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Stop killing people who kill people

According to Amnesty International, 128 countries and territories have abolished the death penalty in law or practice. 69 other countries retain capital punishment. Amnesty counted 22 countries known to have executed prisoners in 2005. In that year, at least 2148 people were executed, but this number is almost certainly an under-estimate. As is usual, most executions took place in a few countries: in 2005, 94% occurred in China, Iran, Saudi Arabia, and the USA.

But there are fresh moves at high levels to achieve a worldwide ban on the death penalty. Last week, UN Secretary General Ban Ki-Moon was in Brussels, Belgium, on his first overseas visit since taking office. Talking to reporters, he gave a cautious nod in the direction of a worldwide moratorium. “There is some growing tendency to see some phase out of the death penalty and I encourage that trend”, he said. Not exactly tough talk, but the death penalty is due to go back on the agenda at the UN, thanks to Italian Prime Minister Romano Prodi, who plans to lobby hard to get a UN-sanctioned moratorium. Ki-Moon was regaining ground after the execution of Saddam Hussein, when he had said it was for individual countries to decide on the use of capital punishment or not. It was that execution which had incensed Prodi to bring the issue back to the UN.

Even in the USA, support for capital punishment is waning. Last year, for the first time in the 20 years Gallup has been polling the US public, the proportion in support of life imprisonment without parole is one point over that voting for the death penalty (48% vs 47%). Shown graphically, the proportions have been converging for most of the polled years, but now the lines have crossed. Several factors are behind this trend. There is a growing recognition that the death penalty does nothing to deter crime and too often punishes the innocent. Since 1973, 123 people sentenced to death in the USA have been shown to be innocent. More recently, horrific reports on botched executions by lethal injection have raised concerns, even with long-time supporters of the death penalty.

The use of lethal injection is facing major legal challenges in the USA, as Leni Koniaris and colleagues describe in a Comment in today’s Lancet. After some recent badly mishandled executions by this method, several states have put the death penalty on hold. The Comment authors argue that the method cannot be “fixed”, as one judge is calling for, and that perfecting the method will need the involvement of doctors and scientists. They continue: “[Lethal injection] is an abominable perversion of the tools of healing. Participation by physicians and scientists in perfecting medical execution is morally wrong.”

Last year, Atul Gawande, journalist and physician, wrote a compelling paper about health professionals who participate in executions. He found four doctors and a nurse who would speak with him about their involvement, one later agreeing to be named publicly. Not all were unaware of the advice of their professional body to take no part. The latest edict from the American Medical Association is no involvement except for certifying death after someone else has pronounced it. Some had rather just drifted into their role, seeing it as almost community service and a type of terminal care. But as Gawande correctly points out, the condemned prisoner is not a patient. Although concluding that the people he interviewed took their moral duties seriously, Gawande added: “It is far from clear that a society that punishes its most evil murderers with life imprisonment is worse off than one that punishes them with death. But a society in which the government actively subverts core ethical principles of medical practice is patently worse off for it.”

The debate over capital punishment has reached a tipping point. Health professionals around the world should speak out now against execution, to use their influence to persuade the public and those in power that capital punishment is a cruel and senseless practice that has no place in the 21st century. A complete and worldwide refusal by doctors, nurses, and other health technicians to have any involvement would show that the tide of opinion has turned against capital punishment, a seachange that must not be stopped. The death penalty should be replaced by life imprisonment without parole, which would be good news for those later found innocent. Despite needlessly languishing on death row, at least they would have time to be exonerated. Put simply, ban the death penalty and there will be no ethical or moral conundrum for anyone. ■ The Lancet.

Resisting prescribing pressure for sildenafil

Last week was a bad week for pharmaceuticals giant Pfizer, which saw the company confirm 10 000 job losses. It was also hit with a lawsuit over its direct-to-consumer advertising of erectile dysfunction drug sildenafil. The AIDS Healthcare Foundation, a not-for-profit organisation, is suing Pfizer because it believes sildenafil has been marketed as a drug to enhance sexual performance rather than its licensed indication to treat erectile dysfunction.

This is not the first time Pfizer has been hauled up for its promotion of the drug. In 2004, the US Food and Drug Administration pulled two television advertisements for sildenafil because they did not disclose the risks associated with the product, failed to mention erectile dysfunction, and made unsubstantiated claims about the return of sexual desire in men taking the drug.

Such marketing suggests that sildenafil can benefit healthy men, as well as those with erectile dysfunction, thereby increasing demand for the drug. Doctors can guard against unnecessary requests for the drug by ensuring that physical examination, medical history, and diagnostic tests, if indicated, are carried out to confirm a diagnosis of erectile dysfunction.

In patients with erectile dysfunction, sildenafil—an oral phosphodiesterase type-5 inhibitor—is not the only drug treatment option. Two other drugs in this class, vardenafl and tadalafil, have been licensed for erectile dysfunction. All three drugs have similar efficacy and toxicity profiles but different durations of effect, so patient preference will come into play here. Although prescribing drug treatment can be easy and effective, addressing the possible underlying causes of erectile dysfunction should not be forgotten. Diabetes, heart disease, and hypertension, for example, increase the risk of erectile dysfunction. Optimum management of these conditions may therefore help patients.

Doctors cannot stop advertisement-driven demand for sildenafil but they can resist prescribing pressure by ensuring that proper diagnosis of erectile dysfunction always takes place. ■ The Lancet

When in doubt, disclose

When do a researcher’s financial or personal interests constitute a conflict that warrants disclosure? Financial interests are the easiest to recognise, but other interests can be more subtle. The desire to advance professionally or to defend an idea one believes in deeply can undermine objectivity as much as a financial stake.

The safest course is to identify and disclose any interest that could undermine the credibility of the research. The decision by Athena Kolbe not to disclose to The Lancet that she was the author of two papers cited in her article written under the pen name Lyn Duff opened her work to attacks that could have been, if not prevented, blunted by disclosure.

Could more explicit conflict of interest guidelines be of help to authors? Right now, guidelines vary from journal to journal and are constantly being revised, either because they are felt to be too strict or not strict enough. A more systematic approach may be in order.

A paper in the current issue of IRB: Ethics & Human Research describes one such approach. The paper presents model language for disclosing the financial interests of participants in clinical research. Surprisingly, few institutions have standard language for disclosing such conflicts. The model was developed by the Conflict of Interest Notification Study (COINS), a project funded by the US National Heart, Lung and Blood Institute.

Working with institutional review boards and conflict of interest committees, the COINS team identified nine major forms of financial conflicts of interest, including salary support, payment of finder’s fees, and the holding of a patent or ownership of equity. They then drew up draft disclosure statements that were not only reviewed by experts but also presented to potential research participants and focus groups. The responses were used to draw up a statement that could be adapted to suit different situations.

Their method was a thoughtful and systematic approach that could be adapted to draw up other models for conflict of interest statements, including, perhaps, one for publication. In the meantime, the best rule remains “when in doubt, disclose”. ■ The Lancet
Intuitive prosthetic limb control

Scientists developing neural interfaces hope to restore function to people with physical disability by harnessing imagery-related or movement-related neural signals from the brain to control an assistive device.1–3 After upper limb loss, the motor pathway—from brain to spinal cord to peripheral nerve—remains intact until the point of amputation, which allows another option: the use of signals from remnant motor nerves, whose action potentials otherwise go unheeded.

Rather than record from these nerves directly, Todd Kuiken and colleagues report in today’s Lancet12 their development of targeted motor reinnervation (TMR), in which the disconnected ends of peripheral nerves are reimplanted into proximal musculature. Contraction of these proximal muscles shows the intended activation of the missing distal muscles. When combined with a myoelectric prosthesis, a command in the CNS to open the hand travels through its usual peripheral nerves, is amplified by the associated patch of reinnervated muscle, and is detected by myoelectric sensors, which trigger the prosthetic hand to open. For the 25-year-old woman in this study, the new procedure enabled substantially better performance in functional movement tests than did her conventional myoelectric prosthesis. In the most important laboratory, the patient’s home, she reported using her TMR prosthesis for many hours a day—the ultimate compliment for a new technology and for its developers.

A prosthetic limb’s function is expected to improve with real-time sensory feedback. For example, the ability and decision to lift a coffee cup from the table to one’s mouth might depend on perception of the force applied to the cup, whether the cup is slipping, and perhaps its temperature. Pressure, slip, and temperature sensors could be placed within the fingers of the prosthetic limb and used to stimulate remnant sensory nerves via indwelling electrodes.13,14 In Kuiken and colleagues’ study, the reinsertion of deafferented sensory nerves into proximal skin patches yielded an alternative means to convey somatosensory signals back to the user. A new sensory map of part of the missing limb was formed on the chest wall which, when touched, transmitted neural signals back to the brain through axons that previously innervated the distal limb. With different sites on the chest wall yielding the sensation of different fingers being touched, one can imagine the use of haptic technology to transmit touch, temperature, and even joint position from a prosthetic limb back to the brain. Kuiken’s report, along with three previously successful TMR procedures also mentioned, suggest that amputees might be able to use natural movement commands to drive multiarticulate prosthetic limbs and receive back complex sensory information.

