoms worsen or do not go away32,33,35,36,38,42 New additional symptoms (eg, pain)32,33,35,36,38,42 Severe symptoms that reach crisis point32,33,35,36,38,42 Symptoms affect everyday life32,33,35,36,38,42

Fear

Fear of embarrassment

Fear of being seen as a time-waster or as neurotic, especially for those with diverse mild symptoms37–39,42,43 Fear that even the patient’s family think the symptoms are psychosomatic32,35 Men view help-seeking as unmanly32,33,35,36 Embarrassment of sensitive or sexual area32,33,34,35,36,37,38,42,43,44,45

Fear of cancer

Serious and painful symptoms, fatal incurable disease33,34,35,36,37,38,39,40,41,42,43,44,45

Previous negative experiences of cancer33,34,35,36,37,38,39,40,41,42,43,44,45

Fear of unpleasant treatment32,33,35,36,37,38,39,40,41,42,43,44,45

Loss of sexuality after treatment32,33,34,35,36,37,38,39,40,41,42,43,44,45

Shame associated with dirt and uncleanness32,33,34,35,36,37,38,39,40,41,42,43,44,45
Panel 2: What does the synthesis add?

How does the patient’s sex affect help-seeking?

Men viewed help-seeking as not masculine enough and did not want to appear neurotic.15

Men indicated that women found help-seeking easier because of greater contact with health services for themselves and their family.15,18,31,34

Men and women embarrassed about the sexual area of the body.15

Women more often cited competing priorities of work and family over their own health.12,13,18,31

Fear of loss of sexuality after treatment.15


How does sanctioning affect help-seeking?

Patients’ help-seeking sanctioned by family (especially partners), directly or indirectly forcing contact with health professionals or challenging management.15

Help-seeking sanctioned by leaving symptoms until they interfere with life, especially work.15,16,18,19,37–39

Symptoms ignored until they reach crisis point, legitimising contact through emergency services.15,18,19,30

Patients show apparently trivial symptoms when consulting for another problem.15,29,31,35,45

Use of knowledge to legitimise help-seeking (eg, from textbooks or the media).17


The recognition and interpretation of symptoms is vital in the reduction of delay, but is not a sufficient enough trigger to seek help.21 In a study of testicular cancer only the patient with an obvious lump attributed his symptoms to cancer, but he still delayed presentation for 6 months before seeking help, which shows that other factors affect delay.

“I knew I was ill a long time before I did anything about it.”22

After patients had recognised symptoms, fear was noted as a major barrier to seek help in 26 papers.15–25,27–31,33–38,42–44 Fear predominantly manifested as fear of embarrassment and fear of cancer. Fear of embarrassment was a strong theme,15–25,27,29,31,33–38,42–44 men and women who delayed, especially those with diverse symptoms, worried about being labelled as neurotic, a hypochondriac, or a time-waster. They worried about bothering the doctor with seemingly minor symptoms and being told “there is nothing wrong” (p 148).35 Men associated consultation with weakness, and thought that the admission of illness was not masculine and therefore should only be done under extreme circumstances. Women worried that symptoms would be attributed to menopause. Some patients with lung cancer were afraid that their symptoms would not be taken seriously because they were smoking-related.27 Data from two studies indicated that older patients41 and those living in a rural area42–44 were associated with a reluctance to bother the doctor.

Patients who sought help quickly had few inhibitions about wasting doctors’ time, were regular users of health services, and thought that doctors could allay fears associated with symptoms or refer them for specialist care. In some cases of early presentation, doctors made benign diagnoses, which reinforced the fear of being a time-waster. A patient with testicular cancer reported of being told off, and therefore delayed a year before reconsulting.35 Yet, some patients noticed that these fears were ungrounded.

“If I had known I was going to see anybody as marvellous as she was . . . I would have gone months before” (p 44).22

Fear of embarrassment was also related to the discussion of sensitive or sexual areas of the body and the invasiveness of physical examinations. Symptoms related to the penis and testicles were embarrassing for men to discuss and symptoms related to the rectum were embarrassing for both men and women.

“The sensitivity, physical and mental really . . . the emotional unburdening, telling someone that one has a physical problem in that highly sensitive area, the sexual organs . . . The physical examination itself, embarrassing yes, because one is baring that part of the body that isn’t usually seen even on the beach at Marbella . . . To have somebody explore, examine and hold that part of the body, was potentially threatening. I think it’s almost an invasion of privacy, an invasion of the self. It’s hardly the equivalent of a rape, but I would suggest that it is an invasion, you are allowing someone to do something to you that in other circumstances you would never permit” (p 148).35

“It was the very British thing about not wanting people to poke their fingers up my bottom” (p 44).22

Such fears were not reported in studies of women with breast cancer. Men with prostate and testicular cancer thought that women would find consultations easier because they were more used to dealing with sexual health services and talking about illness than men.31 Patients, especially those with specific symptoms, also had fears about painful cancer treatments, suffering, and death. For many individuals, cancer was regarded as a recurrent, incurable disease.

“The only experience I’d had about cancer was of people who’d died . . . Of course since then I’ve had cancer myself, I’ve met loads of people who are cancer survivors . . . but you don’t normally know that information about people until they share it with you” (p 44).22

Past experiences were identified as a factor affecting patients’ reluctance to seek help.27 A negative experience of cancer in friends and family led to strong fears of cancer, but the effect of such experiences was not consistent. For some patients, such experience prompted self-examination or immediate consultation for symptoms. Fear of the effect of treatment, on sexual relationships, and body image was important. Men were concerned about places where others could see their bodies, such as sports changing rooms.15 African and
Afro-Caribbean patients with breast cancer\(^2\) feared mastectomy and worried about fertility and their ability to keep sexual partners. Notably, although other patients with breast cancer talked about their fears of treatment, they did not mention the effect on their sexuality.\(^3\) Two studies of African and Afro-Caribbean women\(^2\) discussed the belief that cancer was a contagious disease, associated with dirt or uncleanness, and something to be ashamed of. Other fears raised in individual papers were fear of health-care costs\(^2\) and of not fulfilling social or economic roles.

Small sample sizes and a focus on gender-specific cancers meant that individual studies could not explore issues related to the patients’ gender extensively. Our synthesis allowed comparison of experiences for both men and women and across different cancer sites, revealing additional fears associated with gender-specific roles or identity. Although men and women expressed embarrassment about consultations with doctors if symptoms affected a sexual area of the body, men especially feared weakness and loss of masculinity associated with seeking help.\(^1\) Patients’ gender also affected help-seeking in other ways. In a study\(^2\) of men and women and studies of patients with testicular and prostate cancer, men used gender-specific reasons to explain their reluctance to seek help.\(^2\) Men thought that women could seek care more easily and discuss sensitive body areas because of their perceived regular use of health services for themselves and their dependants.

“For all their macho image, men are more reluctant to talk about that part of body than are women, who are quite happy to present themselves at clinics in order to have smear tests” (p 149).\(^1\)

Notably, women in other studies\(^1,2,7,22,33,34\) described how the responsibility for the health and domestic needs of other family members meant that their own health needs were not always prioritised. However, those who sought help quickly did so irrespective of other similar demands.

The sanctioning of help-seeking, for example by the media or by friends and family, legitimised help-seeking and allowed patients to lessen their fear of being labelled as time-wasters. Men often legitimised help-seeking if their symptoms started to affect their ability to work. Some patients legitimised help-seeking by raising issues when consulting for another set of symptoms or disease, but for others the fear of presenting apparently trivial symptoms was so strong that they allowed symptoms to reach a crisis point, and accessed emergency care rather than care from their family doctor.

“I was lucky, I didn’t have to go to my GP because I collapsed in church” (p 476).\(^1\)

Thus, the severity of patients’ symptoms allowed them to seek help without fear of being seen as a time-waster. Sanctioning of help-seeking was especially important for men, because wives or partners would often encourage, persuade, or take action on their behalf. Some husbands also took this action for women with breast cancer.

**Discussion**

Our analysis showed that of the studies we identified, patients with different types of cancer and from different countries had similar help-seeking experiences. Main themes in delay in presentation were recognition and interpretation of symptoms, and fear of consultation (with respect to embarrassment and to the idea of cancer itself). The patient’s gender and the sanctioning of help-seeking also affected help-seeking.

This synthesis of qualitative research allows the integration of findings from small studies to understand better how individuals with cancer symptoms seek help. Meta-ethnography can be used to synthesise studies with various qualitative methods (not only with ethnographic research), to explore a wide range of experience while simultaneously increasing the size and diversity of the total sample.

Quantitative cancer studies have shown delay in patients who did not perceive their symptoms as serious and did not attribute them to cancer.\(^1\) The presence of a lump is associated with prompt help-seeking in breast cancer,\(^4\) but a lump is not the most common symptom for all types of cancer and our synthesis indicates confusion about less specific symptoms in patients who delay in seeking help. This confusion has implications for health educators, since patients and their partners need to recognise changes in their bodies and functioning, rather than merely relying on identifiable lumps. Men and women need to be aware of cancer symptoms that are specific to both sexes, since we have shown the importance of close relatives, especially female partners, in the sanctioning of help-seeking.

The fears identified in this synthesis confirm other research in breast-cancer,\(^1,5\) but our synthesis shows that these findings apply to men and women, as well as different cancers. Our synthesis also expands on previous work by showing the difficulties faced by patients with cancer when attempting to effectively communicate their apparently trivial symptoms. For family doctors, the diagnosis of cancer is challenging: the likelihood of seeing some rare cancers is very low, and the time needed to investigate and reassure patients who show an array of symptoms is difficult. However, an awareness of the problems faced by patients is vital. Fear of embarrassment is especially difficult for health-care practitioners to tackle. Specific concerns exist for patients presenting with symptoms related to sexual and private body areas, especially for men.

Symptom recognition and fear of being a time-waster are barriers to patients seeking help for other illnesses. A meta-ethnography of people’s experiences of diabetes\(^1\) showed that patients needed to trust their own observations about body changes and to become informed about
the disease, and be less subservient towards health-care providers to avoid the fear of being labelled as a time-waster. Our synthesis emphasises that help-seeking for cancer symptoms differs from other illnesses because pronounced fears are associated with embarrassment of the affected body part and with the perception of cancer itself.

The effect of gender on patients’ help-seeking behaviour was not necessarily apparent in individual studies. This synthesis suggests that practitioners should consider fears about the potential effect of treatment on gender identity (notably masculinity), the importance of gender-specific roles and priorities, potential gender-related embarrassment, and differences in how men and women access services. This difference has been partly addressed for women by attempts to increase access to female doctors or women-only clinics, but how the issue could be resolved for men is unclear. The sanctioning of help-seeking was also central to this synthesis, to reduce fears associated with consultations for cancer, especially for men. This sanctioning might come from the media or friends and family, and has been identified elsewhere as an important trigger for help-seeking.16

Our synthesis has shown negligible differences in the help-seeking experiences of patients in different countries. Most of the studies identified were European (21 papers), and 15 were from the UK. This distribution could indicate the responses to policy initiatives aimed at reducing patients’ delay in presentation, differential use of research methods between countries, or possibly publication bias. Two international differences in patients’ delay were apparent in this synthesis. First, two of six papers from the USA25,43 reported delays due to patients’ delay were apparent in this synthesis. First, two

**References**


**Contributors**

All the authors designed the study. L. K Smith undertook publication searches and identified the papers to be included in the study. L. K Smith and C. Pope synthesised the data. L. K Smith and C. Pope wrote the paper and all authors contributed to the final version.

**Conflict of interest statement**

We declare that we have no conflicts of interest.

**Acknowledgments**

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41 Cameron S, Horsburgh ME. Comparing issues faced by younger and older women with breast cancer. Can Oncol Nurs J 1998; 8: 40–44.
Public-health impact of accelerated measles control in the WHO African Region 2000–03

M Otten, R Kezaala, A Fall, B Masresha, R Martin, L Cairns, R Eggers, R Biellik, M Grabowsky, P Strebel, J-M Okwo-Bele, D Nshimirimana

Summary

Background In 2000, the WHO African Region adopted a plan to accelerate efforts to lower measles mortality with the goal of decreasing the number of measles deaths to near zero. By June, 2003, 19 African countries had completed measles supplemental immunisation activities (SIA) in children aged 9 months to 14 years as part of a comprehensive measles-control strategy. We assessed the public-health impact of these control measures by use of available surveillance data.

Methods We calculated percentage decline in reported measles cases during 1–2 years after SIA, compared with 6 years before SIA. On the basis of data from 13 of the 19 countries, we assumed that the percentage decline in measles deaths equaled that in measles cases. We also examined data on routine and SIA measles vaccine coverage, measles case-based surveillance, and suspected measles outbreaks.

Findings Between 2000 and June, 2003, 82·1 million children were targeted for vaccination during initial SIA in 12 countries and follow-up SIA in seven countries. The average decline in the number of reported measles cases was 91%. In 17 of the 19 countries, measles case-based surveillance confirmed that transmission of measles virus, and therefore measles deaths, had been reduced to low or very low rates. The total estimated number of deaths averted in the year 2003 was 90 043. Between 2000 and 2003 in the African Region as a whole, we estimated that the percentage decline in annual measles deaths was around 20% (90 043 of 454 000).

Interpretation The burden of measles in sub-Saharan Africa can be reduced to very low levels by means of appropriate strategies, resources, and personnel.

Introduction Measles is an important cause of child mortality in sub-Saharan Africa. Estimates of the annual number of measles deaths in the WHO African Region (which now includes all countries south of the Sahara except Somalia and Djibouti; Algeria is included, but Sudan is not) made by different methods have been in the same range: 445 000 in 1998,1 482 000 in 1999,2 and 452 000 in 2000.3 The WHO reported that in 2000 sub-Saharan Africa had 58% of worldwide measles deaths.4 In 1996, seven countries in southern Africa (Botswana, Lesotho, Malawi, Namibia, South Africa, Swaziland, and Zimbabwe) began a measles-elimination initiative based on the successful strategy used in the Americas.5 In 1998, the WHO African Region Office drafted a plan of action to decrease the number of measles deaths to near zero in response to the measles mortality burden in the rest of the African countries. This plan emphasised four components: improved routine immunisation, a second opportunity for measles vaccination during supplemental immunisation activities (SIA), measles case management, and measles surveillance. Owing to shortage of funding and potential adverse effects on the polio-eradication programme, supplemental immunisations in a limited age-group (children aged 9 months to 4 years) were given in seven countries for 3 years from December, 1998, to 2001.6 Because surveillance data indicated that targeting of this age-group did not have the desired effect on the burden of disease from measles,7 in December, 2001, SIA began to target children aged 9 months to 14 years in eastern and western African countries. In 2001, a joint WHO and UNICEF global plan for measles mortality was formulated,8 with one of the four strategies being provision of a second opportunity for measles immunisation for all children through SIA or routine immunisation systems. The target for the overall measles-mortality reduction plan was a 50% decrease in the number of measles deaths by 2005 compared with 1999.8 A new partnership supporting measles-mortality reduction in Africa, the Measles Initiative, started in 2001. Initial partners were the American Red Cross, the WHO, the US Centers for Disease Control and Prevention, the United Nations Foundation, and UNICEF. Subsequently, the Canadian International Development Agency, the Bill and Melinda Gates Foundation, the Church of Latterday Saints, and the Global Alliance for Vaccines and Children (GAVI) have joined the partnership. Partnership funds permitted the financing of SIA in the extended age-group. With funding primarily from the Measles Initiative, 12 African countries undertook SIA in children aged 9 months to 14 years from December, 2001, to June, 2003. In addition, seven southern African countries carried out their first round of follow-up SIA in children aged 9 months to 4 years from 2000 to 2003 mainly using national funds.
Starting in 1999, routine immunisation services began to improve in several African countries, owing to better resources, more staff, and attention to immunisation because of the polio-eradication and measles programmes, and a focus on improving routine immunisation by the new GAVI. We report on the estimated effect of these accelerated control activities on the numbers of measles cases and deaths, and thus monitor progress towards the goal of lowering measles mortality. We used three sources of epidemiological data to assess the effect of accelerated control efforts on the burden of measles: aggregate routine surveillance data, case-based surveillance data, and information from outbreak investigations.

Methods
Aggregate routine surveillance data
All African countries include notification of measles cases in their routine surveillance or health-information systems. The national aggregate number of cases is reported each year to WHO, which maintains a global database with this information, with data starting in 1980.7

For 19 African countries that undertook measles SIA between 2000 and June, 2003 (table 1), we compared the average annual number of reported measles cases in the 6 years before the start of SIA with the average annual number of reported measles cases after the SIA. For the 12 countries that undertook SIA from December, 2001, to June, 2003 (Benin, Burkina Faso, Burundi, Cameroon, Ghana, Kenya, Mali, Rwanda, Senegal, Tanzania, Togo, Zambia), we used 1996–2001 as the pre-SIA years. We imputed the number of cases for the missing years by using the average of the previous 6 years. In seven of the 12 countries (Benin, Burundi, Cameroon, Ghana, Kenya, Senegal, Tanzania), we used 2003 as the post-SIA comparison year. For Burkina Faso, Togo, and Mali (the only countries with 2 complete years after nationwide catch-up SIA), we averaged nationwide data for 2002 and 2003. For Rwanda (SIA in February, 2003), we used data from March, 2003, to February, 2004, and for Zambia (SIA in June, 2003), we used data from July, 2003, to June, 2004. For the seven southern African countries (table 1), we used 1990–95 as the pre-SIA comparison period and all available data for the years after the initial SIA until 2003 (ie, 6 years of data for Namibia and South Africa; 5 years for Malawi, Botswana, and Zimbabwe; 4 years for Swaziland; and 3 years for Lesotho) as the post-SIA comparison period.

To estimate the number of measles deaths averted in 2003 in each of the 19 countries, we assumed that SIA resulted in the same percentage reduction in measles deaths as was observed for measles cases. This assumption was based on the following experience in 13 of the 19 countries. After the initial SIA until 2003 (ie, 6 years of data for Namibia and South Africa; 5 years for Malawi, Botswana, and Zimbabwe; 4 years for Swaziland, and 3 years for Lesotho) as the post-SIA comparison period.

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### Table 1: Dates, target population, and measles vaccination coverage of SIA, 2000 to June, 2003

<table>
<thead>
<tr>
<th>Country</th>
<th>Dates of SIA</th>
<th>Children 9 months to 14 years covered (%)</th>
<th>Target number of children (millions)</th>
<th>SIA coverage (%)</th>
<th>Routine immunisation coverage, 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>December, 2001</td>
<td>35</td>
<td>0.9</td>
<td>98 (A)</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>December, 2002</td>
<td>65</td>
<td>2.0</td>
<td>105 (A)</td>
<td></td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>December, 2001 Nationwide</td>
<td>5.2</td>
<td>97 (S)</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Burundi</td>
<td>June, 2002 Nationwide</td>
<td>3.2</td>
<td>90 (A)</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Cameroon</td>
<td>December, 2001</td>
<td>34</td>
<td>2.8</td>
<td>93 (A)</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>December, 2002</td>
<td>66</td>
<td>5.1</td>
<td>90 (A)</td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td>December, 2001</td>
<td>9</td>
<td>0.8</td>
<td>98 (S)</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>December, 2002</td>
<td>91</td>
<td>7.7</td>
<td>102 (A)</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>June, 2002 Nationwide</td>
<td>13.6</td>
<td>94 (S)</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Mali</td>
<td>December, 2001 Nationwide</td>
<td>5.1</td>
<td>99 (S)</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Rwanda†</td>
<td>February, 2003 Nationwide</td>
<td>3.1</td>
<td>96 (S)</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Senegal</td>
<td>January, 2003 Nationwide</td>
<td>5.0</td>
<td>98 (A)</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Tanzania</td>
<td>September, 2001</td>
<td>3.3</td>
<td>3.7</td>
<td>104 (A)</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>September, 2002</td>
<td>67</td>
<td>7.0</td>
<td>97 (A)</td>
<td></td>
</tr>
<tr>
<td>Togo</td>
<td>December, 2001 Nationwide</td>
<td>2.4</td>
<td>95 (S)</td>
<td>43</td>
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<tr>
<td>Zambia</td>
<td>October, 2002</td>
<td>11</td>
<td>0.7</td>
<td>110 (A)</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>June, 2003</td>
<td>89</td>
<td>5.0</td>
<td>108 (A)</td>
<td></td>
</tr>
</tbody>
</table>
| Southern African countries undertaking follow-up campaigns in children aged 9 months to 4 years
| Botswana         | May–June, 2001 Nationwide     | 0.3                                      | 85 (A)                              | 79               |
| Lesotho          | April–July, 2003 Nationwide   | 0.2                                      | 87 (A)                              | 63               |
| Malawi           | August, 2002 Nationwide       | 1.5                                      | 95 (A)                              | 81               |
| Namibia          | June, 2000 Nationwide         | 0.3                                      | 89 (A)                              | 69               |
|                  | June, 2003 Nationwide         | 0.3                                      | 89 (A)                              | 46               |
| South Africa     | May–June, 2000 Nationwide     | 4.5                                      | 91 (A)                              | 95               |
| Swaziland        | June, 2002 Nationwide         | 0.2                                      | 86 (A)                              | 80               |
| Zimbabwe         | July, 2002                    | 1.8                                      | 85 (A)                              | 70               |

*S=survey, A=administrative; administrative coverage is the reported number of children immunised divided by the estimated number targeted. †SIA done in children aged 9 months to 14 years in 16 districts and aged 6–14 years in 23 districts. ‡SIA done in children aged 7–14 years.

See http://www.vaccinealliance.org
southern African countries, the number of reported measles cases declined by 99.8% and the number of reported measles deaths by 100%. After similar SIA in Mali, Burkina Faso, and Togo, the number of reported measles cases declined by 91.0% and the number of measles deaths by 84.0%. After SIA in Benin and Cameroon, the number of reported measles cases declined by 97.0% and the number of measles deaths by 96.0% (unpublished data, WHO African Regional Office). In Zambia, the number of reported cases declined by 87% and the number of deaths by 99%. Because there are few vital-event systems registering a high proportion of deaths in Africa, we used previously published estimates of the number of measles deaths before the SIA (1998 baseline year). We chose 1998 as the baseline year because it was the last year before measles SIA began in non-southern African countries.

Because there are few vital-event systems registering a high proportion of deaths in Africa, we used previously published estimates of the number of measles deaths before the SIA (1998 baseline year). We chose 1998 as the baseline year because it was the last year before measles SIA began in non-southern African countries.

These estimates were based on: the estimated number of surviving infants in 1998 in each country; a vaccine efficacy of 85%; the 1998 national routine measles coverage percentage as reported to WHO; the assumption that all susceptible children would be infected with measles; and an estimated measles case-fatality rate of 6.0% in west and central Africa, 2.0–3.0% in east African countries, and 0.5–3.0% in southern African countries.

Case-based surveillance
After completing nationwide measles SIA, all countries started case-based reporting of suspected measles cases with laboratory confirmation. A case of suspected measles was defined as an illness characterised by rash, fever, and cough, coryza, or conjunctivitis, or any illness that a clinician suspected to be measles. Surveillance was classified as case-based if individual data, such as date of onset of rash, district of residence, age, and vaccination status, were collected on a case form or line list and sent to the national level. The serum sample was sent to the national measles laboratory to be tested for measles IgM antibody by Enzygnost (Dade-Behring, Marburg, Germany) diagnostic kits. The national measles laboratories are part of a WHO measles laboratory network that requires successful completion of a proficiency panel of serum samples each year. Measles case-based data are reported electronically to the WHO African Regional Office monthly. This office monitors surveillance reporting and publishes measles surveillance results and quality indicators in both bloc bulletins and regional feedback bulletins. After the SIA, most countries continued aggregate measles reporting in parallel with measles case-based reporting.

We used data from case-based surveillance to assign each country to one of three categories of measles transmission: very low; low intermittent; or moderate continuing. These categories were based on the proportion of suspected cases of measles with laboratory samples that were positive for measles IgM: less than 10% was classified as very low; 10–49% as low; and 50% or greater as moderate. This epidemiological profiling was based on nearly a decade of experience with surveillance after SIA in more than 40 countries in the Americas and Africa.

Measles outbreaks after SIA
After completing nationwide SIA, countries began to carry out measles outbreak investigations on a nationwide basis. The WHO African Regional Office has distributed guidelines to all African countries detailing recommended procedures for investigation of measles outbreaks, including village-level searches for additional suspected cases, laboratory confirmation, reporting, and analyses. In the African Region, a measles outbreak is defined as at least three laboratory-confirmed or five suspected measles cases in a district in any month that
occurred more than 60 days after the SIA. All suspected and laboratory-confirmed cases are routinely mapped by district and examined for place and time clustering. Where outbreaks were detected, we examined the case-based information and attempted to define the extent and cause of each outbreak.

Routine measles-vaccination coverage
For the years 1990 to 2003, a weighted average of coverage with one dose of measles vaccine was calculated for the two groups of countries (southern Africa and eastern and western Africa) by use of the annual measles-vaccination coverage information that is officially reported to WHO.7 The weighted average was calculated from the 1995 population estimate for each country from the United Nations Population Division.15

Role of the funding source
No funding source had any role in the study design; collection, analysis, or interpretation of data; or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the paper for publication.

Results
Between January, 2000, and June, 2003, 19 African countries carried out SIA and had at least 12 months of post-SIA measles-surveillance data (table 1). 12 countries in western and eastern African undertook SIA in children aged 9 months to 14 years (total children targeted 73·0 million), and seven southern African countries carried out follow-up SIA in children aged 9 months to 4 year (total children targeted 9·1 million). Five countries completed the SIA nationwide over 2 years (Benin, Cameroon, Ghana, Zambia, and Tanzania). Thus, the total number of children targeted in these SIA was 82·1 million. The reported measles vaccination coverage was 85% or higher for all SIA. The average SIA measles vaccination coverage for the six countries that did surveys was 97% (table 1).

In the 12 western and eastern African countries, the number of reported measles cases declined from 85 000–250 000 during 1990–2001 to 12 073 in 2003 (figure). In the seven southern African countries, the number of reported measles cases fell from 24 000–140 000 during 1990–97 to 2081–7057 per year from 1999 to 2003 (figure). The average proportional decrease in reported measles cases was 89% for the 12 eastern and western African countries and 91% for all 19 countries (table 2). Three countries had an average decline of less than 70%. The low percentage decreases for Burkina Faso (67%) and Namibia (65%) were probably due to measles outbreaks. The low percentage decrease for Botswana (64%) was probably due to misreporting of rubella cases as measles cases in 2000; of

<table>
<thead>
<tr>
<th>Country</th>
<th>Estimated nationwide number of deaths before SIA*</th>
<th>Average number of reported cases per year before SIA†</th>
<th>Number of reported cases per year after SIA‡</th>
<th>Percentage decrease in number of cases§</th>
<th>Number of deaths averted per year¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>2990</td>
<td>4051</td>
<td>217</td>
<td>95</td>
<td>2830</td>
</tr>
<tr>
<td>Burkina Faso‡</td>
<td>15626</td>
<td>7147</td>
<td>2345</td>
<td>67</td>
<td>10499</td>
</tr>
<tr>
<td>Burundi</td>
<td>4472</td>
<td>8022</td>
<td>224</td>
<td>97</td>
<td>4347</td>
</tr>
<tr>
<td>Cameroon</td>
<td>9398</td>
<td>13260</td>
<td>899</td>
<td>93</td>
<td>8761</td>
</tr>
<tr>
<td>Ghana</td>
<td>12899</td>
<td>24581</td>
<td>1919</td>
<td>92</td>
<td>11882</td>
</tr>
<tr>
<td>Kenya</td>
<td>9669</td>
<td>9529</td>
<td>65</td>
<td>99</td>
<td>9603</td>
</tr>
<tr>
<td>Mali</td>
<td>11014</td>
<td>5568</td>
<td>475</td>
<td>91</td>
<td>10075</td>
</tr>
<tr>
<td>Rwanda</td>
<td></td>
<td></td>
<td>2448</td>
<td>2425</td>
<td>52</td>
</tr>
<tr>
<td>Senegal</td>
<td>6855</td>
<td>9275</td>
<td>1638</td>
<td>82</td>
<td>5644</td>
</tr>
<tr>
<td>Tanzania</td>
<td>13955</td>
<td>10078</td>
<td>1673</td>
<td>83</td>
<td>11638</td>
</tr>
<tr>
<td>Togo</td>
<td>5475</td>
<td>2082</td>
<td>329</td>
<td>84</td>
<td>4610</td>
</tr>
<tr>
<td>Zambia</td>
<td></td>
<td></td>
<td>3781</td>
<td>17609</td>
<td>2963</td>
</tr>
<tr>
<td>Subtotal</td>
<td>98582</td>
<td>113629</td>
<td>12819</td>
<td>89</td>
<td>85430</td>
</tr>
<tr>
<td>Southern African countries with follow-up campaigns in children aged 9 months to 4 years, 2000–03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botswana</td>
<td>62</td>
<td>1767</td>
<td>636</td>
<td>64</td>
<td>40</td>
</tr>
<tr>
<td>Lesotho</td>
<td>126</td>
<td>1246</td>
<td>73</td>
<td>94</td>
<td>119</td>
</tr>
<tr>
<td>Malawi</td>
<td>2686</td>
<td>9581</td>
<td>173</td>
<td>98</td>
<td>2637</td>
</tr>
<tr>
<td>Namibia</td>
<td>96</td>
<td>2515</td>
<td>879</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>South Africa</td>
<td>1034</td>
<td>11118</td>
<td>112</td>
<td>99</td>
<td>1024</td>
</tr>
<tr>
<td>Swaziland</td>
<td>55</td>
<td>2151</td>
<td>112</td>
<td>95</td>
<td>52</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>704</td>
<td>22592</td>
<td>817</td>
<td>96</td>
<td>679</td>
</tr>
<tr>
<td>Subtotal</td>
<td>4763</td>
<td>50967</td>
<td>2800</td>
<td>95</td>
<td>4613</td>
</tr>
<tr>
<td>Grand total</td>
<td>103345</td>
<td>164396</td>
<td>15619</td>
<td>91</td>
<td>90043</td>
</tr>
</tbody>
</table>

*Based on data from 1998. †Average for 1996–2001 in the 12 eastern and western African countries, and for 1990–95 in the southern African countries. ‡2003; Mali, Togo, and Burkina Faso had 2 years of post-SIA data (2002, 2003), which were averaged. §Average number before SIA minus number after SIA, divided by pre-SIA average, × 100. ¶Pre-SIA deaths multiplied by percentage decrease in cases. ||Rwanda post-SIA data were from March, 2003, to February, 2004, Zambia data were from July, 2003, to June, 2004.