Challenges lie ahead. 5 or more months seem to be needed between TMR surgery and the use of a TMR prosthesis, to allow time for functional peripheral axon connections to be made with the new host skin and muscle. If direct nerve or cortical recordings were used to control the prosthetic limb, control could theoretically be achieved immediately after electrode implantation. Such direct neural recordings might also provide the finer resolutions of control that would be useful for dexterous manipulation. Although the results of targeted sensory reinnervation show the potential to convey a broad range of useful sensory modalities back to the user, the appropriate transducers still need to be incorporated into the prosthetic limb itself to make use of this option. Non-manipulated patches of skin could be used to receive these sensory inputs, and
one might simply learn the meanings of these stimuli. Further studies should identify what specific sensory information is most useful for functional tasks, and how signals from artificial sensors should be transformed into neural (or skin) activation patterns that are intuitively understood by the user. The general integrity of human motor cortical function\textsuperscript{11,12} and sensory perception\textsuperscript{12} after deafferentation and de-orientation are interesting to try to reconcile with detailed studies of sensorimotor plasticity.\textsuperscript{15–18} The tenets shown in these plasticity studies could both challenge and motivate different techniques for restoring sensory and motor function. These initial reports of targeted reinnervation are an important step forward in the seamless integration of replacement limbs into the body. Progress here should inspire a surge of research in high-density recording and stimulation interfaces, micro-electro-mechanical systems, microscale implanted wireless systems, optimum signal extraction and processing methods, osteointegration, and methods of reinforcing beneficial sensorimotor cortical representations while preventing aberrant pain signals.\textsuperscript{19} As these fields of biology and technology come together, disability because of amputation could someday be greatly reduced, and perhaps eliminated. Technologies developed for prosthetic limb applications will also benefit people with paralysis from injury\textsuperscript{20} or neurological disease, and will move the field closer to a neurotechnology-enabled restoration of movement and sensation.

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Haemoglobin targets: we were wrong, time to move on

Anaemia occurs in nearly all patients with moderate-to-severe chronic kidney disease. The most widely used treatment options are erythropoiesis-stimulating agents (eg, Epogen, Procrit, and Aranesp), with an economic burden of US$10 billion in sales worldwide in 2006, and $2 billion Medicare expenditure for dialysis patients in 2006 in the USA alone.\textsuperscript{1} Administration of erythropoietin rapidly increases haemoglobin
concentrations in most patients with chronic kidney disease. Observational studies have shown that increased concentrations of haemoglobin are associated with improved quality of life and survival in chronic kidney disease.\textsuperscript{2} Notwithstanding the widely accepted benefits of proper management of anaemia in chronic kidney disease, debate has raged about the optimum haemoglobin target concentrations. This uncertainty has been a dominant theme in nephrology research and practice since the US Food and Drug Administration licensed synthetic erythropoietin in 1989, on the basis of little controlled data and with almost exclusive emphasis on quality of life, a surrogate endpoint.\textsuperscript{3} For almost 20 years, there have been debates on anaemia in general, and haemoglobin targets in particular, which have been a major topic in nephrology journals and meetings worldwide, seemingly disproportionate to the clinical importance of the topic and the quantity of valid data from controlled trials in the context of other major themes in nephrology research. These debates, based mainly on observational data, have supported the coincidence of normalisation or optimisation of haemoglobin with the concept of increasing concentrations to a maximum, and suggested survival advantages, even though trials and meta-analyses clearly pointed in the opposite direction.\textsuperscript{4}

In today’s *Lancet*, Arintaya Phrommintikul and colleagues present a meta-analysis which brings an expected end to a somewhat artificially delayed story. Their meta-analysis includes nine randomised trials that have compared different target haemoglobin concentrations in more than 5000 patients.\textsuperscript{5} By contrast with prevailing beliefs, observational data, and what would be commercially advantageous, all outcomes in their analysis favoured lower, rather than higher, haemoglobin target concentrations. All-cause mortality was increased by about 20%, arteriovenous access thrombosis by 30%, and poorly controlled blood pressure by 30% (all in relative terms) in individuals in the higher haemoglobin target group compared with those in the lower target group. A forest plot of trials that reported a composite outcome of major cardiovascular events confirms that the mechanism for increased mortality is via serious cardiovascular events, which are increased, also by about 30%, in the higher target group and independent of kidney disease stage (predialysis vs dialysis, interaction p=0.95; figure). In absolute terms, for every 100 patients randomised to a higher haemoglobin target concentration, about 12 more patients developed a serious cardiovascular event, compared with those assigned a lower target. These findings are consistent with earlier meta-analyses, but have been strengthened with the inclusion of two new large-scale trials (n=2035, which is about 40% of patients randomised in haemoglobin trials to date) published on Nov 16, 2006, in the *New England Journal of Medicine* (NEJM): the Correction of Hemoglobin and Outcomes In Renal insufficiency (CHOIR) trial,\textsuperscript{6} done in the USA, and the Cardiovascular Risk reduction by Early Anemia Treatment with Epoetin beta (CREATE) trial, done in Europe, Asia, and Mexico.\textsuperscript{7}

**CHOIR**\textsuperscript{6} \hspace{1cm} \textsuperscript{CREATE}\textsuperscript{7} \hspace{1cm} Besarab et al\textsuperscript{8} \hspace{1cm} Overall

<table>
<thead>
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<th></th>
<th>High haemoglobin (n/N)</th>
<th>Low haemoglobin (n/N)</th>
<th>RR (95% CI)</th>
<th>Weight (%)</th>
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<td>CHOIR\textsuperscript{6}</td>
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<td>31.46</td>
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<td>47/302</td>
<td>1.24 (0.87-1.76)</td>
<td>15.22</td>
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<tr>
<td>Besarab et al\textsuperscript{8}</td>
<td>202/618</td>
<td>164/625</td>
<td>1.23 (1.03-1.48)</td>
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<tr>
<td>Overall</td>
<td>385/1634</td>
<td>308/1632</td>
<td>1.25 (1.09-1.42)</td>
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</tr>
</tbody>
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Test for heterogeneity: $\chi^2=0.11$, df=2 ($p=0.95$), $I^2=0$

Test for overall effect: $Z=3.30$ ($p=0.0010$)

**Figure:** Effects of different haemoglobin target concentrations on serious cardiovascular events

RR=relative risk.