Table 2: Estimated annual measles deaths averted by SIA completed between 2000 and June, 2003
210 blood samples tested during that year, 170 (81%) were positive for rubella IgM and none for measles IgM.16

The total estimated number of annual deaths averted in 2003 was 90 043: 85 430 for the 12 eastern and western African countries and 4613 for the southern African countries. The pre-SIA baseline estimate of the annual number of measles deaths for all countries in the African Region in 1998 was 454 000. Therefore, for the African Region as a whole, the estimated proportional decrease in annual measles deaths was 20% (90 043 divided by 454 000) resulting from control activities in these 19 countries from 2000 to June, 2003.

In 2002–03, the proportion of suspected measles cases that were confirmed to be positive for measles IgM ranged from 2% in Zambia to 74% in Burkina Faso (table 3). Among the 11 western and eastern African countries other than Burkina Faso, 10% (588 of 5929) of samples tested were positive for measles IgM antibody. Among the 12 western and eastern African countries, six countries had very low measles transmission (less than 10% of the laboratory samples positive for measles IgM), five had low measles transmission profiles, and one country (Burkina Faso) had moderate transmission. Among the seven southern African countries, five had very low transmission, one had low transmission, and one (Namibia) had moderate transmission (table 3). In southern Africa, 643 (10%) of 6619 samples tested were positive for measles IgM.

In 2002–03, 16 measles outbreaks occurred 60 days or longer after an SIA (table 4). In 11 outbreaks there were more than ten cases. Five of the 11 outbreaks were in areas bordering countries that had not undertaken SIA (southern Mali bordering Guinea, Cameroon bordering Nigeria [three outbreaks], and Mpumalanga Province, South Africa, bordering Mozambique). One outbreak occurred mainly among individuals aged 15 years and older among nomads in northern Mali. Two outbreaks occurred in island populations that had very low coverage during the catch-up campaign (Pemba island, Tanzania, and Bonassama district, Cameroon).

In Burkina Faso, the number of reported cases was only partly reduced after SIA (1744 in 2002 and 2946 in 2003). Burkina Faso was the only country of 19 countries that had measles transmission during the entire period after the initial SIA as shown by case-based and aggregate surveillance data. An outbreak investigation showed that the continuing transmission was related to a large number of unvaccinated children returning from Côte d’Ivoire during a time of political turmoil.17

In Namibia, after 4 years of no measles circulation, an outbreak (1218 cases and 13 reported measles deaths) continued for 18 months during 2002–03. In Zimbabwe, an outbreak with 80 cases and 20 reported deaths occurred 4 years after the initial SIA and after the first follow-up SIA. The Zimbabwe outbreak was restricted and occurred near the border with Mozambique, which

### Table 3: Results of case-based measles surveillance with laboratory confirmation in areas after SIA, 2002–03

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Number of reported measles cases*</th>
<th>Number of cases with laboratory samples taken and results available</th>
<th>Positive for measles IgM</th>
<th>Epidemiological profile of measles transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>2002</td>
<td>76</td>
<td>70 (92%)</td>
<td>22 (31%)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>215</td>
<td>211 (98%)</td>
<td>58 (27%)</td>
<td>Low</td>
</tr>
<tr>
<td>Burkina Faso</td>
<td>2002</td>
<td>1337</td>
<td>1029 (77%)</td>
<td>709 (65%)</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>6315</td>
<td>2682 (42%)</td>
<td>1997 (78%)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Burundi</td>
<td>2002</td>
<td>89</td>
<td>79 (89%)</td>
<td>3 (4%)</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>33</td>
<td>33 (100%)</td>
<td>5 (15%)</td>
<td>Low</td>
</tr>
<tr>
<td>Cameroon</td>
<td>2002</td>
<td>147</td>
<td>85 (58%)</td>
<td>6 (7%)</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>1487</td>
<td>1148 (77%)</td>
<td>46 (4%)</td>
<td>Very low</td>
</tr>
<tr>
<td>Ghana†</td>
<td>2002</td>
<td>147</td>
<td>85 (58%)</td>
<td>6 (7%)</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>1487</td>
<td>1148 (77%)</td>
<td>46 (4%)</td>
<td>Very low</td>
</tr>
<tr>
<td>Kenya</td>
<td>2002</td>
<td>1391</td>
<td>1736 (97%)</td>
<td>59 (3%)</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>533</td>
<td>63 (12%)</td>
<td>22 (35%)</td>
<td>Low</td>
</tr>
<tr>
<td>Mali</td>
<td>2002</td>
<td>226</td>
<td>130 (58%)</td>
<td>61 (47%)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>533</td>
<td>63 (12%)</td>
<td>22 (35%)</td>
<td>Low</td>
</tr>
<tr>
<td>Rwanda</td>
<td>2002</td>
<td>48</td>
<td>47 (98%)</td>
<td>7 (15%)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>33</td>
<td>250 (75%)</td>
<td>23 (9%)</td>
<td>Very low</td>
</tr>
<tr>
<td>Senegal</td>
<td>2002</td>
<td>348</td>
<td>199 (58%)</td>
<td>32 (11%)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>665</td>
<td>260 (39%)</td>
<td>17 (7%)</td>
<td>Very low</td>
</tr>
<tr>
<td>Tanzania</td>
<td>2002</td>
<td>333</td>
<td>250 (75%)</td>
<td>23 (9%)</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>275</td>
<td>250 (91%)</td>
<td>11 (4%)</td>
<td>Very low</td>
</tr>
<tr>
<td>Zambia</td>
<td>2002</td>
<td>2315</td>
<td>600 (26%)</td>
<td>10 (2%)</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>2315</td>
<td>600 (26%)</td>
<td>10 (2%)</td>
<td>Very low</td>
</tr>
<tr>
<td>Seven southern African elimination countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Five countries‡</td>
<td>2002</td>
<td>1159</td>
<td>1015 (88%)</td>
<td>30 (3%)</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>4780</td>
<td>4535 (95%)</td>
<td>233 (5%)</td>
<td>Very low</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>2002</td>
<td>489</td>
<td>489 (100%)</td>
<td>59 (12%)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>646</td>
<td>422 (65%)</td>
<td>300 (71%)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Namibia</td>
<td>2002</td>
<td>163</td>
<td>158 (97%)</td>
<td>21 (13%)</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>2003</td>
<td>163</td>
<td>158 (97%)</td>
<td>21 (13%)</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Cases reported within 60 days of the end of the SIA are excluded. †Central province of Ghana only. ‡Botswana, Lesotho, Malawi, South Africa, and Swaziland.
is the only country in southern Africa that has not undertaken measles SIA.

In 2000, nine of the 12 countries that undertook initial SIA in 2001–03 reported routine measles vaccination coverage of less than 80% (table 1). In 2003, reported measles vaccination coverage had increased by 10% or more in all of these nine countries. In the 12 eastern and western African countries, the weighted average of routine measles vaccination coverage increased from 64% in 2000 to 78% in 2003 (figure). In the seven southern African countries, the weighted average of routine measles vaccination coverage was stable at 78–83% before the SIA (1990–95) then increased to 87% in 2000 during the period of initial SIA. In 2001 and 2002, routine coverage decreased to 72% and 73%, respectively, largely owing to lower reported coverage in Namibia, Swaziland, and Zimbabwe. In 2003, reported coverage was 81%.

Discussion
In 19 of 46 countries in the African Region, analyses of three types of surveillance data indicate a substantial reduction in the number of measles cases after SIA. On the basis of aggregate surveillance data from these 19 countries, there was a 91% reduction in the number of reported measles cases after SIA targeting of a wide age range. Furthermore, the low proportion of suspected measles cases confirmed as true cases and the infrequent occurrence of outbreaks are consistent with a striking reduction in measles transmission immediately after the SIA. Extrapolating these findings to the effect on measles deaths, we estimated a 20% reduction in the annual number of measles deaths in the African Region as a whole in 2003. This estimated decline represents substantial progress towards the Regional goal of near-zero measles deaths and the worldwide goal of 50% reduction in measles deaths by 2005.

To allow assessment of progress toward these mortality reduction goals, we made a crucial assumption that the proportional reduction in measles deaths was equal to the proportional reduction in measles cases. We believe that this assumption was realistic for the following reasons. First, after initial SIA in 13 of the 19 countries, the decline in reported measles deaths closely matched the decline in reported measles cases. Second, case-based surveillance after the SIA confirmed that measles transmission was low or very low in 17 of the 19 countries and outbreaks that did occur were small (five to 130 cases). At high SIA coverage and with such low rates of transmission, to conceive of a plausible scenario in which the death reduction would not approximate the case reduction is difficult. Third, the proportional decline in routinely reported measles cases could underestimate the true reduction in mortality after SIA, because only 10% of reported measles cases were confirmed as measles after SIA.

We used available surveillance data to measure the effect of the programme. Common criticisms of surveillance data include under-reporting and variable quality in some areas. Nevertheless, we found striking decreases in aggregate reported measles cases in all 19 countries immediately after implementation of wide-age-range SIA. The quality of measles case-based surveillance is monitored by the WHO African Regional Office with two indicators: the rate of suspected measles cases with blood samples collected (target at least 1·0 per 100 000 total population) and the proportion of districts with at least one suspected measles case with a blood
Routine measles vaccination coverage increased 14% of these activities to increase population immunity complete their initial catch-up SIA. Ethiopia and the Democratic Republic of Congo countries with low routine vaccination coverage such as in Africa are undertaking follow-up campaigns and large only model approach and a disease-measurement SIA in Namibia. The discrepancy between a coverage-after SIA in Burkina Faso and after the first follow-up unexpected increase in measles cases came immediately cases, which led to investigations and responses. The surveillance detected unexpected increases in measles verified by a standard cluster survey (table 1). Yet measles in the region; in Burkina Faso, post-SIA coverage was reported measles SIA coverage similar to other countries transmission lasting longer than 12 months despite countries had episodes of continuous measles transmission for 3 years or longer depending on the pre-existing routine vaccination coverage. If we assume that the effect of SIA lasted 4 years when routine measles coverage was 80% or higher and 3 years if routine measles coverage was less than 80%, the total projected number of deaths that would be averted over the next 3–4 years is 304 212: 285 783 in the 12 eastern and western African countries and 18 429 in the seven southern African countries. These projections provide a rough estimate of the public-health impact of accelerated measles control efforts in the African Region over the medium term.

The advantage of estimating mortality reduction on the basis of measured declines in reported disease (over a model based on vaccination coverage) is shown by the examples of Burkina Faso and Namibia. These two countries had episodes of continuous measles transmission lasting longer than 12 months despite reported measles SIA coverage similar to other countries in the region; in Burkina Faso, post-SIA coverage was verified by a standard cluster survey (table 1). Yet measles surveillance detected unexpected increases in measles cases, which led to investigations and responses. The unexpected increase in measles cases immediately after SIA in Burkina Faso and after the first follow-up SIA in Namibia. The discrepancy between a coverage-only model approach and a disease-measurement approach might become magnified once more countries in Africa are undertaking follow-up campaigns and large countries with low routine vaccination coverage such as Ethiopia and the Democratic Republic of Congo complete their initial catch-up SIA.

The mostly likely explanation for the observed sudden reduction in the number of cases after SIA is the ability of these activities to increase population immunity rapidly and thereby prevent measles transmission. Routine measles vaccination coverage increased 14% over a 3-year period in the 12 eastern and western African countries but remained unchanged in the seven southern African countries. A gradual increase in routine immunisation measles coverage will decrease accumulation of susceptible children and might allow countries to increase the time between follow-up SIA from 3 years to 4–5 years.

Our study had several limitations. Because measles deaths are not routinely reported to WHO, we relied on available WHO estimates for the number of deaths before the SIA. For most non-southern African countries, we had surveillance data for only 1 year after SIA. However, data from southern African countries showed an effect that has lasted 4–8 years, as long as regular follow-up SIA are undertaken. In addition, we did not have information on changes in case management (eg, use of vitamin A) or changes in age distribution of patients with reported measles, and we could not assess changes in surveillance quality of the routine (aggregate) surveillance system. A substantial decline in measles transmission might result in a shift in the age distribution of measles to older individuals, in whom the case-fatality rate is lower, thereby resulting in an underestimate of the reduction in measles burden.

There is active debate about the positive and negative effects of mass vaccination campaigns on routine primary-health-care services.\textsuperscript{19,33} On the positive side, mass campaigns, if well planned and executed, achieve equity by reaching children who are missed by routine services and result in protection of children who are vulnerable (eg, owing to HIV infection) or unvaccinated by reducing transmission to very low rates. Benefits of campaigns can be increased by addition of interventions such as oral poliovirus vaccine, vitamin A, insecticide-treated bednets, and anthelmintics and through new equipment (eg, for the cold chain) and training (eg, for injection safety) put in place for the campaign. On the negative side, mass campaigns divert staff and resources such as vehicles that were intended for other primary-care services. Furthermore, if training and logistics are inadequate, they can lead to unsafe injection practices, difficulties with waste disposal, and adverse events due to human error. Measles SIA are done only once every 3–4 years and, despite their disruption of routine health services, they can be highly cost-effective disease-control activities in settings where country infrastructure is weak. Although more data are needed, the available evidence suggests that countries can both complete high-quality SIA and increase routine coverage.

SIA in children aged 9 months to 14 years have been superior to those in children aged 9 months to 4 years during the past 5 years in most African settings.\textsuperscript{7} The number of deaths averted is three times higher with SIA in children aged 9 months to 14 years than with those in the narrower age range. In countries with moderate to high routine coverage, SIA in children aged 9 months to 4 years lowered the number of measles cases by half for
1–2 years; SIA in children aged 9 months to 14 years lower the number of measles deaths to near zero for nearly twice as long (3–4 years). We hypothesise that reduction of transmission to near zero is the reason for the better effect of the wider-age-range SIA. With no measles transmission, all measles vaccinations (even those given at ages 1–4 years) are given before infection, no measles cases occur before the time of vaccination at 9 months, older children do not act as reservoirs to infect younger non-immune children, and children who are missed by the routine vaccination programme or who have experienced vaccine failure are not infected.

The total donor costs for the SIA in the 19 countries were US$68·1 million (Measles Initiative and WHO African Regional Office, unpublished data). From the donor’s perspective, the cost per child targeted was US$0·83 and cost per death averted was US$224. More detailed economic studies are needed for assessment of the costs and benefits of accelerated measles-control strategies in the African setting, for example from societal and government perspectives.

The goal of the African Regional measles plan of action is to sustain measles mortality at near zero. The southern African countries showed sustainable measles control, having maintained the striking reduction in measles cases for 5 years or longer (figure). The challenges for the future are to increase routine measles immunisation coverage to more than 80% in every district so that follow-up SIA targeting children aged 9 months to 4 years would be required only every 4 years, to identify resources to undertake regular follow-up SIA to sustain the number of measles deaths near zero, and to maintain continuous monitoring and feedback through surveillance. The cost of follow-up SIA every 1–4 years for all countries of the African Region (until 2010) is estimated at US$30–40 million per year (annual WHO African Regional Office measles plan of work, 2003, unpublished).

During the past 5 years, a partnership has been formed between ministries of health, non-governmental organisations, and civil society that has been able to ensure high equitable coverage with live-saving vaccines through SIA while increasing coverage of routine services. The immunisation programme has also established an information system to measure coverage and impact continuously at the district level. The potential exists to use similar partnerships, programme infrastructure, and information systems to reach nationwide high coverage for other child survival interventions (eg, insecticide-treated bednets).**

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
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References

Contributors
M Ottén, R Kezaala, A Fall, B Masresha, R Martin, R Eggers, R Biellik, M Grabowsky, J-M Okwo-Bele, and D Nshimirimana helped with designing and implementing data-collection systems and the measles control programme. P Strelé and I Cairns helped write the report. All the authors critically contributed to the final preparation of the report. The views expressed are solely those of the authors and are not those of the WHO.
Differences between fetal and adult skin could be important in inducing scar-free tissue repair.1 In both animals and people, fetal skin outside the amniotic environment is very efficient in healing rapidly and without scars, emphasising that fetal cells themselves are responsible. Animal work and characteristics of fetal cells show unique features of fetal wound healing in collagen production, transforming growth factor-beta (TGF-β) response, and cell surface receptors that are important in cell-signalling, migration, and nerve stimulation.2–4

Allograft rejection is mediated by genes of the MHC, including HLA genes. Expression of fetal MHC antigens is age dependent and organ specific.5 Many difficulties of tissue engineering such as immunological rejection, small growth capacity, and matrix compatibility could be reduced by use of fetal tissue. Careful selection of a donor and extensive screening for infectious diseases provide a safe source of cells for therapeutic use.

In a protocol approved by the local ethics committee, written informed consent (obtained when the donor patient was admitted 24 h before procedure) was sought for fetal skin biopsy (4 cm²) after pregnancy termination at 14-weeks' gestation. The donor was managed by a medical team independent from the study and could decline participation at any time. She was screened during hospital stay and 3 months later for infectious diseases. Karyotype and post-mortem of the fetus were obtained. With one fetal organ donation (4 cm² skin), a skin-cell bank was developed that was capable of producing several million skin constructs (9×12 cm) for therapeutic use (figure 1, A).

Cells were expanded from tissue fragments and grown in Dulbecco’s modified Eagle’s medium (DMEM, Gibco, Paisley, Scotland, UK) supplemented with 10% fetal calf serum (FCS) (Hyclone, Fetal Clone III, Logan, Utah, USA) and frozen in liquid nitrogen in dilutions used directly for the matrix seeding (early passages—eg, 3–4). For construct development, collagen sheets (Baxter, Volketswil, Switzerland), 2 mm dry collagen, 9×12 cm were seeded at a density of 2·5×10³ cells/cm², and a

Figure 1: Fetal construct preparation and immunogenecity

(A) Fetal skin donation was expanded in tissue culture to establish a cell bank and fetal construct preparation (histological frozen sections, 20 μm stained with haematoxylin and eosin [H&E]). (B) HLA-DPB1 RT-PCR on old, young, and fetal cells up to passage 20. GAPDH was used as a positive control.
growth period of 2 days (37°C incubator at 95% relative humidity and 10% CO₂) was selected for the clinical trials (figure 1, A, haematoxylin and eosin [H&E] staining of construct).

Cells derived from fetal skin were examined for the presence of HLA DP histocompatibility type, beta 1 subunit HLA-DPB1) mRNA (European Molecular Biology Laboratory accession NM_002121, position 598 to 816 bp), related to tissue rejection. Culture techniques did not alter antigenic loci in fetal cells as portrayed by the absence of HLA-DPB1 (figure 1, B). Three additional fetal cell lines from 14–18 weeks were also negative (data not shown). Control cells from young and old skin, established under the same conditions, tested positive for HLA-DPB1. Fetal cells were not positive for HLA-DP, DQ, or DR l by immunofluorescence (anti-HLA, clone CR3/43, Dako, Glastrup, Denmark). Fetal skin cells were 100% positive for vimentin (clone 3B4, Progen, Heidelberg, Germany). 10% positive for cytokeratin cocktails (AE1AE3, C11, MNF116, Novocastra, Newcastle upon Tyne, UK); no cells were positive for Melan A (clone A103, Dako, Glastrup, Denmark), CD1a (clone O10, Immunotech, Marseille, France) or smooth muscle actin (clone 1A4, Sigma, St. Louis, MO, USA).

Eight children presenting with burns who were candidates for autograft (mesh or full thickness) after an average of 10 days of traditional treatment were included in the study. The study protocol was approved by the local

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Type of injury</th>
<th>Body site/ size of graft</th>
<th>Delay before treatment (days)</th>
<th>Number of constructs</th>
<th>Time to closure (days)(months)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14 months/female</td>
<td>Second and third degree burn—scalding coffee</td>
<td>Hand 3.8×4 cm 3.4×4 cm</td>
<td>8</td>
<td>5</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>8 years/female</td>
<td>Second and third degree burn—scalding water</td>
<td>Buttokes 29.5×18 cm</td>
<td>8</td>
<td>5</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>15 months/male</td>
<td>Second and third degree burn—scalding water</td>
<td>Foot and leg 2.8×5.8 cm 2.9×13.9 cm</td>
<td>21</td>
<td>6</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>9 years/female</td>
<td>Second and third degree burn—hot oil</td>
<td>Hand &amp; arm 15.9×11.8 cm 13.5×9.7 cm</td>
<td>10</td>
<td>3</td>
<td>17</td>
<td>16</td>
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<tr>
<td>5</td>
<td>9 years/male</td>
<td>Second degree burn—gasoline fire</td>
<td>Hand 14.4×7.8 cm</td>
<td>9</td>
<td>6</td>
<td>16</td>
<td>13</td>
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<tr>
<td>6</td>
<td>17 months/female</td>
<td>Second and third degree burn—iron</td>
<td>Hand 2.9×4.2 cm</td>
<td>5</td>
<td>3</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>2 years/male</td>
<td>Second and third degree burn—iron</td>
<td>Foot 2.5×5.6 cm</td>
<td>14</td>
<td>5</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>5 years/female</td>
<td>Second degree burn—furnace</td>
<td>Buttokes 8.8×12.3 cm</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>15</td>
</tr>
</tbody>
</table>

Mean (SD) 10 (5·2) 4·3 (1·8 ) 15·3 (5·5) 16·5 (3·1)

Table: Summary of patients

Figure 2: Patient follow-up after application of fetal skin constructs
Photos of five representative patients in early weeks of treatment and follow-up at several months. A=before treatment; B=2 weeks after treatment; C=at follow-up.
We have shown that fetal skin is a substitute for retraction or secondary breakdown of healed surfaces. Aesthetic and functional results were excellent in all eight patients treated with the wound closing from the border of the lesions. In view of the therapeutic effects of this technique along with the simplicity in application, fetal skin cells could have great potential in tissue engineering.

Mean time before first application of the construct was 10 days (SD 5.2) and mean number of constructs applied was 4.3 (1.8). Mean time to healing for the burns was 15.3 days (5.5) after the first construct application and the range of follow up was 13–21 months. After skin closure, total recovery of mobility, especially in hands and fingers, was documented (patients 1, 4, 5 and 6; table, figure 2). Moreover, recovery of skin pigmentation was noted in patients with dark skin (patient 4). General anaesthesia or nitrous oxide analgesia were used less than for traditional dressings, with an average number of 3–4 sessions (2–7). Because donor cells were male, we needed to know whether engraftment took place in female patients. We therefore asked patient 2, who had the largest, concealed burned surface, for consent to biopsy (1 cm² representing around 2500 epidermal cells and 3500 dermal cells) 6 months after therapy. The whole surface was screened by fluorescence in situ hybridisation (FISH), showing absence of Y-chromosomes (data not shown).

No child needed traditional grafting because fetal construct applications alone led to wound closure. All wounds were closed at just over 2 weeks with no hypertrophic granulation tissue as often seen with traditional methods. Fetal-skin constructs lack polarity, are easily applied, and mould to the anatomy of small areas such as fingers and toes. No additional fixation devices (ie, glue, staples, stitches, silicones) were needed, and application of constructs was painless (anesthesia was used only for young non-cooperative children). Aesthetic and functional results were excellent in all eight children showing little hypertrophy of new skin with no retraction or secondary breakdown of healed surfaces. We have shown that fetal skin is a substitute for biological skin that can provide burned patients with a very high quality of skin in a short time with no additional grafting techniques. Other investigators reported using collagen alone or collagen with newborn skin-cells to treat burns, wounds, and autograft sites of burned patients.\(^3\)\(^7\) In such studies, a two-step surgical procedure was needed with either split-thickness grafting or autologous keratinocytes and fibroblasts. When two-step procedures are necessary, the recovery period can be long, frequently being 1–5–3 months. Fetal cells are able to exert promoting effects on adhesion, proliferation, and migration of existing cells, most probably by the secretion of growth factors.\(^6\)\(^7\) This effect was seen in all eight patients treated with the wound closing from the border of the lesions. In view of the therapeutic effects of this technique along with the simplicity in application, fetal skin cells could have great potential in tissue engineering.

Acknowledgments
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References

Contributors
L A Applegate, J Hohlfeld, and P Hohlfeld had the original idea and participated in the conception and design of this study, acquisition and interpretation of data, and drafting and review of the report.
A de Buys Roessingh, N Hirt-Burni, C Scaletta, P Chau bert, and S Gerber made important contributions to one or more of: study design, and acquisition, analysis, or interpretation of data. The article was revised and approved by all contributors.

Conflict of interest statement
L A Applegate and P Hohlfeld hold a patent pending on the use of fetal skin-cells for treatment of skin disorders and participated in the spin-off of the University Hospital, Neocutis.
Cluster headache: pathogenesis, diagnosis, and management

Anne May

Cluster headache is a stereotyped primary pain syndrome characterised by strictly unilateral severe pain, localised in or around the eye and accompanied by ipsilateral autonomic features. The syndrome is characterised by the circadian rhythmicity of the short-lived attacks, and the regular recurrence of headache bouts, which are interspersed by periods of complete remission in most individuals. Headaches often start about 1–2 h after falling asleep or in the early morning, and show seasonal variation, suggesting that the hypothalamus has a role in the illness. Consequently, the vascular theory has been superseded by recognition that neurovascular factors are more important. The increased familial risk suggests that cluster headache has a genetic component in some families. Neuroimaging has broadened our pathophysiological view and has led to successful treatment by deep brain stimulation of the hypothalamus. Although most patients can be treated effectively, some do not respond to therapy. Fortunately, time to diagnosis of cluster headache has improved. This is probably the result of a better understanding of the pathophysiology in combination with efficient treatment strategies, leading to a broader acceptance of the syndrome by doctors.

Clinical features

“Imagine, your eye is pushed out of its socket and your right eyelid is beginning to swell shut. You start squinting and your eye is tearing, you are convinced there was blood pouring out. A red-hot knife is crushed into your head, excruciating, horrible, horrible pain. Your only saving grace is to pace from room to room, crying, flinging yourself to the floor, until eventually the pain drains from you. Waiting for the next attack to happen is a terrible, scary feeling. I sometimes think that I will go mad. I’m exhausted but then the next one hits.”

This is an example of how a cluster headache patient might describe his pain in an outpatient setting. Cluster headache, one of the most severe pain syndromes—female patients describe each attack as being worse than childbirth—is still underdiagnosed and suboptimally managed in primary care. Results of a recent health-related quality-of-life study in 56 patients suggest that cluster headache has substantial effects on patients’ ability to function, even when appropriate treatments are used. Typically, attacks can strike up to eight times a day, are relatively short-lived, and are characterised by strictly unilateral severe head pain accompanied by autonomic symptoms. A side shift is mentioned in only about 15% of cases. Unlike individuals with migraine, patients with cluster headache are restless and prefer to pace about or sit and rock back and forth. Some patients will exert pressure on the painful area with a hand over the affected eye and temple. Many will isolate themselves during the headache or leave the house to get into cold or fresh air, and tend to become aggressive during an attack.

The unilateral autonomic symptoms such as ptosis, miosis, lacrimation, conjunctival injection, rhinorrhea, and nasal congestion occur only during the pain attack and are ipsilateral to the pain, indicating parasympathetic hyperactivity and sympathetic impairment (figure 1). In some patients, the signs of sympathetic paralysis (miosis and ptosis) persist indefinitely, but intensify during attacks. Sweating and bloodflow to the skin also increase on the painful side, particularly in areas of sympathetic deficit. About 3% of patients have no autonomic symptoms, and in rare cases sympathetic disturbances persist on the previously affected side of the face in patients in whom cluster headaches have switched sides.

Another clinical feature of the syndrome is the circadian rhythmicity of the painful attacks, which are relatively short (15–180 min). In the episodic form, headaches occur daily for some weeks followed by a period of remission. On average, a cluster period lasts 6–12 weeks, and remissions can last up to 12 months. In the chronic form, attacks occur without substantial periods of remission. When chronic cluster headache is unresponsive to medical treatments, it becomes a serious problem and surgical options may have to be considered.

Epidemiology and genetics

Compared with migraine, cluster headache is uncommon. The disorder has a prevalence of less than 1%, and mostly affects men. The episodic form is most common, affecting 80–90% of cluster headache patients. It is characterised by periods of headaches (clusters or bouts) and periods of remission. During a

Search strategy and selection criteria

I searched MEDLINE with the keywords “cluster headache”, “trigemino-autonomic headache”, “paroxysmal hemicrania”, “SUNCT”, “pathophysiology”, “treatment”, and “trial” (last search in January, 2005). All papers published in English or German were considered when they described a controlled trial or a case series on the treatment of at least five patients (or fewer in paroxysmal hemicrania or SUNCT syndrome). Papers located by this search were reviewed, as were references cited therein. Additionally, review books and the German treatment recommendations for cluster headache were considered.
Note the Horner syndrome ipsilateral to the headache and increased facial sweating exclusively around the left eye.

Figure 1: Patient soon after a left-sided cluster headache attack

Note the Horner syndrome ipsilateral to the headache and increased facial sweating exclusively around the left eye.

The nature of the sex-related and age-related pattern of cluster headache onset is unclear. However, the increase in the diagnosis in women might also be the result of increased awareness and acceptance of the disorder by doctors, due to improved understanding of cluster headache pathophysiology.10–22

The medical history often reveals a high incidence of head trauma with brain concussion,23–25 but it is hard to prove a cause-and-effect relation. Interestingly, up to 85% of patients with chronic headache are also chronic cigarette smokers.23 Quitting smoking has no effect on the disease. The question arises whether chronic nicotine consumption is needed as a trigger to initiate the syndrome, possibly on the basis of some genetic background.

Before 1990, cluster headache was not generally thought to be an inherited disorder.24–27 However, reports of cluster headache in monozygotic twins28 and familial occurrence of cluster headache in 7% of families, resulting in a 14-fold increase in risk of cluster headache in first-degree relatives and a two-fold increased risk for second-degree relatives,29 show that genetic factors should be considered. In a study of 186 index patients and 624 first-degree relatives, investigators showed a positive family history of cluster headache in 11% of the index patients. They concluded that no precise mode of inheritance could be ascertained.10 A complex segregation analysis of cluster headache has suggested that an autosomal dominant gene has a role in some families,31 although some evidence exists for autosomal recessive or multifactorial inheritance in others.13 However, future studies should take into account that since cluster headache can start between the ages of 7 years13 and 83 years,11 the distinction between affected and unaffected individuals is clearly provisional. To date, the increased familial risk strongly supports the hypothesis that cluster headache has a genetic component, at least in some families.21 However, no clear molecular genetic clues have yet been identified. In view of the parasymptomatic character and circadian and circannual rhythmicity of the disease, future studies need to focus on ion channel genes and clock genes.