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on a composite primary endpoint (death, myocardial infarction, hospitalisation for congestive heart failure, and stroke) were measured, and a significantly increased risk of this endpoint was found with the higher haemoglobin target compared with the lower target (hazard ratio [HR] 1.34, 95% CI 1.03–1.74). CREATE randomly assigned 603 patients with chronic kidney disease (glomerular filtration rate 15–35 mL/min per 1.73 m²) to a haemoglobin target of 130–150 g/L or of 105–115 g/L, and measured the effect of these interventions on a composite primary endpoint (time to first cardiovascular event, sudden death, myocardial infarction, acute heart failure, stroke, transient ischaemic attack, angina pectoris resulting in hospitalisation for 24 h or more or prolongation of hospitalisation, complication of peripheral vascular disease, or cardiac arrhythmia resulting in hospitalisation for 24 h or more). No significant difference in the likelihood of a first cardiovascular event was found between the groups, but the point estimate favoured the lower haemoglobin target (HR 0.78, 95% CI 0.53–1.14) and the CI were compatible with a 47% reduction and up to a 14% increase in the risk with the higher haemoglobin target. Furthermore, contrary to the secondary hypothesis of the study, end-stage kidney disease requiring renal replacement therapy occurred more often in the higher haemoglobin target group than it did in the lower target group (111 patients starting dialysis in the lower group vs 127 in the higher group, p=0.03). The dramatic increase found in the risk of several patient-level endpoints with higher compared with lower haemoglobin targets in chronic kidney disease is entirely consistent with the results of earlier trials. Surprisingly, faced with the coherence of all the available evidence, many try to downplay these key findings and their response indicates strongly held beliefs discordant with what is now a sizeable and consistent body of evidence that higher haemoglobin targets are not better than lower. In the accompanying editorial to CHOIR and CREATE, the authors stated that: “taken together, these two studies suggest caution in the full correction of anemia in patients with chronic kidney disease. Currently, there are several additional multicenter trials of complete as compared with partial correction of anemia in patients with chronic kidney disease.” How are clinicians, researchers, and ethics committees going to interpret “caution”? On Dec 23, 2006, The Lancet published a Comment by Robert Steinbrook that was much stronger than the NEJM editorial, stating that, “on the basis of available data, the maintenance of haemoglobin concentrations above 130 g/L appears to be unsafe in patients with chronic renal failure”, and “although ongoing trials will provide more information, results are not imminent”. It is remarkable that a clearer reaction came from outside, published in the Wall Street Journal, indicating that Steinbrook submitted his comment to the NEJM to accompany the publication of CHOIR and CREATE, but this was rejected in favour of a “less critical” piece written by a deputy editor and a member of the editorial board. David Armstrong of the Wall Street Journal, in view of the economic implications, called into question an obvious protagonist: the articulation of conflicts of interest. Debates about conflicts of interest are at best partly informed. The fundamental questions now are what targets should be aimed for by patients and clinicians, and whether there is sufficient equipoise to justify ongoing lower versus higher haemoglobin trials. Other editorials, commentaries, and reviews have been published since the results of CREATE and CHOIR were made available in a preliminary form, before full publication of the trial results. All focus on the existing burden of cardiovascular disease in chronic kidney disease and the need for aggressive management of cardiovascular risk factors, including...
treatment of anaemia, rather than emphasising the observed results of published trials, which collectively show a net clinical harm of targeting higher haemoglobin concentrations. This harm was initially identified nearly 10 years ago by Anatole Besarab and colleagues in the first large-scale trial of haemoglobin targets in dialysis. Patients at highest cardiovascular risk were chosen, to increase the likelihood that a beneficial effect would be found, but mortality was higher in the normal haemoglobin target group. Incidentally, similar findings have also been reported in trials in cancer patients, in whom larger erythropoietin doses have been used; several of these trials were stopped early because of unexpectedly higher mortality in the higher haemoglobin target groups. Rather than conclude that the findings of Besarab and co-workers could reasonably be extrapolated to patients at lower cardiovascular risk, trialists, guideline writers, and experts postulated an implausible qualitative effect interaction produced by pre-existing cardiac disease, even though this type of interaction is exceedingly rare in epidemiological studies. Higher targets have been advocated in routine practice, but some uncertainty has been explicitly acknowledged and additional trials have been done. Now completed, these trials have only confirmed the findings of the first trial, despite being done in a different group (in patients with stage 3 and 4 chronic kidney disease). There are over 5000 patients enrolled in multiple large (and smaller) randomised trials of haemoglobin targets reporting mortality and cardiovascular endpoints, and which consistently favour a lower haemoglobin target of around 100–115 g/L and in which the clinical bottom line is clear.

Why do some still recommend the continuation of existing trials of haemoglobin targets? What justification could there be for ethics committees, and for the relevant steering committees and data and safety monitoring committees, to continue randomisation or treatment in haemoglobin target trials? One such trial is the Trial to Reduce cardiovascular Events with Aranesp Therapy (TREAT), due to enrol about 4000 patients, randomised to achieve a target haemoglobin concentration of 130 g/L (or ≥90 g/L) with darbepoetin alfa therapy versus a haemoglobin target of less than 90 g/L. Given existing published trial data, how can clinicians entering or continuing to treat patients in this trial be uncertain as to which arm will confer net benefit?

With excess mortality and cardiovascular risk with higher haemoglobin target concentrations, quality-of-life benefits have been consistently promulgated in support of normalisation of haemoglobin target concentrations in chronic kidney disease. Such claims have not been supported by good quality evidence, as we have outlined in detail. Unvalidated scales, and selective reporting of outcomes (eg, some but not all domains, time points, and patients) have been major and consistent methodological pitfalls, perpetuated by CREATE, and weaken the claim of quality-of-life benefit with complete normalisation.

On the basis of the existing published trials, summarised by Phrommintikul and colleagues, we contend that more trials of haemoglobin target concentrations in patients with chronic kidney disease are no longer required, should be stopped, or at least it should be made fully and publicly explicit what reasons grant their continuation. We say this because of the rights of patients, and the credibility of the scientific nephrological community, after such a long history of contradictions. The question has been answered: higher haemoglobin target concentrations increase mortality via cardiovascular endpoints. Part rather than complete correction of anaemia is appropriate, although commercially less attractive, and it is time to move on. A serious reconsideration of the rationale and of the relevance of ongoing studies is necessary, because the effects of erythropoiesis-stimulating agents are not fully understood. Not only do they increase haemoglobin concentrations, but they also might act through alternative dose-dependent pathways that could be harmful. Doing trials of target haemoglobin concentrations, rather than of fixed or maximum dose, could mean that at-risk, relatively unresponsive patients are receiving harmful doses of erythropoiesis-stimulating agents. A trial of different erythropoietin doses administered to patients with chronic kidney disease, independent of haemoglobin target concentrations achieved, could be done to test whether dose (rather than haemoglobin concentration) is what really matters. Redrafting the scenario of the optimum roles of anaemia control is now in the hands of independent trials, sponsored by investigators and with public health (rather than haemoglobin or increased use of erythropoietins) as a target.
Sexuality in chronic illness: no longer ignored

Even though many diseases and their treatments impair sexual function, medical publications often omit sexual issues. However, national probability samples and clinical studies from many countries confirm that most men and women regard sexual wellbeing as centrally important. The majority of 480 men made paraplegic by spinal-cord injury confirmed that regaining sexual function was their major priority. That sexual function is a legitimate aspect of medicine is shown in the draft working definition of the WHO declaration of sexual rights in 2002. “Sexual rights...include the right of all individuals...to (achieve) the highest attainable standard of sexual health...and to pursue a satisfying, safe and pleasurable sexual life.”

Being invited to edit and coauthor a series on sexual medicine is a welcome honour: I had a long-term dream of submitting six papers (the ultimate sextet) to the *Lancet*. Instead, today’s *Lancet* sees the first of three papers: sexual sequelae of common chronic diseases will be followed by reviews on sexual repercussions of endocrine disorders and neurological disorders. All three papers give examples of increased prevalence of sexual dysfunction with comorbid depression. Interdisciplinary fields such as psychoneuroendocrinology confirm that matters of the mind greatly modulate immunological, neurological, and endocrinological systems. Improved mental state from regained satisfactory sexual life might well ameliorate the conditions we seek to treat.

Sexual dysfunction may herald serious underlying disease. Increasing data indicate that generalised erectile dysfunction—in sleep, during self-stimulation, or during partner interaction—could signify generalised endothelial dysfunction and be regarded as a marker of asymptomatic coronary-artery disease.

The series emphasises the need to address iatrogenic sexual dysfunctions, including those from non-nerve-
sparing pelvic surgeries, chemotherapy, and other treatments. Understanding sexual response cycles in men and women allows us as physicians to recognize and assess the interruption of sexual response caused by therapeutic interventions or by the disease, and to provide the needed assistance. Assessment and therapy can be guided by current sex research. Psychophysiological measures of genital congestion, functional brain imaging, and corresponding data of subjective arousal from sexual stimulation have given some understanding to the complexities of sexual arousal (and its absence), and to important differences between the sexes. Examples of treatment to medically augment a damaged sexual response include phosphodiesterase inhibition to reverse male sexual dysfunctions of erection, desire, and ejaculation induced by selective serotonergic reuptake inhibitors; and local oestrogen treatment to lessen vulvar vaginal atrophy from severe oestrogen depletion associated with aromatase antagonism in survivors of breast cancer.

Some forms of sexual dysfunction are common. Pain on every occasion of intercourse is experienced by 14–40% of women and is thus more prevalent than erectile dysfunction in individuals younger than 50 years. However, the prevalence of chronic dyspareunia in sub-Saharan African countries and parts of the Middle East and south Asia due to genital mutilation is unknown: the clinical impression is that it affects the majority. Although the most common cause of dyspareunia in North America and Europe (ie, vulvar vestibulitis) is being investigated for its genetic, neurological, psychological, and endocrinological components, our ability to change the attitudes and beliefs underlying the practice of genital mutilation seems to be a daunting challenge. Moreover, these women are not free to choose non-penetrative sex.

Areas of uncertainty include the safety and efficacy of supplemental testosterone and oestrogen. Improvements in sexual desire, nocturnal erections, and ejaculation from testosterone supplementation are unquestionable in younger hypogonadal men. However, the physiological reduction in testosterone in ageing men is not associated with any precise sexual syndrome or with clear evidence of sexual benefit from supplementation.3 All women cease to make ovarian oestrogen by midlife, and yet dyspareunia from vulval atrophy is by no means universal. Genetic polymorphisms of steriodogenic enzymes might clarify subgroups of women at risk for various sexual dysfunctions on the basis of low activity of oestrogen and testosterone. These sex hormones continue to be produced intracellularly from precursor hormones, including androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulphate. Long-term safety of oestrogen started at menopause in sexually symptomatic women remains unclear, but observational, cohort, and case-controlled studies that do not focus on asymptomatic women are encouraging.5 By contrast, no data exist for the long-term safety of concomitant treatment with transdermal testosterone, soon to be approved for women with past bilateral oophorectomy; however, the reduced androgen activity is permanent. Off-label use will lead to many women with natural menopause being supplemented with testosterone before adequate safety and efficacy data warrant such use. In view of the non-correlation between sexual function and serum androgen in women,3 who should receive supplementation is unclear. Although androgen deficiency for women cannot be defined by serum concentrations of androgens or their precursors, measurement of serum androgen metabolites might yet uncover a deficiency.12

However, matters could be more complex: genetic polymorphisms of the genes encoding the androgen receptor and various androgen coregulators might have to be investigated to truly define any androgen deficiency state. Moreover, these various markers of androgen activity should be investigated in women with and without diagnosed sexual dysfunction. To control for the many psychosocial factors known to greatly affect sexual function will be challenging.

In the foreseeable future, we could have new, sexually neutral antidepressants and selective modulators for oestrogen receptors that possess needed genital oestrogen action. More widespread use of nerve-sparing surgeries for pelvic cancer might be possible. Using plastination methods to preserve dissections, pelvic surgeons at the Leiden University Medical Centre are being taught autonomic nerve-sparing techniques by one of the series authors.4

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After months of intensive investigation, US District Court Judge Jeremy Fogel recently concluded that California’s “implementation of lethal injection is broken”, creating “an undue and unnecessary risk that an inmate will suffer pain so extreme that it offends the Eighth Amendment”. Fogel identified “critical deficiencies”, including unreliable screening of members of the execution team, lack of meaningful training and supervision, unreliable record-keeping, improper preparation and administration of the anaesthetic thiopental, and inadequate and poorly designed facilities. He suggested that such procedural deficiencies could have been responsible for the botched California execution of Robert Lee Massie, who the state’s expert witness admits “may well have been awake when he was injected with potassium chloride”.

California is not alone in either reconsidering the death penalty or discovering problems with its implementation. The death penalty is currently on hold in 11 US states. Illinois and New Jersey are debating the death penalty itself. The others, Arkansas, California, Delaware, Florida, Maryland, Missouri, North Carolina, Ohio, and South Dakota, are evaluating the method of lethal injection. Missouri executions have been halted partly because the individual in charge admitted to possessing no written protocol and to halving the dose of anaesthesia. Recently, in Florida, technical ineptitude prolonged the execution of Angel Diaz. Diaz was awake and apparently speaking 24 min after the first injection, and was finally declared dead after 34 min and two sets of injections. 30 cm chemical burns in both antecubital fossae were found at autopsy, which prompted the medical examiner to conclude that the intravenous lines were misplaced and the drugs were delivered subcutaneously. Although state officials did not comment on whether he suffered, Diaz probably experienced extreme pain and progressive paralysis, ultimately succumbing to suffocation. Executions continue in other states, although similar deficiencies in training and implementation have been identified. For example, Alabama executioners indicated their intent to establish intravenous access in non-existent vessels, citing the “external carotid vein” and the “saphenous vein in the arm”.

Such examples of bungled executions and ill-trained execution teams are evidence that unrecognised suffering in lethal injection can occur due to inadequate anaesthesia, as previously reported. Rather than the
clean, clinical procedures they mimic, lethal injections are furtive affairs, characterised by the slipshod efforts of poorly trained personnel, with no monitoring for anaesthesia and no expert review. Even so, Judge Fogel and others have determined that lethal injection “can be fixed” and quickly.1 Fogel ordered California to conduct a thorough review of the protocol, ensure that a sufficient dose of anaesthetic reaches the inmate, and justify the use of the three-drug cocktail when an overdose of anaesthetic could suffice. If California fails to respond adequately, the judge will rule lethal injection unconstitutional. 2 days after Diaz’s execution, the Governor’s office has indicated it will issue a report by May 15, 2007, and has requested that deliberations be done in secret.4 In Florida, Governor Jeb Bush created a Commission on Administration of Lethal Injection to provide recommendations on changing the protocol by March 1, specifying that the commission reflect a cross-section of the legal, corrections, medical, and scientific communities.9,10 US District Judge Fernando Gaitan Jr ordered that Missouri executions could proceed if board-certified anaesthesiologists were enlisted to assure anaesthesia.11

Implicitly and explicitly then, Judges Fogel and Gaitan and Governor Bush have ordered that medical and scientific experts should evaluate and perfect lethal injection. (Indeed, three physicians have already been named to the Florida panel.) As death-row challenges mount, others will probably follow suit and forcibly extend the long dark history of expert involvement in execution. Guillotin, a noted French physician of his time, is now best known for his instrument of death. Thomas Edison aided a committee of physicians and a dentist in the creation and implementation of the electric chair. Physicians were directly responsible for the development of lethal injections and gas chambers used by the Nazis.12 Physicians recommended the current lethal injection protocol and some participate actively in executions.31,14 Except for the Nazis, those involved invariably believed they were “fixing” the process and rendering execution more humane. The condemned are often society’s worst and most brutal members who have sometimes murdered precious and vulnerable people. Without debating the death penalty itself, however, we believe that lethal injection cannot be “fixed”. It is an abominable perversion of the tools of healing. Participation by physicians and scientists in perfecting medical execution is morally wrong.13 Judicial or executive commandeering of medical tools and personnel to kill is also wrong. The expertise of doctors and biomedical researchers was developed by individuals, institutions, and science dedicated to saving and improving human lives. Appropriating that knowledge to kill is an appalling betrayal of the core values of medical research.

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Population growth and the Millennium Development Goals

Return of the Population Growth Factor: its impact on the Millennium Development Goals, a report of hearings held in the UK Parliament in 2006, focuses on the devastating impact of population growth on the Millennium Development Goals (MDGs). The report was released on Jan 31. The Inquiry Chairman, Richard Ottaway, Member of Parliament (MP), concludes: “The evidence is overwhelming: the MDGs are difficult or impossible to achieve with the current levels of population growth in the least developed countries and regions.”

Experts from around the world who testified to the hearings described the beneficial effects of slowing rapid population growth, as did Cleland and colleagues recently in The Lancet. Slower population growth permits greater investment in education and health, helping to lift nations out of poverty (MDG 1). By contrast, high birth rates in sub-Saharan Africa have helped increase the number living in extreme poverty from 231 million in 1990 to 318 million in 2001. In Ethiopia, 8 million people already live on permanent food aid, and the projected population growth from 75 million today to 145 million in 2050 presents an insurmountable challenge. Rapid population growth has a detrimental effect on the hope of achieving universal primary education by 2015 (MDG 2). Girls in large families are less likely to begin school and more likely to drop out early. The UK Department for International Development (DfID) sees “The ability of women to control their own fertility [as] absolutely fundamental to women’s empowerment and equality” (MDG 3).

Given the same level of health care, a child born less than 18 months after an older sibling has three times the death rate of a baby born after an interval of 36 months (MDG 4). An estimated 35% of all maternal deaths could be forestalled by simply preventing unintended births (MDG 5). For HIV/AIDS (MDG 6), many unintended pregnancies occur in women who are HIV-positive, and improved access to family planning is the most cost-effective way of preventing vertical transmission. Rapid population growth is a counterforce against environmental conservation (MDG 7). Consumption in the developed world contributes enormously to global ecological problems, but rapid population growth in developing countries also leads directly to deforestation, land degradation, and threats to water quality.

Some past population policies were coercive and Christine McCafferty, MP, Chair of the All Party Parliamentary Group on Population, Development and Reproductive Health, which sponsored the hearings, emphasises that possible solutions must be framed in a “human rights perspective”. The need for family planning must be met among the estimated 125–200 million women around the world who would like to limit or space their childbearing but are not using contraception. Return of the Population Growth Factor calls for much greater investment in international family planning, and stresses the critical importance of breaking down the many barriers to contraceptive use that are based not on medical evidence but on cultural beliefs, prejudices, and assumptions. In Kenya, for example, the poorest economic quintile has more than twice the total fertility rate. However, while this quintile have less than one-third of the contraceptive use of the richest, it also has almost three times the unmet need for family planning, which suggests that this group finds it difficult to access modern contraception (figure).

Currently, there are serious shortages of contraceptives and Parliamentarians at the hearing were interested to hear Dr Baige Zhao, Vice Minister of China’s National Population and Family Planning Commission, mention China’s willingness to share contraceptive commodities with developing countries.