Pathophysiology

Although the syndrome is well defined from a clinical point of view and has been recognised for more than two centuries,26 its pathophysiology is still poorly understood. However, the past decade has seen remarkable progress toward solving the pathophysiological puzzle.32 Any pathophysiological model needs to explain the three major features of cluster headache: trigeminal distribution of the pain, ipsilateral cranial autonomic features, and (circadian) episodic pattern of attacks. The vascular theory, which is based on an inflammation of the walls of the cavernous sinus (the only peripheral anatomical location where a single pathology could involve trigeminal C-fibres and sympathetic fibres),33 has been superseded by recognition that neurovascular events and some central impulse generator or oscillator seem to be more important. The severe unilateral pain is likely to be mediated by activation of the first (ophthalmic) division of the trigeminal nerve, whereas the autonomic symptoms such as lacrimation are due to activation of the cranial parasympathetic outflow from the seventh cranial nerve.34
Autonomic features
The sympathetic paralysis (miosis and ptosis) is due to a neuropraxic injury of postganglionic fibres in most patients.\(^{37}\) Currently, at least three possible sources of the autonomic symptoms are discussed: (1) the autonomic dysregulation might originate centrally in association with a hypothalamic disturbance;\(^{38,39}\) (2) a vasodilation or perivascular oedema (due to trigeminal-parasympathetic overactivity during attacks) compromises the carotid canal and consequently the traversing sympathetic fibres;\(^{40}\) and (3) the autonomic symptoms are secondary to trigeminal discharge.\(^{41,42}\)

The possibility that parasympathetic hyperactivity is solely responsible for ocular sympathetic deficit has been discussed.\(^{43}\) About 3% of patients have no autonomic symptoms;\(^{7}\) and patients with and without autonomic symptoms have been described in the same families.\(^{44,45}\) In rare cases pain and autonomic symptoms may fully dissociate.\(^{46}\) However, a typical cluster attack will be strictly one-sided and will have prominent ipsilateral autonomic symptoms.\(^{1}\)

The relapsing-remitting course,\(^{46}\) its seasonal variation,\(^{16}\) and the clockwise regularity\(^{47}\) of single episodes are characteristic, and suggest that the biological clock—namely the hypothalamus—is involved in the origin of the illness.\(^{48-51}\) Substantially lowered concentrations of testosterone in the plasma of men with cluster headache provided the first evidence of such a role.\(^{11}\) This evidence is further supported by a reduced response to thyrotropin-releasing hormone\(^{52}\) and a range of other circadian irregularities that have been reported in patients with cluster headache.\(^{50,53,54}\) Melatonin, in particular, is a marker of the circadian system; a blunted nocturnal peak in melatonin and complete loss of circadian rhythm have been reported in cluster headache.\(^{55,56}\) The endogenous circadian rhythm is controlled by an oscillator in the suprachiasmatic nuclei in the ventral hypothalamus, and is entrained to temporal environmental cues by light conditions via a retino-hypothalamic pathway.\(^{57,58}\) Clinical observations thus suggest the hypothalamus or a closely related structure as a candidate trigger for the acute attacks of cluster headache.

Functional imaging
Functional imaging work with PET has confirmed a highly specific activation of the hypothalamic grey matter in nitroglycerin-triggered and spontaneous cluster headaches.\(^{37,59}\) suggesting involvement in the pain process in a permissive or triggering manner rather than simply a response to first division nociception per se.\(^{60}\) Although the headache syndromes that form the group known as trigemino-autonomic cephalgies (cluster headache, paroxysmal hemicrania, and short-lasting neuralgiform headache with conjunctival injection and tearing [SUNCT]) share typical clinical features,\(^{61}\) in most cases a subclassification is possible and reasonable, as therapeutic regimens and responses differ. Since many of the basic features of SUNCT are shared by cluster headache and paroxysmal hemicrania, investigators have questioned whether there is a shared pathophysiological basis that might be expressed in similar cerebral activation patterns.

Neuroimaging in related syndromes
Using blood-oxygen-dependent functional MRI, three independent case reports investigating four patients with spontaneous SUNCT episodes uniformly found an activation next to the hypothalamic spot that was activated in cluster headache.\(^{62-64}\) The same prominent activation in the hypothalamic grey matter was found in a patient suffering from excruciating trigemino-autonomic headaches, in whom frequency and duration of attacks and therapeutic response allowed no clear-cut classification.\(^{65}\) These findings suggest that the underlying cause of trigemino-autonomic cephalgies might indeed be similar, and the variation in duration and frequency might be generally dependent on a different disorder of the hypothalamic grey matter, perhaps a modulation of neuronal activity or a different involvement of the trigemino-vascular system. These case studies underline the conceptual value of the term trigemino-autonomic cephalgies for the group of headaches focused around the trigeminal-autonomic reflex. Moreover, these findings emphasise the importance of the hypothalamus as a key region in the pathophysiological process of such headaches.

Another unilateral headache that is accompanied by trigeminal autonomic features is hemicrania continua. It is a strictly unilateral, continuous headache of moderate intensity, with superimposed exacerbations of severe intensity that are then accompanied by autonomic features and migrainous symptoms.\(^{66}\) The syndrome is exquisitely responsive to indometacin. Although, for theoretical reasons, it is not included among the trigeminal-autonomic headaches,\(^{1}\) a substantial activation of the contralateral posterior hypothalamus and ipsilateral dorsal rostral pons has been described in seven patients with hemicrania continua.\(^{67}\) Additionally, there was activation of the ipsilateral ventrolateral midbrain, which extended over the red nucleus and the substantia nigra, and bilateral pontomedullary junction. This study showed that the neuroimaging markers of both the trigeminal autonomic cephalgies (hemicrania)\(^{65,68}\) and migraine (brainstem)\(^{69,70}\) are noted in hemicrania continua, mirroring the clinical phenotype that, in fact, shows some overlap with trigeminal autonomic headaches and migraine.\(^{44}\) Taken together, just as in the case of an atypical trigemino-autonomic headache,\(^{71}\) the functional imaging data in hemicrania continua\(^{44}\) emphasise that primary headache syndromes can be distinguished on a functional neuroanatomical basis by areas of activation specific to the clinical presentation. However, in view of
the consistency of the PET findings with the clinical presentation, the question remains whether the brain of such patients is indeed structurally normal.

**Hypothalamic deep brain stimulation**

Recently, voxel-based morphometry has shown a structural difference in grey matter density—a lesion coinciding with the inferior posterior hypothalamus—in patients with cluster headache (but not those with migraine) compared with healthy volunteers. In terms of the stereotactic coordinates, the lesion occurs in about the same area in which activation during an acute cluster headache attack is noted in PET (figure 2). This work has even led to the successful introduction of a therapeutic target using deep brain stimulation of the posterior hypothalamic grey matter. So far, successful operations have been reported in 20 patients with intractable chronic cluster headache, some with a follow-up of more than 4 years.

Attacks reappear when the stimulator is switched off, and disappear when it is turned on again. Notably, it takes several days or even weeks between turning the unipolar stimulator on or off and change of the clinical picture. The method is reversible and the procedure is well tolerated in most patients, with no substantial side-effects. However, one patient had an intracerebral hemorrhage during the operation. This event led to the development of strict criteria and technical prerequisites for the selection of patients who should have operations. From a clinical point of view, it is interesting that trigeminal hypaesthesia and anaesthesia did not occur in any of the patients who received hypothalamic deep brain stimulation, and that hypothalamic stimulation does not affect anaesthesia dolorosa. This observation strengthens the hypothesis that the pain of cluster headache does not arise from a primary dysfunction of the trigeminal nerve itself, but is generated directly from the brain. In this context, it is noteworthy that electrical stimulation of the superior sagittal sinus, a trigeminally innervated structure, activates the supraoptic nucleus and posterior hypothalamic area, and a monosynaptic pathway connecting the hypothalamus and trigeminal nucleus has been documented. The posterior hypothalamus is able to both decrease or enhance nociceptive responses in the trigeminal nucleus caudalis. Little is known about the circuits and mechanisms underlying the effect of deep brain stimulation; however, activation of thalamo-cortical pathways and changes in cortical activity are probably involved. Further research in this field is urgently needed and the recently developed possibility of combining deep brain stimulation with PET will certainly help to unravel the brain circuitry implicated in stimulation-produced analgesia.

In summary, the pathogenesis of cluster headache is complex and remains incompletely understood. It is probably better to regard the condition as a hypothalamic syndrome rather than as a simple headache. In doing so, the contributions of both peripheral and central structures are considered, and this description takes into account the hypothalamic symptoms such as aggressiveness, sleep disturbance, restlessness, and endocrine and vegetative symptoms typically encountered in many patients. Whether it is primary to the disease or only an epiphemomenon, the peripheral nervous system’s role in episodic cluster headache is beyond dispute. Interestingly, the peripheral part of the trigeminal nerve is not necessarily needed for some chronic forms of the disease, which means that the syndrome may be progressive. Whether inflammation of the walls of the cavernous sinus occurs, a process that has been thought to obliterate venous outflow and thus injure the traversing sympathetic fibres of the intracranial internal carotid artery and its branches, is controversial. That the hypothalamus is involved, at least in primary cluster headache, seems indisputable. At a minimum, primary cluster headache is characterised by hypothalamic activation with

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**Figure 2: Functional imaging studies showing specific involvement of the hypothalamus in cluster headache**

(A) PET-activation studies in nine patients with cluster headache during the nitroglycerin triggered acute headache phase compared with the resting state and (B) single-subject study in another patient during the spontaneous acute headache phase. Activation of the inferior posterior hypothalamus (coloured area) was found ipsilateral to the headache side and is specific for this type of idiopathic headache syndrome. Even in a patient with trigemino-autonomic headache attacks, in whom frequency, duration, and therapeutic response allowed no clear-cut classification to one of the subtypes of trigeminal autonomic cephalgia, the same prominent activation in the hypothalamic grey matter was noted. An important structural difference in grey matter was solely found in the inferior posterior hypothalamus. In terms of the stereotactic coordinates, it is virtually the same area as in the activation studies. Use of functional imaging and definition of the exact brain area that is inherent to the disease led to the successful introduction of a therapeutic target using deep brain stimulation of the posterior hypothalamic grey matter.
secondary activation of the trigemino-facial reflex, probably via a trigemino-hypothalamic pathway (figure 3). In long-standing chronic cluster headache, the autonomic symptoms and headache may be generated entirely through central mechanisms, as activation of the trigemino-facial reflex is no longer necessary to display the full clinical picture.

**Diagnosis**

The diagnosis of cluster headaches is exclusively clinical. The International Classification of Headache Disorders' uses explicit diagnostic criteria (panel), which are “unambiguous, precise and with as little room for interpretation as possible”. That at least 14 synonyms for cluster headache have been used in the past shows the earlier lack of understanding of aetiology, and the importance of operational, explicit diagnostic criteria for research and clinical practice. Cluster headache, in its typical form, is unmistakable. However, no single instrumental examination can define, ensure, or differentiate idiopathic headache syndromes.

Nevertheless, in the clinical setting, the use of neuroimaging (cranial CT, MRI, MR angiography, etc) in patients with headache varies widely. Electrophysiological and laboratory examinations, including examination of the CSF, are not helpful. For the initial diagnosis and in the case of an abnormal neurological examination, a cranial CT scan and cranial MRI should be considered, to exclude abnormalities of the brain. Mass lesions or malformations in the midline have been described in patients with symptomatic cluster headache, especially older patients.

**Differential diagnosis**

The trigemino-autonomic cephalgias are outlined in the revised version of the classification of the International Headache Society. All these syndromes have two features in common: short-lasting, unilateral, severe

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Figure 3: Schematic model showing most of the putative actors in pathogenesis of cluster headache

Pain afferents from the trigeminovascular system synapse on the trigeminocervical complex (TNC), and then project to the thalamus and lead to activation in cortical areas known to be involved in pain transmission. Either a direct effect of the hypothalamus or a reflex activation of the parasympathetic outflow from the superior salivatory nucleus (SSN) predominantly through the pterygopalatine (sphenopalatine) ganglion, leads to the parasympathetic symptoms ipsilateral to the pain. A third-order sympathetic nerve lesion, thought to be caused by vascular changes in the cavernous sinus loggia with subsequent irritation of the local plexus of nerve fibres, results in a partial Horner’s syndrome. The key site in the CNS for triggering the pain and controlling the cycling aspects is in the posterior hypothalamic grey matter region, modulated by phase-shifting in the suprachiasmatic nucleus. HT=hypothalamus. ICA=internal carotid artery. NV=trigeminal nerve. PPT=pterygopalatine. SCG=superior cervical ganglion. SN=suprachiasmatic nucleus.
headache attacks accompanied by typical autonomic symptoms. The syndromes differ in duration, frequency, and rhythmicity of the attacks, in the intensity of pain and autonomic symptoms, and in treatment options (table). There are reports of aura in cluster headache and even a “hemiplegic cluster”. There seem to be some cases of cluster headache without headache, as well as the opposite: cluster headache without autonomic symptoms, and even bilateral cases. In a series of case reports presenting three atypical cluster headaches, it has been suggested that as more cluster patients are seen by headache specialists, new forms of this well-defined primary headache syndrome will be identified. However, the concept of trigemino-autonomic syndromes is certainly useful for clinicians seeking a pathophysiological understanding of the primary neurovascular headaches, and allows us to put the various treatment and prevention strategies in context.

### Management

The guidelines of the International Headache Society represent a compromise between scientific rigour and practicality. However, because the syndrome is quite rare, it is still essential to collect and publish large case series regarding clinical manifestations, differences between the sexes, and treatment options in cluster headache. Case reports are also important as it becomes clearer that chronic headache is part of a larger spectrum of primary headache syndromes and that overlap with other trigemino-autonomic headache syndromes may occur.

The treatment of cluster headache is based on empirical data rather than on a pathophysiological
oral zolmitriptan 10 mg were also effective within controlled trials, sumatriptan nasal spray 20 mg and reduction in pain within 20–30 min. A disadvantage of headache respond to this treatment with a substantial reduction for minutes to hours, rather than completely aborted. In the latter case, oxygen intake must be restricted; otherwise, the frequency of attacks may increase. About 60% of all patients with cluster headache respond to this treatment with a substantial reduction in pain within 20–30 min. A disadvantage of oxygen is that patients must have continuous access to the oxygen supply (usually an oxygen tank and regulator), which may be impractical. Although hyperbaric oxygen has been much discussed as a therapeutic option, a placebo-controlled, double-blind trial has confirmed unambiguously that it is ineffective in preventing cluster headache attacks. In double-blind, placebo-controlled trials, the 5-HT1D agonist sumatriptan injected subcutaneously was effective in about 75% of all cluster headache patients (ie, pain-free within 20 min). It is safe, with no evidence of tachyphylaxis or rebound in most patients, even after frequent use. Contraindications are cardiovascular and cerebrovascular disorders and untreated arterial hypertension. The most uncomfortable side-effects are chest pain and distal paresthesia. In open and double-blind, placebo-controlled trials, sumatriptan nasal spray 20 mg and oral zolmitriptan 10 mg were also effective within 30 min. I have found 5 mg zolmitriptan nasal spray to be highly effective (unpublished data). The pre-emptive use of 5-HT1D agonists (triptans) in cluster headache remains controversial. 100 mg oral sumatriptan given three times a day was not effective in preventing cluster headache attacks in a placebo-controlled trial. In open trials, 40 mg eletriptan per day or 2.5–5.0 mg naratriptan per day reduced the number of cluster headache attacks.