In the next 50 years, global population will grow by another 1.5–4.5 billion people. In 1994, the Cairo Programme of Action concluded that “even the
difference of a single decade in the transition to stabilization levels of fertility can have a considerable positive impact on quality of life”.

Tragically, a decade of potential progress has been lost, and today the international family-planning budget is only 10% of that projected in 1994 as necessary in 2005. *Return of the Population Growth Factor* documents why the donor community must once again place population and family planning at the centre of global efforts to fight poverty, improve education and health, and attain a humane standard of living for everyone.

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We were both oral witnesses at the Parliamentary hearings.


**Clarification: Human rights abuse and other criminal violations in Port-au-Prince, Haiti**

*Human rights abuse and other criminal violations in Port-au-Prince, Haiti: a random survey of households* was published online on Aug 31, 2006, and in print on Sept 2, 2006. Within days, *The Lancet* was informed that co-author Athena Kolbe had previously written about Haiti as a journalist under the name of Lyn Duff. Because Kolbe had worked as a volunteer at an orphanage in Haiti founded by President Aristide and had written sympathetically about Aristide after he was deposed, concerns were expressed about the paper’s findings.

In response to credible allegations that one author’s former activities might constitute an undisclosed conflict of interest, *The Lancet* began an inquiry. The authors’ institution, Wayne State University (Detroit, Michigan, USA) was asked to investigate the matter, and the issue was referred to the Committee on Publication Ethics (COPE).

Eileen Trzcinski, Professor and Interim Director of Research at Wayne State University School of Social Work, audited 100 questionnaires selected by computerised randomisation. Outcome details on the original handwritten records corresponded with the project’s computerised database. The overall distribution of rapes and murders were re-analysed according to alleged perpetrators, and the results agreed with the published findings. Outcomes were then compared by political affiliation of the interviewer and for Kolbe’s own data (as an interviewer). Again, there was no evidence of systematic bias. On the basis of this investigation, *The Lancet* has confidence in Kolbe and Hutson’s findings as published.

The printed journal includes an image merely for illustration.
COPE recommended that readers should be made aware that Athena Kolbe had published as a reporter under the name of Lyn Duff, and that failure to disclose a separate name, under which relevant material had been published and cited in her Lancet paper, constitutes an undeclared conflict of interest. The Lancet’s position on transparent disclosure of potential conflicts of interest is in accordance with guidelines established by the International Committee of Medical Journal Editors.1 The Lancet has made this position prominently available to readers and to authors,6 and stated clearly that incomplete disclosures will be amended in a published statement in the Department of Error section, which will also be linked electronically to the publication in electronic databases. Such a correction for this study appears in today’s Lancet.

To realise their full potential to benefit populations, research findings must influence practice. Intelligent debate is part of that process. The Lancet encourages genuine debate, and will always consider seriously allegations of scientific misconduct. It is unfortunate, however, that in this case much of the debate was aimed at exploiting historical divisions in Haiti. That process has obscured the message of Kolbe and Hutson’s research and detracted from the real issue—the welfare of civilians in Haiti—to whom attention should now turn.

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Cancer—a call for papers

Cancers of the lung, breast, bowel, stomach, prostate, and liver account for more than 50% of all oncology diagnoses: in 2002, about 5·8 million people worldwide were diagnosed with one of these six cancers and 3·6 million people died as a result of their disease.3 Despite improvements in prevention, screening, early diagnosis, and treatment, cancer burden is expected to increase substantially in the future because of a rapidly ageing population. The Lancet and The Lancet Oncology are therefore issuing a joint call for papers that address these six diseases. We are specifically interested in the results of randomised controlled trials and other original clinical studies that will have a profound effect on clinical practice. Accepted papers will be published, at our discretion, in either The Lancet or The Lancet Oncology, and publication will coincide with the annual meeting of the American Society of Clinical Oncology (ASCO), due to be held in Chicago, IL, USA, on June 1–5, 2007. Published articles will be made freely available at the ASCO meeting, and we are therefore especially interested in research that will be presented at this conference, but we will also consider other suitable articles. If your submission describes, in part or wholly, a study accepted for presentation at the ASCO annual meeting, please let us know the precise details of the type of presentation (such as poster or oral presentation), including dates and times, so that publication in The Lancet or The Lancet Oncology can be scheduled to comply with ASCO’s embargo policies. Articles can be submitted via either The Lancet’s or The Lancet Oncology’s online submission services, but all authors must clearly state in the covering letter that their submission is in response to the TL/TLO Call for Papers. If a paper does not include this message in the covering letter, or is submitted after March 23, 2007, we cannot guarantee publication will coincide with the ASCO annual meeting.

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To submit a paper, clearly marked with the phrase TL/TLO Call for Papers, go to either http://ees.elsevier.com/thelancet or http://ees.elsevier.com/thelancetoncology.
US FDA seeks more pharmaceutical industry cash

The US Food and Drug Administration (FDA) will formally ask Congress to increase industry user fees in a bid to improve its drug safety practices. But the new Democrat-controlled Congress has bigger plans for reform at the agency. Todd Zwillich reports from Washington.

In January this year, the FDA proposed to boost pharmaceutical industry fees in a bid to improve its drug safety monitoring. The embattled agency said it would soon formally ask Congress to increase industry user fees by US$87 million per year and use the money to hire dozens of new personnel dedicated to drug safety surveillance. Manufacturers, who helped craft the proposal, said it would also increase the government’s ability to scrutinise controversial direct-to-consumer drug advertisements.

The announcement came as the new Democrat-controlled Congress prepares to revisit the 15-year-old user fee law and also rolls up its sleeves on a broader range of promised FDA reforms. The recall of the COX-2 inhibitor Vioxx in 2004, along with a series of safety concerns on several classes of widely used drugs, have increased Congress’s appetite for an overhaul.

FDA Commissioner Andrew von Eschenbach said the increased fees would lead to “an impressive expansion and modernisation of our drug safety system”. About a third of the proposed increase would go to hiring 82 new employees to help improve drug safety epidemiology. Although officials have not yet said how additional personnel would be used to improve safety.

Industry user fees are credited with shortening drug approval times at the agency, which explains the industry’s enthusiasm for adding to the roughly $305 million it pays in fees already each year. But to some, the fees symbolise a cosy relationship between companies and regulators that helped to lead to recent safety lapses. “At a time when countless drugs have safety problems, it isn’t enough to just rely on money paid by the pharmaceutical industry to fund needed drug safety reforms”, said Bill Vaughan, senior policy analyst at the Consumer’s Union.

Although few are calling for an end to user fees, lawmakers who will be charged with formulating the FDA reforms expressed scepticism that fee increases alone can deliver needed changes at the agency. Senator Charles E Grassley, a Republican from Iowa and the Congress’s sharpest FDA critic, says the agency needs more money to do a better job of approving new drugs and policing those already on sale. But he worries that increasing user fees could heighten perceptions that drug companies have become the FDA’s paying customers. “If you enhance those fees, to the people who think it’s bad, it’ll just look worse”, Grassley told The Lancet.

In an interview, Senator Edward Kennedy, who chairs the Senate committee with jurisdiction over the FDA, suggested he would not support large fee increases that are not paired with a boost in taxpayer spending at the FDA. “I’m strongly against user fees in place of appropriations”, the Massachusetts Democrat said. Still, the fee hikes are likely to be the least of the changes lawmakers attempt this year.

Kennedy plans to back legislation giving the agency the authority to compel companies to undertake safety trials on drugs already on the market and unilaterally order changes to prescription safety labelling.

Grassley plans to push for reshuffling the FDA by taking the office responsible for post-market safety surveillance away from the control of the office that approves new drugs. The current arrangement, Grassley argues, allows new drug reviewers to exert undue influence over how drugs are monitored once there are on pharmacy shelves.

In announcing their user fee proposal, FDA officials said the new fees would go a long way to improving the agency’s safety practices. Lawmakers seem intent on going much further. “No amount of money will do any good if we don’t change the culture”, said Grassley.

Todd Zwillich
HIV/AIDS conference highlights Lesotho’s progress

Lesotho is improving access to HIV/AIDS prevention and treatment programmes by mainstreaming these activities into non-health sectors, the government’s HIV/AIDS coordinator told a recent conference in Germany. Samuel Loewenberg reports from Berlin.

AIDS first surfaced in the small southern African country of Lesotho in 1986. Its path was quick and devastating. In 1993, the HIV infection rate had reached 4% of the population. By 2001, over 31% of the population were infected, making it the fourth highest rate of infection in the world.

But there is progress being made. Through an innovative approach known as mainstreaming, local public-health authorities have made much progress in establishing education and treatment programmes. Beginning in 1997, public-health officials adopted a multisector approach to HIV/AIDS education, implementing programmes in the military, schools, and agriculture and construction industries. This approach, which integrates the struggle against the disease into daily life, “has broken the silence, broken the stigma of testing”, said Malitlallo Majara, the HIV/AIDS coordinator in the Ministry of Local Government of Lesotho. Mainstreaming, she recently told an audience of public-health officials in Berlin, “makes it everybody’s responsibility.”

Majara was one of many experts from around the world who gathered in the German capital last November to address new approaches to the prevention and treatment of HIV/AIDS. The conference, entitled “AIDS Mainstreaming—Paving the Way towards Universal Access”, was organised by the United Nations Programme on HIV/AIDS (UNAIDS) and the Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ), the German government’s development agency. Germany is actively promoting mainstreaming; as the new head of the G8, it will promote an integrated approach to tackling HIV/AIDS, linking programmes for sexual and reproductive health, human rights, tuberculosis, and other communicable diseases.

The focus on mainstreaming reflected the experience described by Majara in Lesotho, where public-health authorities have come around to the idea that HIV/AIDS cannot just be treated as a medical problem. The pandemic has drastically altered the nation’s social fabric. The high rate of mortality in adults has led to a massive brain drain. It has also created 180 000 orphans in the country. Part of the new approach is to provide free schooling for these children.

Other social and medical aspects of HIV/AIDS prevention and treatment that authorities in Lesotho have now integrated into their approach include food security, counselling, and identifying drug-resistant strains of the virus. One crucial gap in Lesotho health workers’ knowledge, said Majara, is research about the effect on babies of drinking breastmilk containing antiretroviral drugs.

From the time when HIV/AIDS first surfaced during the mid-1980s through to the end of the 1990s, Lesotho’s health authorities were very slow to react to the new disease, said Majara. Even since then, there have been many bureaucratic entanglements that made it difficult for afflicted citizens to get access to care. Over the past two decades, public-health practitioners in Lesotho have had a learning curve, said Majara, which has led them to a more confident and independent approach to taking on HIV/AIDS.

In the early stages of the epidemic, “we were too much dependent on external expertise”, Majara said. Through the mainstreaming approach, the fight against the disease has been integrated into everyday life, she said. “People are doing it for themselves.”

One recent innovation, which Majara is hopeful will improve services, is a new law that holds non-governmental organisations (NGOs) legally liable if funds for HIV/AIDS are misspent. The premise is that this will give donors more confidence in supporting the country’s public-health efforts.

The experience of Lesotho was echoed by other presenters at the conference. GTZ integrates HIV/AIDS programmes into a third of all of their work in Africa. “We include it from the beginning”, said Peter Conze, the director general of the organisation’s Africa department.

Gertrud Helling-Giese of the German Development Service described how they emphasise HIV/AIDS education in the workplace. “It’s a great entry point”, she said. In Guinea, for instance, HIV-prevention programmes were integrated into projects to build schools, roads, and infrastructure for water distribution. Under the development scheme, contractors had to supply employees
with condoms on the construction site free of charge and to present HIV/AIDS education programmes.

But mainstreaming may have a downside. Several of the panellists expressed the concern that HIV/AIDS mainstreaming might be used as an excuse to cut funds from programmes focused specifically on the disease. Franklin Apfel, the conference’s moderator and the managing director of World Health Communication Associates, a public-health networking and training organisation, told The Lancet that although mainstreaming has many benefits, it is not a panacea for the many complexities of implementing AIDS education and treatment: “If you are too focused on one diagnosis, you can miss some of the larger issues”, he said.

Other panellists noted that with the influx of money from high-profile donors, such as the Global Fund to Fight Against AIDS, Tuberculosis, and Malaria and The Bill and Melinda Gates Foundation, the challenge now is to develop a public-health infrastructure in developing countries to take advantage of the newly available funds.

Informally, several public-health and NGO workers said that even with all the recent attention to HIV/AIDS from these massive donors, the funds have still been slow to be put into use. “There is supposed to be all of this money available, but where is it? We don’t see any of it on the ground”, said the NGO official, who asked that her name not be used for fear of retribution.

The effectiveness of spending remains a difficult issue. Christoph Benn, the external relations director of the Global Fund to Fight AIDS, Tuberculosis, and Malaria said “we think we have good evidence to say yes”. The agency’s current estimate is that 75% of their grants achieved success, he said, although he did not explain how “success” was defined.

And while with all of the new funds there is also a new emphasis on accountability, even that can have an unintended effect. Several panellists noted that donors seem to favour treatment over prevention, because the success of the distribution of funds is more easily quantifiable.

But others asserted that funds spent on HIV/AIDS could also lead to improvements that benefit the entire public-health system. The new deputy director of Country and Regional Support for UNAIDS, Helena Eversole, cited a recent project in Bosnia, where money from the Global Fund is being used to strengthen the surveillance capabilities throughout the country’s medical infrastructure. “If funds are spent right, it can significantly improve public health across the board”, said Eversole.

Even countries fortunate enough to have a low rate of HIV infection face unique problems. Holger Till, a technical adviser on HIV and AIDS in Ghana, said that in such countries one particular difficulty is showing people the benefits of prevention, even when AIDS is not a glaring problem. One successful approach, said Till, is to point out to mothers the benefits of AIDS prevention for their unborn children.

For public-health practitioners working to fight HIV/AIDS in the developing countries, the educational and prevention strategies are a constant moving target, said Apfel. “The ability to deal with marginal groups is not something you learn in medical school”.

Public education is not enough by itself. Rustica Tembele, director of the community response department of the Tanzanian Commission for AIDS said that although HIV awareness has increased, many people do not have access to condoms because of financial restrictions and religious opposition. Instead, people have been known to use plastic bags, she said.

The German government has a policy of not funding groups that forbid the use of condoms. In some cases, the government has even jumped in to restore funding for condom distribution when it was cut because of religious opposition from the USA, said Jochen Böhmer, from the German Ministry for Economic Cooperation and Development.

Many of the public-health experts expressed concern about the influence of religious groups that oppose condom distribution. “They say this while standing on the graves of dead children”, said Majara.

Samuel Loewenberg
Serbia rebuilds and reforms its health-care system

After more than a decade of turmoil, Serbia is slowly rebuilding and reforming its health-care system. Michael McCarthy interviewed Snežana Simić, who leaves her post as acting Minister of Health this month after 4 years with the ministry, about the country’s reform effort.

When Snežana Simić joined the Republic of Serbia’s Ministry of Health in 2002, she looked forward to putting into practice what she taught her students as professor of public health at the School of Medicine, Belgrade University. “I knew all the concepts and all the advantages and disadvantages of the different approaches”, Simić said in a recent interview in her offices in the Ministry of Health. “I wanted to see what worked.”

At the time, Serbia had weathered more than a decade of political and economic turmoil. Shortly after the 1989 election of the ultranationalist Serbian leader Slobodan Milosevic, Yugoslavia broke up. The subsequent years were marked by political and economic chaos, ethnic strife and civil war, United Nations (UN) sanctions and international isolation, and, finally, a punishing 6-week North Atlantic Treaty Organisation (NATO) bombing campaign in 1999.

The country is far from recovered. Not including Kosovo, which remains under UN administration, Serbia’s population of 7·4 million still includes 300,000 refugees and 220,000 internally displaced people. About 20% of Serbians live on less than US$90 a month, with 10% on less than $70 a month. Surprisingly, many health indicators seem to have improved or held steady during the 1990s. But assessing the true state of health in Serbia is difficult, says Simić, because data collection over the past decade has been patchy at best. Her impression, however, is that there has been an overall decline in the nation’s health. Today, the leading causes of death are heart disease, stroke, and cancer. Smoking alone is thought to cause 30% of deaths in Serbia, which is not unexpected in a country where half the men and a third of women smoke.

On paper, Serbia seems to have a relatively good health system with a well developed network of primary, secondary, and tertiary care centres, Simić says. “Formally, you could say we had everything.” But the system was inefficient and underfunded; equipment and facilities were out of date; and the staff were underpaid and demoralised. A 2002 European Agency for Reconstruction study found that only a third of hospitals had functioning sterilisation equipment and 75% of the medical equipment in health facilities was more than 10 years old. In 2000, the average doctor was paid a salary of €130 a month and nurses €90, compared with the national average monthly salary of €176, according to the World Bank. Health workers routinely accepted on the side informal payments from patients and supplemented their income with private practices. Patients had to buy their own hospital supplies out-of-pocket, even for items such as bandages and catheters.

The goal of the government’s health reform, says Simić, has been to “build on the good points of the old system”—in particular the primary-care networks—but to shift away from a longstanding emphasis on curative medicine to an emphasis on health promotion, prevention, and screening.