Oral ergotamine has been used in the treatment of cluster headache attacks for more than 50 years and is effective when given very early in the attack. It is recommended as an aerosol spray for the treatment of acute cluster headache. However, modern trials are scarce. The intranasal application of dihydroergotamine in cluster headache attacks was no better than placebo in a single trial. Recently, the intravenous application of 1 mg dihydroergotamine over 3 days has been shown to be effective in stopping severe cluster attacks in an open retrospective trial. Use of ergotamine for short-term prophylaxis has also been studied. Ergotamine suppositories need a long time until the onset of effectiveness; a dose of 2 mg in the evening has been proposed to prevent cluster headache attacks during the night. The nasal application of lidocaine (1 mL with a concentration of 4–10%, ipsilateral to the pain; the head should be reclined by 45° and rotated to the affected side by 30° to 40°) is effective in at least a third of patients. The drug is thought to block the sphenopalatine fossa region. The use of lidocaine evolved from investigations to determine whether the observed clinical usefulness of cocaine in aborting acute cluster headache attacks was due to the drug’s anaesthetic or euphoric properties.

Prioritisation of acute therapy
Because of the rapid onset and short time to peak intensity of cluster headache pain, subcutaneous sumatriptan is the treatment of choice. The absorption and pharmacological actions of oral medications are usually too slow. Oxygen is the other standard treatment. Topical application of lidocaine is comparatively less efficient and has inconsistent effects. However, one could argue that every patient should try it at least once, since it works, it is easy to administer and has no systemic side-effects, which is important since patients can sometimes have as many as eight attacks a day.

Preventive pharmacotherapy
The importance of an effective preventive regimen cannot be overstated. Since many patients have between one and eight attacks a day, repeated attempts at abortive therapy may result in overmedication or toxicity. The primary goal of preventive therapy is to suppress attacks and to maintain this suppression over the expected duration of the cluster period. To achieve this goal, an individual treatment regimen must be formulated with the patient. In episodic cluster headache, medication should be withdrawn when the expected cluster period is over. In chronic cluster headache, medication should be gradually reduced once every other month, to assess whether it is still necessary.

The cornerstone of maintenance prophylaxis is verapamil. A daily dose of 240–320 mg verapamil is the established treatment of choice in the prophylaxis of episodic and chronic cluster headache, although few sufficient double-blind, placebo-controlled trials are available. Results of placebo-controlled trials showed efficacy of both verapamil and lithium, with verapamil...
...acting more rapidly than lithium. \textsuperscript{120,121} In some cases, a daily dose of more than 720 mg verapamil may be necessary.\textsuperscript{34,122} Because of this apparent dose-response relation, a total daily dose of 480–720 mg is recommended before the treatment is regarded as unsuccessful. Regular ECG monitoring is required. Side-effects of verapamil are bradycardia, oedema, gastrointestinal discomfort, constipation, and dull headache.\textsuperscript{123} However, the drug is generally well tolerated and can be used safely in conjunction with sumatriptan, ergotamine, corticosteroids, and other preventive agents. No evidence is available for an optimal dosage for verapamil. An increase of 80 mg every 3 days is recommended. The full effect of verapamil can be expected within 2–3 weeks. Both the regular and extended-release preparations have been shown to be useful, but no direct comparative trials are available. Since verapamil is usually well tolerated, it is also the drug of choice for continuous treatment in chronic cluster headache. In the first 2 weeks of verapamil administration, steroids may also be given (30–100 mg prednisone or 2$\times$4 mg dexamethasone per day). In two small open studies, nimodipine was also effective.\textsuperscript{124,125}

Lithium has been studied in cluster headache prophylaxis in a daily dose of 600–1500 mg in more than 20 open trials.\textsuperscript{148} The proportion of patients that had an improvement in chronic cluster headache was reported to be as high as 78% (63% in episodic cluster headache). A placebo-controlled trial, however, did not reproduce the beneficial effect in episodic cluster headache.\textsuperscript{127} However, in a comparative, double-blind crossover study, lithium and verapamil showed similar efficacy (with a more rapid improvement with verapamil) and tolerability was better with verapamil.\textsuperscript{128} The concentration of the drug in the plasma should be monitored and kept between 0.6 mmol/L and 1.2 mmol/L.\textsuperscript{35} Regular monitoring of liver, renal, and thyroid function and of electrolytes is needed. Major side-effects are hyperthyroidism, tremor, and renal dysfunction. As lithium in general has a narrow therapeutic window, it is particularly recommended for chronic cluster headache when other drugs are ineffective or contraindicated.

Methysergide has been recommended for episodic cluster headache,\textsuperscript{148,150–153} but no placebo-controlled, double-blind studies are available. In open studies, the number of patients who benefited from methysergide ranged from 20% to 73%; the drug was more effective in episodic cluster headache.\textsuperscript{144} The doses given in the open studies varied from 4 mg to 16 mg. Usually, methysergide is administered at a daily dose of 4–8 mg and can be increased up to 12 mg (starting with 1 mg per day). Methysergide is metabolised to an active metabolite, methylergometrine,\textsuperscript{155} and should be used with caution when patients are receiving other ergotamine derivatives or triptans. The short-term side-effects include nausea, muscle cramps, abdominal pain, and pedal oedema. Since a high incidence of pulmonary and retroperitoneal fibrosis is seen with long-term use, the continuous use of methysergide is limited to 3–4 months.\textsuperscript{134,137}

No adequate randomised, placebo-controlled trials are available for the use of corticosteroids in cluster headache. Several open studies and case series have been published and reviewed.\textsuperscript{156,157} All the open studies confirmed the clinically well-known efficacy of steroids given in different regimens (>30 mg prednisone per day, 2$\times$4 mg dexamethasone per day). These drugs are a very effective option for initial prophylaxis, rapidly suppressing attacks during the time needed for the longer-acting preventive agents to take effect. However, some patients are attack-free only with steroids, and continuous administration of steroids is necessary. As with verapamil, no evidence for the best regimen of steroid administration is available. For the beginning of steroid treatment, 60–100 mg of prednisone given once a day for at least 5 days is recommended, then decreasing the dose by 10 mg every day. About 70–80% of all cluster headache patients respond to steroids. Intravenous and oral administration of steroids can also be successfully combined.\textsuperscript{156}

**Refractory patients**

In 10–20% of patients, the above medications are not effective or the cluster periods develop resistance. Intolerance or contra-indications may further limit standard treatments. The following medications have some importance as third-line therapy, mostly based on small, open studies.

The antiserotonergic drug pizotifen (3 mg per day) has been shown to be effective in cluster headache prophylaxis in a single-blind, placebo-controlled trial.\textsuperscript{158} However, a review of seven small studies\textsuperscript{146} suggests that pizotifen has only a modest effect. Side-effects such as tiredness and weight gain further limit this drug’s use. Valproic acid has been studied in three open trials, with inconsistent results.\textsuperscript{141,142} These trials suggest that valproic acid can be tried as a drug of third choice in a daily dose of 5–20 mg per kg bodyweight. Likewise, some open studies suggest that topiramate is effective in the prophylaxis of cluster headache.\textsuperscript{146,147} The recommended dose is at least 100 mg per day, with a starting dose of 25 mg. The main side-effects are cognitive disturbances, paraesthesias, and weight loss. The drug is contra-indicated in patients with nephrolithiasis.

For the ipsilateral intranasal application of capsaicin, two open trials\textsuperscript{148,149} and one double-blind, placebo-controlled trial\textsuperscript{154} have been published, showing efficacy in about two-thirds of patients after repeated application. Intranasal application of civamide showed a modest efficacy in a double-blind, placebo-controlled study.\textsuperscript{151}

10 mg of oral melatonin was effective in a double-blind, placebo-controlled study.\textsuperscript{152} In otherwise refractory
cluster headache, however, melatonin did not produce any additional efficacy.155 There is meagre evidence from a small open study for the efficacy of baclofen (15–30 mg),156 and there is no sufficient evidence for the efficacy of botulinum toxin157 or transdermal clonidine158 in the prophylactic treatment of cluster headache.

Although there is no valid evidence that combinations of various prophylactic drugs work better in cluster headache, some patients may do better with a combination than with extensive high doses of a single drug. In clinical practice, a combination of drugs is often needed, generally using a moderate dose of verapamil (240–480 mg) as the standard medication and any of the above prophylactic drugs as add-on therapy. On the basis of a consensus obtained at the 9th International Headache research seminar, some combinations of drugs have been recommended in patients otherwise refractory to single preventive treatment.157

**Surgical treatment**

If all drugs are ineffective and a secondary cluster headache has been excluded, surgical treatment can be discussed with the patient. Surgical procedures should be considered with great caution because no reliable long-term observational data are available and because they can induce trigeminal neuralgia or anaesthesia dolorosa. Different methods have been suggested to prevent cluster headache: application of glycerol or local anaesthetics into the cisterna trigeminalis of the Gasserian ganglion;159 radiofrequency rhizotomy of the Gasserian ganglion160 or of the trigeminal nerve;161 microvascular de compression;162 and resection or blockade of the greater superficial petrosal nerve163 or of the ganglion sphenopalatinum.164 However, there are also case reports of the complete inefficacy of surgical treatment in cluster headache and related syndromes.164-166 In some cases, blockade of the greater occipital nerve was effective, and this approach may be tried before any other surgical procedure.167-168 In general, any surgical procedure on peripheral trigeminal structures in episodic cluster headache must be judged with great caution, as the nature of the disorder is to remit. On the other hand, in chronic cluster headache, there is strong evidence that even a complete trigeminal denervation is not effective.154 Deep brain stimulation of the posterior inferior hypothalamus has been shown to be effective in most of a sample of patients with intractable cluster headache.169-171 Recommendations for the selection of patients for this procedure have been published.172

**Prioritisation of preventive therapy**

Patients with chronic and long-lasting active periods of episodic cluster headache should be principally treated with verapamil. Because of the relatively long time required for increasing the dosages of verapamil until it takes effect, corticosteroids, ergotamine, or even triptans with a long half-life can be used as an effective initial prophylactic option. Methysergide or corticosteroids are the medication of choice in short-lasting active cluster periods (less than 2 months). Lithium and valproic acid are thought to be helpful, but only as second-line, therapy. When patients cannot tolerate standard medications, or these are contraindicated, combinations of other drugs should be explored. Corticosteroids should, if at all possible, be used only for short-term prophylaxis. Surgical procedures should be viewed with great caution; despite excellent results, even hypothalamic deep brain stimulation must be regarded as highly experimental.

**Unresolved issues and the future**

Why do cluster headache attacks start and, more importantly, why do they stop after a fairly defined period of time? What exactly causes the switch from inactive to active periods, and vice versa? The role of the human clock system implicates the suprachiasmatic nucleus and, consequently, photoperiod changes have been thought to be a crucial external factor. However, this theory implies that light therapy should work, whereas in my experience it does not. Moreover, melatonin has no effect, and in most patients the circadian rhythm is indeed stereotyped (highly homogeneous), whereas the annual rhythm is highly individual.

The relevance of the high proportion of smokers among patients with cluster headache is not known. In the active period, cluster headache is reliably triggered by alcohol, histamine, and nitrates,9 but the mechanism whereby these factors induce an attack is not understood. One common feature of histamine, alcohol, and nitrates is their vasodilating effect. Nitroglycerin is a pro-drug for nitric oxide, which can activate the trigeminal vascular system. However, recent data indicate that neither the vessels nor the peripheral part of the trigeminal system are needed in development of a full-blown attack.

The mechanism of the effectiveness of oxygen in treating cluster headache is not understood. Reductions in cerebral blood flow, cerebral vasoconstriction, activation of descending inhibitory neurons from the brainstem, and an abnormal chemoreceptor sensitivity in cluster headache have been suggested. Notably, none of the preventive medicines used in cluster headache are given on the basis of proven theoretical background their use is based on purely empirical evidence.

Deep brain stimulation of the hypothalamus is highly specific and successful in patients with intractable cluster headache. However, it is still highly experimental. How stimulation of an area that is thought to act as a pacemaker for acute cluster attacks can prevent these attacks is not known.

The past decade has seen remarkable progress toward unravelling the mystery of primary headache disorders.
Because cluster headache and trigeminal autonomic headaches are much less common than migraine, most funding for headache research goes into migraine. Consequently, we have excellent quality-of-life data and a fairly accurate neurobiological model for migraine, with substantial knowledge of the genetic basis and thorough data on peripheral and central pain modulation. This information has led to a highly specific acute treatment designed just for migraine, notably the triptans, which, incidentally, also work in cluster headache but not, for example, in tension type headache. Understanding the fascinating basis of a relapsing-remitting headache syndrome on the basis of a precise circadian and circannual mechanism will not only benefit patients, but will also help to unravel the physiological interaction between the internal biological clock and pain perception and control. Bearing in mind that the excruciating pain in cluster headache has led to it being coined a “suicide headache”, we need to accept the challenge.

Conflict of interest statement
I declare that I have no conflict of interest.

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References


The origin of bovine spongiform encephalopathy: the human prion disease hypothesis

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The cause of the original case or cases of bovine spongiform encephalopathy (BSE) remains an enigma. Sheep scrapie or a previously undetected sporadic bovine transmissible spongiform encephalopathy (TSE) have long been considered as candidates, but no convincing evidence to support these proposals has come to light. We present a new theory, with three related hypotheses: (1) that BSE was acquired from a human TSE (prion disease); (2) that the route of infection was oral, through animal feed containing imported mammalian raw materials contaminated with human remains; and (3) that the origin was the Indian subcontinent, from which large amounts of mammalian material were imported during the relevant time period. Human remains are known to be incorporated into meal made locally, and may still be entering exported material. Further investigations are needed into the sources of animal by-products used in animal feed manufacture, and into the transmissibility of human TSEs to cattle.

Transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative diseases that affect human beings and several other mammalian species. TSE pathogenesis involves the modification of a normal cellular protein, known as prion protein (PrPc), into a pathogenic form designated PrPSc or PrPres. TSEs can be genetically determined, acquired via TSE-infected material, or sporadic. No cattle TSE had ever been recognised until 1986 when the first case of BSE was reported in Britain. The incidence of the disease rapidly reached epidemic proportions,1 peaking in late 1992. More than 180 000 cases have been recorded in the UK. BSE has also subsequently been detected on a much smaller scale in 19 other European countries, Israel, Japan, and recently Canada and the USA. Exposure of cattle to the BSE agent had almost certainly begun by 1981, and unrecorded cases probably occurred before this year,2,4 in the 1970s or earlier.3

The emergence in 1995 of a new type of human TSE, now designated variant Creutzfeldt-Jakob disease (vCJD), led to the hypothesis that vCJD was probably a direct result of BSE transmission to man. More than 150 cases of vCJD have been diagnosed in the UK. There have also been four patients in Ireland, Canada, the USA, and Japan, who were potentially exposed in the USA, and a further nine patients in France and one in Italy for whom no infection in the UK could have occurred.