Some progress has been made. To improve morale and working conditions, salaries have increased by 40% and buildings are being refurbished and re-equipped. To improve efficiency and quality, a “patient-centred focus” is being emphasised. Patients now are asked to fill out questionnaires about their care. In addition, the Ministry has established a reporting system to monitor such indicators as hospital mortality rates, average length of stay, and use of health services.

Simić says clinics have become very competitive in their efforts to improve their rankings. Under new payment systems, funds will no longer automatically go to providers as they did in the old system but will “follow the patients”, Simić says. “We are going to pay on the basis of how many patients a doctor sees and the quality of their care.”

Last month’s national elections will bring in a new government, so Simić will be leaving the ministry this month to return to teaching, though she may continue to serve as a special adviser. One lesson she says she has learned from her 4 years at the Ministry is that while different sectors can work together to improve health services, “management and coordination at the national level is the condition sine qua non for health reform”.

Michael McCarthy
Book
An argumentative but admirable analysis of medical journals

All of Richard Smith’s friends and colleagues will remember his escape to Venice a few years ago. He went to think and to write. It was a kind of sabbatical mixed with holiday. A single city version of the Grand Tour. Richard’s sojourn in his Palazzo paid huge dividends. For one, this marvellously and outrageously scorching analysis of medical journals—a cause to which he has devoted some of the most creative years of his professional life. But Richard also returned a more reflective man. Whereas once he was passionate about the BMJ, now he seemed detached. He appeared to see the whole enterprise of journals as misguided, even dangerous.

He once asked me whether I really did believe journals contributed anything useful to the world. He clearly worried that they might not. The crazy chase after impact factor, endless circular and unresolved debates about peer review and authorship, and the whole business of pleasing an ultimately ignorant and ungrateful owner (in his case, the British Medical Association) all conspired to make his working life seem pretty joyless. Then, at a pivotal personal moment, he received a call that gave him the impetus to leave. He jumped ship into the mad world of dismembering the National Health Service, replacing its paralysed limbs with allegedly bionic private prostheses. Most people were surprised that Richard left the BMJ, now he seemed detached. He appeared to see the whole enterprise of journals as misguided, even dangerous.

The responses to the BMJ review are far more interesting than the review itself. They show just what a polarising figure Richard was—and remains. All of which is to the benefit of medicine. His friends have come out to fight in force. Iain Chalmers, who has done more than any other person alive to keep editors true to their mission, praises Richard for challenging the research community “to assess whether the public is getting good value for its money”. Liz Wager, a keen observer of publication ethics and a troubadour for pharmaceutical integrity, defends Richard’s view that patients should be more closely involved in journals. And Pritpal Tamber, who may be a future editor of the BMJ himself, writes that Richard’s book “is brimming with important ideas”, neglected by the reviewer and, Tamber adds more ominously, by the BMJ. But Richard does have his detractors and they deserve a hearing. Ray Tallis, probably the most acute critic of medicine today, claims that Richard marginalises the vast contribution science has made to patients’ care. And Alex Paton, a retired physician who once worked for the BMJ, sharply points out Richard’s own personal inconsistencies and contradictions and his virtual abandonment of what journals should be all about—their readers.

After carousing through this book and the visceral responses it has provoked, my feeling is that this debate was necessary. It was necessary for Richard to collate his frustrations into a coherent case for the prosecution of medical journals. He does the job stunningly well. The responses to the BMJ review are far more interesting than the review itself. They show just what a polarising figure Richard was—and remains. All of which is to the benefit of medicine. His friends have come out to fight in force. Iain Chalmers, who has done more than any other person alive to keep editors true to their mission, praises Richard for challenging the research community “to assess whether the public is getting good value for its money”. Liz Wager, a keen observer of publication ethics and a troubadour for pharmaceutical integrity, defends Richard’s view that patients should be more closely involved in journals. And Pritpal Tamber, who may be a future editor of the BMJ himself, writes that Richard’s book “is brimming with important ideas”, neglected by the reviewer and, Tamber adds more ominously, by the BMJ. But Richard does have his detractors and they deserve a hearing. Ray Tallis, probably the most acute critic of medicine today, claims that Richard marginalises the vast contribution science has made to patients’ care. And Alex Paton, a retired physician who once worked for the BMJ, sharply points out Richard’s own personal inconsistencies and contradictions and his virtual abandonment of what journals should be all about—their readers.

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Perspectives

The responses to the BMJ review are far more interesting than the review itself. They show just what a polarising figure Richard was—and remains. All of which is to the benefit of medicine. His friends have come out to fight in force. Iain Chalmers, who has done more than any other person alive to keep editors true to their mission, praises Richard for challenging the research community “to assess whether the public is getting good value for its money”. Liz Wager, a keen observer of publication ethics and a troubadour for pharmaceutical integrity, defends Richard’s view that patients should be more closely involved in journals. And Pritpal Tamber, who may be a future editor of the BMJ himself, writes that Richard’s book “is brimming with important ideas”, neglected by the reviewer and, Tamber adds more ominously, by the BMJ. But Richard does have his detractors and they deserve a hearing. Ray Tallis, probably the most acute critic of medicine today, claims that Richard marginalises the vast contribution science has made to patients’ care. And Alex Paton, a retired physician who once worked for the BMJ, sharply points out Richard’s own personal inconsistencies and contradictions and his virtual abandonment of what journals should be all about—their readers.

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about health should be primarily directed: patients and the public.

I don’t agree with Richard’s conclusion that journals are corrupt, that we are too fond of the mass media, that we are overinfluenced by the pharmaceutical industry, that we are neglectful of patients, and that the studies we publish are “increasingly” found to be fraudulent. I think that journals, at their best (and, Richard, were we not always striving to be at our best?), are acutely sensitive to those who lack voice, to the manipulations of mammon and media, and to the need to be vigilant about research integrity.

Journals can change the world for the better. Almost every day I meet or talk with physicians and scientists who want to make this planet a safer, healthier, and more sustainable place not only for themselves but for others and for future generations. I recognise the same risks as you do Richard. But I don’t feel defeated by them. I feel inspired by a community of medicine that, at its heart, is committed to a professionalism that puts the patient first, that fights against forces that undermine the values of medicine, and that puts science in the service of human compassion.

Since Richard left theBMJ, the journal has been redesigned and relaunched under the leadership of a new editorial team. The new look and feel of theBMJ reflects a generational change—and it is an impressive revision of the journal’s purpose and personality, one that deserves applause. TheBMJ is now more a lively magazine than a sombre journal, more nationally focused than globally diffuse, more news and features led than research and science responsive, more interested in primary care than trying to appeal to all types of care, more online than print.

Richard used to say that theBMJ was in the debate (not the truth) business. That mantra has been firmly discarded. TheBMJ’s tag-line today is “helping doctors make better decisions”. Richard saw the journal as a place to mediate an intellectual ferment. His successors see theBMJ as a locus for collegial support. At a time when the profession in the UK feels unloved and under threat, that more pacifying approach may be sound. For now. But don’t rule out a comeback for Richard Smith. Journals need colour. And he was a bright and vital rainbow of surprise, optimism, and revolt.

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In brief

Exhibition Paranoid visions

“You are cautiously invited to the opening of paranoia”, read the exhibition invitation. Walking up the garden path towards the house in Hampstead, London, where Sigmund Freud spent the last year of his life, three crudely lettered signs—“NO ENTRY”, “KEEP OUT”, and “NO TRAVELLERS”—could have been intended to halt the faint-hearted in mid-stride.

Inside, all was confusion with a large-screen video projection accompanied by a soundtrack of loud music in the normally hushed entry hall; and a throng of people, including several performance artists, crammed into the other rooms. The highly chaotic form of this exhibition is evidently a major part of its content, challenging spectators to sort what is real from what is distorted. “The exhibition presents the essence of paranoia as the deluded interpretation of events, not the perception of the events themselves”, says the show’s curator Predrag Pajdic. Indeed, the 42 international artists whose work is displayed inParanoia seem to have found a spiritual home.

A bearded man in traditional white Jewish dress sat impassively in the dining room, with downcast eyes and outstretched fingers resting on his knees, on a utilitarian chair in the middle of a wire sheep pen. Did he evoke a terrorist detainee or a lamb for ritual slaughter? On the half-landing, two bearded men, one dressed as an Orthodox Jew and the other as a Muslim, offered simultaneous right-hand and left-hand massages, seated on either side of rather self-conscious guests trying to project bravado. A little later, the men had swapped sides. Perhaps this was intended to reflect the shifting political stances in the Middle East or to suggest that the two sides had more in common that is usually acknowledged? Three women in traditional Muslim black dress and veils went from room to room, moving as one in a beautifully choreographed sequence, alternately swooping forward in unison to peer intently at exhibits and leaning back abruptly. Were they aesthetically gratified or recoiling in horror from decadent western art?