Most authorities agree that the main route of propagation of the BSE epidemic was via the recycling of contaminated remains of BSE-infected cattle in the manufacture of cattle feed.1,4,5 However, the source of the original bovine case or cases remains controversial. The cause could have been intrinsic (arising spontaneously in individual cattle) or extrinsic (acquired by transmission from another species; table).

An intrinsic event, the mechanism favoured by some experts,7 could have been a somatic or germ-line mutation of the prion protein gene PRNP, or a post-translational conversion of PrP to PrPSc (table). However, no genetic TSEs in cattle have ever been identified. A retrospective histopathological survey of cattle brains archived before 1985 found no evidence of earlier TSE cases to support the existence of a sporadic strain in cattle. In countries where BSE cases have been detected over several years, the incidence over time has generally shown a progressive rise or rise and fall,4 suggesting an acquired cause. Large-scale screening of cattle in different countries has brought to light the existence of bovine TSE strain variations4 that could be sporadic. However, it seems more likely that these cases were acquired.7 The atypical strains were found in about a quarter of the cases that were investigated, and it is unlikely that sporadic strains occurring with this frequency could have escaped detection before.

To investigate a possible extrinsic cause of BSE, two categories of evidence need to be considered (panel): potential exposure to infection, and strain similarities between the putative source TSE and BSE. The most widely favoured theory is that BSE originated from transmission of sheep scrapie to cattle.1 It is well known that sheep products were incorporated into cattle feed. However, there is no satisfactory explanation for why BSE did not appear earlier, since: scrapie has been endemic in Britain for at least 200 years; meat and bone meal containing sheep material had been fed to cattle for as long as 70 years;8 and scrapie infectivity must have entered cattle feed in substantial quantities. One proposal was that feed only became infectious after the phasing out in the 1960s to 1980s of a solvent extraction proposal was that feed only became infectious after the phasing out in the 1960s to 1980s of a solvent extraction phase during rendering. However, experimental studies have shown that solvent extraction makes little or no contribution to the modest reduction of scrapie (or BSE) infectivity produced by rendering.9

Support for the scrapie theory could come from identification of a scrapie strain similar to BSE (webtable). Different prion strains were originally defined on the basis of incubation periods and distribution of neuropathology (lesion profile) following transmission to selectively bred mice (conventional strain typing). Prion strains can also be distinguished by molecular analysis of PrPSc, which involves treatment
with proteinase K followed by western blotting of the resulting fragments. More than 270 scrapie cases archived before, during, and since the BSE epidemic have been tested using one of these methods, but no naturally occurring TSE in animals such as Bovidae, Felidae,\(^6\) or African antelope\(^7\) could have caused BSE have not been supported by evidence either of the occurrence of such TSEs at the relevant times and places, nor of incorporation of material from these species into cattle feed.

A causative event could have been facilitated by environmental or biological factors including organophosphate pesticides, high manganese or low copper levels in soil, and autoimmune factors (table). However, there is little experimental or epidemiological evidence to support these conditions as causative factors per se.\(^7\)

The existing theories of the origin of BSE all have significant weaknesses. We propose a new theory, that human TSE-contaminated material was the cause of BSE (hypothesis 1); that this was transmitted orally via animal feed (hypothesis 2); and that the infective material originated in the Indian subcontinent (hypothesis 3). As with any theory of an extrinsic cause, the evidence for potential exposure and for strain compatibility needs to be considered (panel).

### The human prion disease hypothesis

#### Potential exposure

In the 1960s and 1970s, the UK imported hundreds of thousands of tons of whole bones, crushed bones, and carcass parts containing soft tissue of mammalian origin\(^12\) to be used for fertiliser and for the manufacture of animal feed. Nearly 50% of these imports were from Bangladesh (until 1972 known as East Pakistan), India, or Pakistan. Imported materials were sometimes sold in their crude state for use as fertiliser, a largely unregulated industry. Material for production of animal feed, as well as low copper levels in soil, groundnut meal, and other potentially infective material, was used in the UK. This theory has been increasingly unlikely as no evidence has yet been obtained for the transmission of mammalian TSEs via either oral, intracerebral, or intramuscular routes. The evidence that (a) cattle are not susceptible to scrapie via the oral route; and (b) all of the scrapie strains studied show substantial differences from BSE, including the fact that scrapie is believed not to transmit to man, has been supported by evidence either of the occurrence of such TSEs at the relevant times and places, nor of incorporation of material from these species into cattle feed.
Hypothesis

Panel: Categories of evidence for extrinsic theories of BSE

1 Potential exposure
  1.1 Environmental route and geography of exposure
  1.2 Timing
  1.3 Portal of entry and exposure dose

2 Comparison of disease and strain characteristics
  2.1 Comparison of TSE in putative primary species with BSE in field cattle—ie, direct comparison of the diseases as far as possible in their "natural" state
  2.2 Experimental transmission from putative primary species to cattle
  2.3 Reverse transmission of cattle BSE to putative primary species
  2.4 Experimental transmission of putative source, and of BSE, to a tertiary species: mice transgenic for bovine PRNP
  2.5 Experimental transmission of putative source, and of BSE, to a tertiary species: other mouse lines or other species

*The disease and strain characteristics that may be important for comparisons between the two animals include incubation period; duration of illness; symptoms and signs; neuropathology; molecular analysis. The route of infection and dose can affect clinical features and neuropathology.

feed was supposed to be sterilised and might be subjected to further rendering. However, feed and fertiliser were often prepared by the same company, or by farmers themselves, and it became apparent to the authorities that material intended for use in fertiliser was being incorporated into animal feed. The poor controls governing the imports, and the lack of regulation within the countries of origin, particularly those outside Europe, were a source of concern in the UK in the 1960s because of the risk of anthrax and foot and mouth disease. There was no knowledge of any potential risk of transmitting prion disease.

In India and Pakistan, gathering large bones and carcasses from the land and from rivers has long been an important local trade for peasants. Collectors encounter considerable quantities of human as well as animal remains as a result of religious customs. Hindus believe that it is essential for their remains after death to be disposed of in a river, preferably the Ganges. The ideal is for the body to be burned, but most people cannot afford enough wood for full cremation, and simply smoking the pelvis in women or the thorax in men has symbolic importance. Many complete corpses are thrown into the river. The practice occurs on a huge scale. In the holy city of Varanasi on the Ganges, some 40,000 funeral ceremonies take place each year at two main sites in the city. In 2004, a group of volunteers campaigning to reduce pollution retrieved 60 human corpses in 2 days from a 10-km stretch of the Ganges.

The inclusion of human remains in material delivered to processing mills has been clearly described. It is highly likely that the incorporation of human remains into exported materials has occurred at least since the late 1950s and may still be continuing. Media reports exist from various countries of trade in human remains, including an account of the prosecution in 2001 of a dealer in Calcutta (on the Ganges delta) for exporting human bones to other parts of India, Pakistan, and the USA.

In the late 1960s, during an investigation of anthrax cases in dock workers in the French and Belgian ports on the English Channel, a port medical officer confirmed reports of human material in cargoes of mammalian by-products from the Indian subcontinent (Bézu F, personal communication). Following the publicity, an animal feed manufacturing company in the UK that made special use of a high-protein meal imported from the region became alarmed, and took the events seriously enough to re-organise its manufacturing facility (Hams F, personal communication).

Why should BSE have started in the UK rather than elsewhere? Several factors might be pertinent. First, the UK was a large recipient of animal by-products exported from India and Pakistan during the relevant period. For example, of Indian exports between 1967 and 1969, the UK received twice to six times the amount of any other destination country. Second, Britain was an international leader in research and in commercialisation of increasing milk production by feeding high protein meal to cattle. New sources of imports were actively sought, which would have increased the risk of human-TSE-contaminated meal being fed to cattle, and greater use of meat and bone meal derived from rendering UK bovine remains increased the likelihood of onward transmission from any primary cases infected by imports. Third, the UK was also a leader in the practice of feeding meat and bone meal to 1–2-week-old calves, which might have increased the likelihood of initial cases arising in the UK as well as contributing to propagation of the epidemic. Fourth, changes in rendering practices in the UK have been proposed as a factor facilitating the transmission of TSE infectivity, although experimental data suggest that the effect was small.

Little is known about the incidence and types of CJD in the Indian subcontinent. The first case of CJD reported in India was in 1965. Between 1968 and 1997, the Indian National CJD Registry recorded only 69 cases. However, in developing countries, underestimation inevitably occurs because of limited awareness of diagnostic features, shortage of investigatory facilities, a low autopsy rate, and a low reporting rate even when the disease is suspected. The combined incidence of sporadic CJD (sCJD) and familial CJD (fCJD) in India can be roughly estimated from data established in countries where thorough studies have been done. Assuming that the age-specific incidence of CJD in India is similar to that in these countries, we estimate that 150 cases per year would have occurred in India in the late 1960s to 1970s. 80% of the Indian population are Hindus, leading to an estimate of about 120 Hindu people dying from CJD per year.
year. A substantial proportion of the corpses would have been disposed of in rivers, particularly the Ganges, in the traditional manner.

What is the infectivity of a cadaver from a patient with CJD? There are no data about transmission of human infectivity to cattle, but it was possible to transmit human infection by intracerebral inoculation of human brain tissue into primates with as little as \(10^{-4}\) g of infective material.\(^7\) Compared with intracerebral inoculation, the oral route usually requires higher doses to achieve transmission, although exceptions occur.\(^2\) A conservative estimate is that a single infected human cadaver could contain about 300 times the ID\(_{50}\) for cattle, although we accept the limitations of this type of extrapolation.\(^9\)

Prions have legendary resistance to a range of processes that inactivate other types of agent\(^3\) as well as to natural decay.\(^2\) None of the natural processes to which a human cadaver may be subjected, nor partial cremation, would be expected to lead to a substantial reduction of prion infectivity. It was established during studies of the BSE epidemic in the 1980s that bovine prion infectivity could survive the whole chain of processes leading to the production of animal feed, including rendering,\(^5\) and the same reasoning applies to the persistence of human infectivity.

**Strain compatibility**

What type of human prion disease could have been the original cause of BSE? sCJD, fCJD, iatrogenic CJD (iCJD), and kuru existed before the BSE epidemic and are therefore candidates. The original source would be expected to show strain similarities to BSE, and to vCJD, which according to our hypothesis has arisen from reverse transmission. However, strain characteristics can change on transmission between species\(^4\) and on serial passage in the same species, so one would not expect to find an exact match of all characteristics. The available data are summarised in the webtable.

Although emphasis has been placed on the differences between the human TSEs (particularly between vCJD and sCJD), there are many overlapping clinical and neuropathological features.\(^10\) In fCJD, including Gerstmann-Sträussler-Scheinker syndrome and fatal familial insomnia, there is wide variation in clinical features, not only between but also within genotypes, many of which overlap with vCJD. The clinical features of all forms of CJD can be affected by polymorphisms at codon 129 of the PRNP gene, and this introduces further variation in the spectrum of clinical phenotypes. There is wide variation among the human TSEs in the local patterns, and distribution within the brain, of the key neuropathological findings of neuronal loss, gliosis, spongiform change and PrP deposition. So-called “florid plaques” of PrP staining were regarded as characteristic of vCJD but have been observed in iCJD and several animal prion diseases, and do not occur in BSE.

Conventional strain typing in a small number of cases of sporadic CJD showed marked differences from BSE and vCJD.\(^11\) However, transmission of Gerstmann-Sträussler-Scheinker syndrome to mice\(^17\) produced incubation periods close to those of vCJD,\(^14\) although different mouse lines were used for the different experiments. Results of molecular analysis of human and bovine tissue samples show that BSE-associated PrP\(^\text{Sc}^\text{BSE}\) shares its glycoform ratio with some types of fCJD (E200K and D178N), and has a low Mr-ngc (molecular mass of non-glycosylated component produced following partial digestion by proteinase K) similar to that in many cases of sCJD, kuru, and iCJD.\(^38\) It shares both these parameters with a subtype of fCJD (E200K-129V),\(^37\) which although rare could be a candidate for the origin of BSE.

Is vCJD the only phenotype that can result from transmission of BSE to man? Four lines of evidence suggest otherwise. First, every patient with clinical vCJD so far has been methionine homozygous at codon 129 (MM). However, one neurologically asymptomatic patient, heterozygous at codon 129, who had received a blood transfusion from a vCJD patient, was found after death from a ruptured aortic aneurysm to have evidence of PrP\(^\text{Sc}^\text{BSE}\) in lymphoid tissue.\(^5\) Future non-MM clinical cases might occur and could have a different phenotype. Second, experiments in transgenic mice show that transmission of BSE can produce a molecular analysis type typical of sporadic CJD.\(^19\) Third, the incidence of CJD of the sporadic type showed an abrupt two-fold increase in Switzerland in 2001, raising the possibility that the excess cases represented another human disease phenotype resulting from transmission of a bovine TSE to man.\(^40\) Fourth, the discovery of bovine TSE strain variation\(^14\) broadens the range of possible similarities between human and bovine TSEs.

**Discussion**

We have presented substantial circumstantial evidence that human material was imported into the UK with other animal remains used in the production of animal feed over a long period. The incidence of CJD indicates that, on a stochastic basis, infected cadavers would be amongst those remains from time to time. If cattle are susceptible to human TSE transmission by the oral route, it is plausible that these events could have transmitted disease to one or more cattle. Comparisons of human TSE and BSE strain characteristics show sufficient similarities to be consistent with our hypothesis, although the methodology is complex and data are limited.

From the earliest days of BSE, the possibilities of transmission from scrapie or of an intrinsic cause have been recognised. We argue that the paucity of
supporting evidence, despite ongoing attention, makes both these theories unlikely (table), and other possibilities need to be considered. We do not claim that our theory is proved, but it unquestionably warrants further investigation (webpanel).

Our first hypothesis, that BSE was acquired from a human TSE, is the most important. No attempts to transmit human TSEs to cattle have been made, and such experiments should be a priority for further research (webpanel). Further work is also needed on transmissions to mice that are transgenic for bovine PRNP, but there are too many uncertainties with such models to obviate the need for direct experimental work in cattle. The second hypothesis, that the route of transmission was oral via cattle feed, is not novel. However, it has proved very difficult to obtain detailed information about sources of raw materials and past feed-manufacturing practices; further investigation is still needed. Our third hypothesis, that the origin was the Indian subcontinent, is supported by several lines of evidence, but this and other possible geographical sources should also be investigated further. More research is needed into the types of human TSE occurring in India, other parts of the far east, and any other areas from which human remains may have been imported. An important question is whether some countries are still receiving imports of animal by-products contaminated with human remains. Some of these imports might be used for manufacture of animal feed, thus representing a potential route for new human-to-bovine transmission, and providing a possible explanation for the emergence of new strains of bovine TSE.

Both exporting and importing countries are likely to be sensitive to the implications of our hypotheses, and may feel pressurised to issue denials without adequate investigation. Within as well as between countries, it will be particularly important to establish cooperation between public health, agricultural, and industry organisations, as well as researchers, to try to ensure that further investigations are sufficiently thorough. WHO might be the best international body to coordinate this collaboration.

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Conflict of interest statement

We declare that we have no conflict of interest.

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End-of-life: Jewish perspectives

Elliot N Dorff

Foundations in beliefs and methods

Beliefs

Judaism’s positions on issues in health care stem from its fundamental convictions. Those relevant to the end of life include: the body belongs to God; human beings have both the permission and the obligation to heal; and, ultimately, human beings are mortal.

Doctor-patient relationship

Because the body belongs to God, Jews must seek both preventive and curative medical care and follow the expert’s advice in preserving their health. When several forms of therapy are medically legitimate but offer different benefits and burdens, the patient has the right to choose which regimen to follow, as long as it fits within the rubric of Jewish law. Patient autonomy has a smaller role in Jewish sources than in American secular ethics; in Jewish sources, the doctor has much more authority to determine the appropriate course of treatment. Even so, within medically acceptable bounds, the patient does have the right to choose (Bava Metzia 85b). On the other hand, patients do not have the right to demand of their doctor forms of treatment that, in the judgment of the clinician, are medically futile or unwise or that violate the doctor’s own understanding of Jewish law. That is, doctors just as much as patients are full partners in medical care.

Most patients will want to know the truth so that they can plan well and can feel that they exist in a safe respectful environment. Even with the worst prognosis, however, clinicians should spell out what the patient can still hope for, such as pain relief, reconciliation with family members, and other meaningful interactions and activities, including completion of an ethical will, in which the patient records on audiotape or videotape the family history and the patient’s values and hopes.

Role of the rabbi and the Jewish tradition

Because Orthodox and Conservative (Masorti) Jews—at least in theory and often in practice—believe that Jewish law is binding, they want to know and follow their rabbi’s interpretation of Jewish law in determining, for example, whether it is permissible to remove life support systems. The Reform movement, however, champions individual autonomy; Reform Jews might consult a rabbi, but the rabbi’s words will not be authoritative law but an individual’s advice—albeit an honoured individual with expertise in the Jewish tradition.

In addition to these religious differences, cultural factors can also have a role in who makes medical decisions and how. For example, Jews in different countries, generations, or family configurations can vary in how they approach the Jewish tradition generally and medical issues in particular. With respect to critical-care issues in particular, clinicians should ask patients whether they want to consult other family members or their rabbi when filling out an advance directive or in coming to a decision about what to do. When making a decision or giving advice about treatment, the rabbi will probably want to speak directly with the doctor to learn the patient’s medical condition and options so he or she knows how best to advise or serve the patient. In addition to sharing medical information, a doctor should indicate that he or she understands their Jewish concerns and views.

Death and dying

General ideas and categories

Because every person’s body belongs to God, a patient does not have the right either to commit suicide or to enlist the aid of others in the act, and anybody who does aid in this plan commits murder. The patient does have the right, however, to pray to God to permit death to come (RaN, B Nedarim 40a; the Talmud records such prayers: B Ketubbot 104a, B Bava Mezia 84a, and B Ta’anit 23a).

Jewish sources on withholding or withdrawing life-sustaining treatment are sparse. This lack of guidance poses important methodological questions as to how to apply the Jewish tradition to contemporary circumstances that are very different from the past. In general though, Judaism asserts that while we should seek to cure and may not do anything to hasten death, we should not prolong the dying process. Furthermore, we must always decide medical questions with the patient’s benefit as our goal (Tosafot, B Avodah Zarah 27b, sv, lehavyei sha’ah lo hyphen). Balancing these imperatives leads to considerable disagreement on specific clinical issues.

Determining death

The traditional criteria for death in Jewish sources are cessation of breathing and heartbeat; however, the practice was to wait some time after determining that these signs had occurred before beginning burial procedures (SA Yoreh De’ah 338). However, soon after the Harvard criteria for brain death became standard medical practice, Conservative rabbis accepted brain death (including the brainstem) as fulfilling the traditional criteria of cessation of breathing and heartbeat. In 1988, the Chief Rabbinate of the State of Israel approved heart transplantation from accident victims, thus accepting brain death as well, but this decision remains a matter of dispute among Orthodox rabbis. Authorities in the various movements are now assessing the apnoea test to determine death on the basis of...
cessation of respiration alone and the legitimacy of harvesting organs from non-heart-beating donors.

**Foregoing life-sustaining treatment**

The strictest position restricts permission to withdraw or withhold treatment to situations for which doctors assume that the patient will die within 72 h and has lost the swallowing reflex (a goses). Others define the state of goses more flexibly, such that the patient will live up to a year or more, or in terms of symptoms rather than time, and then they apply the permission to withdraw or withhold machines and drugs more broadly. In my legal opinion, approved by the Conservative Movement’s Committee on Jewish Law and Standards, I ruled that as soon as a person is diagnosed with incurable trauma to vital organs or a terminal, incurable disease (a terefah), patients and doctors have permission to withdraw or withhold drugs and machines if it is in the patient’s best interests. Because Jewish law presumes that human beings are not omniscient, doctors are not responsible for knowing what therapy may be developed tomorrow in making these decisions. In all cases, comfort care must be administered.

**Artificial nutrition and hydration**

Most Orthodox and some Conservative rabbis regard artificial nutrition and hydration as food and liquids, which we all need; therefore, even rabbis who allow removal of machines and drugs require these interventions. On the other hand, the nutrients that enter the body through tubes look exactly like drugs administered that way and, more to the point, they do not have the usual characteristics of food, such as varying temperature, taste, and texture. Consequently, in the opinion approved by the Conservative Movement’s Committee on Jewish Law and Standards, I classified the opinion approved by the Conservative Movement’s Committee on Jewish Law and Standards, I classified artificial nutrition and hydration as medicine. Thus, we can and should use them if there is any reasonable prospect for recovery, but when that is not likely, we should remove them, for then they are just prolonging the dying process.

**Heroic measures and advance directives**

As long as there is some hope of cure, heroic measures—that is, use of machines and drugs to try to keep a person alive when there is little hope that they will do that, let alone cure the patient—and untested drugs may be administered, even though this strategy involves an enhanced level of risk. On the other hand, these measures are not required. The controlling factors are the risk/benefit ratio, the patient’s best interests, and their desires. A Jew may sign an advance directive for health care indicating his or her desire to accept or decline such care; all four movements in American Judaism have produced their own versions of a Jewish advance directive, each according to its own understanding of Jewish law.

**Pain control and palliative care**

Most rabbis, including Orthodox ones, maintain that a Jew may enrol in a hospice programme, by which the goal is not to cure the disease but to make the patient as comfortable as possible. Patients may, however, choose to suffer some pain so they remain conscious. On the other hand, it is permissible to prescribe pain drugs that actually hasten the patient’s death, as long as the intent is not to kill the individual but rather to alleviate his or her pain. The Talmud specifically prohibits an action that will have two known effects, one permissible and one not; this is the principle of psik reisha (“can you cut off a chicken’s head and it not die?”). Reisner would, therefore, prohibit the use of an amount of morphine when there is any chance of it leading to death whereas I would permit the use of any amount to alleviate pain as long as it is not known that it will cause death. Moreover, hospice care crucially includes all non-medical ways in which people are supported when they go through crises, including all forms of care provided by family, friends, nurses, social workers, and rabbis.

**Autopsies and organ and tissue transplantation**

**General principles**

The treatment of autopsy and transplantation in Jewish law depends on two primary principles: kavod ha’met, that we should render honour to the dead body as God’s property; and pikkuah nefesh, the obligation to save people’s lives (B Sanhedrin 74a-b).

**Autopsies**

A 1949 agreement between the Chief Rabbinate of the State of Israel and Hadassah Hospital that was later adopted as Israeli law states that because autopsies represent an invasion of the body, which we should respect, they are not to be done routinely. They are sanctioned, however, when one of the following four conditions applies: (1) the autopsy is required by civil law; (2) in the opinion of three doctors, the cause of death cannot otherwise be ascertained; (3) three doctors attest that the autopsy might help save the lives of others with a similar illness; (4) undertaking the autopsy might safeguard surviving relatives from a hereditary disease.

Jews differ as to what medical needs justify an autopsy. People who undertake an autopsy must, in any case, do so with due reverence for the dead, and on its completion they must deliver the corpse and all of its parts to the burial society for interment. Under these conditions, the autopsy is construed not as a dishonour of the body, but, on the contrary, as an honourable use of the body to help the living.

**Living donors**

The command to save lives (pikkuah nefesh) makes it laudatory and, according to many rabbis, mandatory for all Jews who can donate blood with virtually no risk to
themselves to do so often. When the donor will endure days or possibly even weeks of pain and the loss of time on one’s job, as in bone-marrow donation, most rabbis would praise but not require such donation, but some see it as legally obligatory. When there is clear risk of injury to the donor, as in organ donation, although doctors nevertheless regard it as safe for the donor, most rabbis would permit Jews to undertake the risk but not see them as required to do so because our duty to preserve our own life and health supersedes our duty to help others (B Bava Metzia 62a). Clearly, these views represent different assessments of how to balance Judaism’s duties to preserve one’s own life and health with its duty to help others live. The probability of saving the recipient’s life must be substantially greater than the risk to the donor’s life or health.

Cadaveric donors
The default assumption is that a person would be honoured to help another live. Nevertheless, all authorities insist that the family must agree to use their loved one’s body for this reason, both to accord with US law and to assure that, even without burial, relatives of the deceased can effectively carry out the mourning process so that they can have psychological closure and return to their lives in full. Permission of the donor or their family must be procured so that the transplant does not constitute a theft. Feldman and Rosner say that the family’s permission is only advisable in Jewish law but it is mandatory in US law; that view, however, would make it religiously required of American Jews as well, under the Jewish legal principle that “the law of the land is the law” (Dina De-Malkhuta Dina; B Nedarim 28a, etc.).

Rabbis have different opinions about the circumstances under which organs may be transplanted. The strictest view would restrict donations to cases in which there is a specific patient before us (lefeinei neha) who is at risk of losing life or an entire physical faculty (eg, sight). Most rabbis, however, including Orthodox ones, would permit transplantation to restore full function—eg, a cornea for an individual with vision in only one eye. Donation to organ banks is permitted as long as the organ will eventually, but definitely, be used for transplantation. The Rabbinical Assembly, the organisation of Conservative rabbis, has gone further: its Committee on Jewish Law and Standards maintains that Jews have a positive duty to make their organs and tissues available for transplant, and in March, 1986, the Central Conference of American rabbis (Reform) officially affirmed the practice of organ donation.

Animal or artificial parts and organs
Animal or artificial parts—eg, porcine valves—and, if they prove viable, full organs may be used to save life and restore health. They do not have to be from a kosher animal because dietary laws apply only to eating and, contrary to Jehovah’s Witnesses, Jews do not consider xenografts to be the equivalent of eating. Moreover, even if they were regarded as food, saving a human life takes precedence over dietary laws. Thus, those Jews who choose to be vegetarian would nevertheless be obliged to use animal parts for medical reasons if such devices held the greatest promise for cure or saving life.

Donation of one’s body to science
Although rabbis disagree on this topic, most would agree with Israel’s chief rabbi Herzog, who—in the name of the Plenary Council of the Chief Rabbinate of Israel—stated in 1949 that one may make one’s body available to first-year medical students to study anatomy provided that the body parts are subsequently buried according to Jewish law. Conservative rabbi Isaac Klein argues further that if non-Jews are contributing their bodies for this reason, Jews must do so as well to avoid enmity toward Jews and Judaism. These arguments would not apply, however, if there are ample bodies available for dissection or if medical schools follow the example of the University of California, San Francisco, in using computer programs instead of corpses to teach anatomy, for without medical necessity one may not set aside the honour due a corpse to be properly buried.

Social support of the sick
Caring for an individual is not a matter of physical ministrations alone. The Jewish tradition, therefore, imposes the obligation of hiqur holim—visiting the sick. Jewish sources maintain that visitors should sit on the same plane as the patient, enable the patient to talk about the illness, ensure that a will has been prepared, engage the patient in discussion of the usual topics they share (politics, sports, etc), and pray with and for the patient. The Jewish tradition, then, obligates us not only to cure but also to care in fulfilment of the Torah’s commandment to “Love your neighbour as yourself” (Leviticus 19: 18).

Conflicts of interest statement
I declare that I have no conflict of interest.

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Fatal brain necrosis in primary HIV infection

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In November, 2004, a 31-year-old man was admitted to our hospital with a prominent morbilliform rash, pharyngitis, and a fever (40°C). He had been well until 2 weeks earlier, when he developed a fever, rash, and diarrhoea. HIV serology from 4 days earlier was negative. Neurological examination on admission was normal. However, 3 days later, he became lethargic and had a tonic-clonic seizure, necessitating intubation and mechanical ventilation. There was no evidence of hypoxia or hypotension. HIV screening tests done on admission were positive, indicating seroconversion. HIV western blot was indeterminate; p24 antigen was more than 200 pg/mL, plasma HIV-1 RNA was greater than 500 000 copies per mL, and peripheral blood lymphocytes were 4·6×10⁹/L, with 621 CD4-positive cells per μL, and 2759 CD8-positive cells per μL. CT of the brain without contrast was normal, and lumbar puncture showed 217 cells per mL (96% lymphocytes). Culture of blood and cerebrospinal fluid, serology, and PCR did not demonstrate active infection with herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, JC virus, Borrelia burgdorferi, Treponema pallidum, mycobacteria, other bacterial pathogens, fungi, or toxoplasma. Cerebrospinal fluid HIV-1 RNA was greater than 500 000 copies per mL. MRI of the brain showed massive diffuse cortical and laminar necrosis (figure). 6 days after admission, the western blot was positive for HIV-1, and p24 antigen had disappeared.

Despite treatment with zidovudine, lopinavir, efavirenz, and dexamethasone, the patient died 11 days after admission. At that point, plasma HIV-1 RNA had declined to 114 168 copies per mL, and peripheral blood showed 307 CD4-positive cells per μL and 407 CD8-positive cells per μL. Sequences of the HIV-1 reverse transcriptase and protease genes obtained from plasma and cerebrospinal fluid samples revealed no mutations associated with drug resistance and identified the strain as subtype B (accession numbers AJ889842, AJ889843, and AJ889844). At autopsy, the brain showed severe ischaemic neuronal damage, with widespread necrosis in both hemispheres, cerebellum, and brain stem. In the viable zones, discrete mixed perivenous infiltrates were present, with negative immunohistochemistry for CD20, CD3, CD4, CD8, CD68, and syndecan. There was no postmortem evidence of opportunistic infection.

The clinical syndrome of primary HIV infection was described 20 years ago.¹ CNS invasion by HIV-1 early in the course of infection is common and has been supported by many cerebrospinal fluid studies.³ Although one early report describes a fatal case of brain involvement during probable primary HIV infection, T-lymphocyte subset data was not reported.¹ HIV stimulates cytotoxic T-lymphocytes (CTL) responses in recently infected people. The CTL response initially follows the rise of HIV in the blood, and when that response reaches a peak the virus level falls.⁴ In our patient, brain necrosis coincided with the development of CD8-positive lymphocytosis and the disappearance of p24 antigen in the blood. Thus, CTL response rather than HIV virus infection itself may be the cause of brain necrosis; this could not be confirmed postmortem because of extensive necrosis and dexamethasone therapy. Recently, Markowitz et al reported rapid progression in a case of primary multidrug resistant HIV infection.⁵ Our case is a reminder that even in the absence of resistance mutations, HIV can rapidly kill.

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