As might have been anticipated, the single work that resonated the clearest meaning was displayed on a table in Freud’s study and library. A folio book, Die Welt im Der Wir Leben, struck through by a double-edged axe provided an unequivocal and powerful visual analogy for the seismic fracture that occurred on Sept 11, 2001; and heightened global paranoia irreversibly.

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[Image of the exhibition]
Profile
Rosemary Basson: working to normalise women’s sexual reality

In 1973, just after she got her MRCP, Rosemary Basson was working as a locum registrar, caring for young men with spinal-cord injuries. “Basically I was in charge of their bladders and kidneys, catheterising them three times daily”, she recalls. Given her responsibilities, she had thought, “surely someone’s going to ask me about sexual function, and I don’t know the answer”. She went to her superiors for advice. They told her to avoid the issue and even to tell the young man’s wife or girlfriend to find another sexual partner.

Today, clinicians have much more to offer men and women with spinal-cord injuries and other conditions that interfere with sexual function, thanks largely to Basson’s mentor George Szasz, who co-founded the Sexual Medicine Unit at the University of British Columbia in Vancouver, Canada, in 1974. And thanks to Szasz, Basson, and other pioneers in sexual medicine, physicians are now more comfortable discussing sex with their patients than they were three decades ago. “Things are certainly changing”, says Basson, who is Director of Sexual Medicine at the University of British Columbia and a full-time sexual medicine physician at the Center for Sexual Medicine at Vancouver Hospital. But puritanical attitudes mean sexuality’s role in health still doesn’t get the attention it should, she adds, especially in the USA. “Most of my colleagues have the same complaint. The area seems not to have any priority, it’s underfunded.”

As a girl, Basson recalls, she had wanted to find a career that would allow her to keep learning all her life. Science was “a dirty subject” at her all-girls school, but Basson decided on medicine anyway. She practised as a generalist in family medicine until 1986, when she began a fellowship in sexual medicine with Szasz. “He was a very inspiring clinician, a wonderful teacher of students, of physicians, and actually of his patients”, Basson says. “I think the most important thing he taught me was how to listen very, very carefully.”

Szasz says Basson was “quite shy” when they first met. She later told him one of her most traumatic experiences was a televised role-playing exercise on the first day of her fellowship, in which Szasz played a woman with an orgasmic problem and Basson took the clinician’s part. It has been one of the great satisfactions of his career, Szasz says, to see “how she has flowered and how strong she has become and what an incredibly clever overview she has developed”. Colleagues agree Basson is an unusually sympathetic listener. And it was by listening carefully to her patients, she says, that she was able to develop a new concept of women’s sexual response much more in tune with what women were actually feeling. The traditional scheme—a straight line from desire to arousal to plateau to orgasm—rarely applies, according to Basson. Instead, she argues, many women (and probably many men) experience sex as a cycle of overlapping phases influenced by mental and physical factors. Women may not often feel spontaneous desire, especially if they are in long-term relationships, but initiate sex out of a wish for intimacy or to express love for their partner and begin feeling aroused and trigger desire after sexual contact has begun. “Initial desire is desirable, if you like, but not mandatory”, explains Basson. Women are more likely to spontaneously feel the urge to have sex if they are in a new relationship, or perhaps at a certain point in their menstrual cycle, according to Basson.

She says her view of women’s sexual response wasn’t anything new, since past researchers had made similar observations, but she was the first to create a simple, reproducible diagram to illustrate the idea, which she first published in 2000. Szasz says Basson’s diagram “cracked the mould” of how researchers and physicians thought about women’s sexual response and dysfunction. Since the 1970s, he pointed out, the Diagnostic and Statistical Manual of Mental Disorders (DSM) has defined a lack of spontaneous sexual desire in women as hypoactive sexual desire disorder. “Her findings normalised the experience of many women who have been previously labelled as suffering from some sort of terrible sexual disorder”, he added. Basson and several other colleagues have called for the DSM definitions to be changed to include only women who experience no desire at all initially or during sex, never experience pleasure during sex, and never feel aroused. The DSM’s authors have said they will revisit the issue for the 2010 edition.

Basson’s ideas may not have changed that bit of medical dogma, but they have had “a major impact on how clinicians treat women in terms of reassuring women, educating women, and intervening to help them deal with their sexual difficulties”, says Sandra Leiblum, director of the Center for Sexual and Relational Health at UMDNJ-Robert Wood Johnson Medical School in Piscataway, NJ, USA. Leiblum, who spent a sabbatical with Basson in Vancouver, notes that she is unusual in sexual medicine: a skilled therapist with excellent medical credentials who also does rigorous research.

And as a properly sceptical scientist, Basson says she’s worried women will increasingly be given testosterone as a quick fix for sexual difficulties. There’s no evidence for a link between low concentrations of testosterone in women and sexual problems, she notes, and identifying such a link will be extremely difficult given that there is currently no clinically available proven marker for activity of the hormone in women. Basson continues to see patients full time. Even after two decades, she says, her passion for her work remains. “You’ve never really heard anybody’s story before.”

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William Ian McDonald

Leading neurologist who was instrumental in creating diagnostic criteria for multiple sclerosis. Born on April 15, 1933, in Wellington, New Zealand, he died after a heart attack on Dec 13, 2006, in London, UK, aged 73 years.

During the 1950s as William Ian McDonald was earning his BMSc and MBChB from Otago University, New Zealand, neurologists and physiologists were just accepting the idea that nerve impulses travelled by electrical conduction. McDonald was attracted to this idea, and returned to Otago in 1959, after time as a house officer, to join Archie McIntyre’s laboratory, where he set to work on an experimental model of demyelination. Using the model—parenteral injection of diptheria toxin—McDonald showed that electrical conduction was blocked where nerve demyelination began and that following demyelination, conduction was slowed in single active nerve fibres in the dorsal roots after peripheral stimulation.

After his training in general internal medicine and neurology, McDonald set up his own laboratory in the UK at the National Hospital, Queen Square, London, in 1967. Here he replicated his earlier findings but in the central nervous system, where the pathology of multiple sclerosis occurred. He then wanted to confirm the results in human beings. In 1972, he and Tom Sears began a collaboration with Martin Halliday, who was using the visual evoked potential to map the projection of the retina on the visual area of the brain. McDonald quickly linked this work to the many cases of acute but recoverable loss of vision caused by optic neuritis he was seeing at Moorfields Eye Hospital, realising this symptom was often the first sign of multiple sclerosis. “The results were immediate and dramatic”, he later wrote. “There was in 90% of cases a substantial delay in the response from the affected eye. Moreover the delay persisted even when the vision had returned to normal. It was quickly apparent that this method could be used to detect asymptomatic damage in the optic nerves and that accordingly it should be useful as a diagnostic aid in multiple sclerosis.” The technique, which was the first laboratory test for multiple sclerosis, “immediately became relevant for clinical testing”, Alistair Compston, professor of neurology at Cambridge University, Cambridge, UK, told The Lancet. “It became a marker for compression as well as for demyelination, applicable in a range of areas.”

Based on the technique, McDonald developed the first set of diagnostic criteria for multiple sclerosis that incorporated laboratory tests. Later, the usefulness and importance of those criteria faded as MRI came along, said Compston, who met McDonald in 1975 when McDonald hired him to research the genetics of multiple sclerosis. Once again, however, McDonald’s ability to identify MRI’s potential in the clinical setting was critical. He convinced the Multiple Sclerosis Society to fund an MRI that would be used only for research. “That was critical”, said Alan Thompson, who trained under McDonald and is now professor of clinical neurology and neurorehabilitation at Queen Square. “What really stands out was how he was able to translate what he did”, Thompson added. “He was very clinically driven.”

McDonald was inspirational and unselfish with his time, Thompson said. “He was incredibly approachable, and everyone thought they could speak to him. What I could never understand about him was how he managed to do everything. He used to get up at 4 am and take little catnaps every day”, Thompson recalled. McDonald served as editor of Brain from 1991 until 1997. That year, he retired from Queen Square, and became the Harveian Librarian of the Royal College of Physicians until 2004.

He was also a wonderful pianist, said Charles Poser, of Harvard Medical School, Boston, USA, who helped write 1983 guidelines for multiple sclerosis that were updated in 2001 by a group led by McDonald. “My wife and I had dinner with him at his home on several occasions and he would invariably give a recital on his piano.” In 2004, it was McDonald’s difficulty reading music that made him realise that he had had a stroke. “I had been asked to turn the pages for a performance of the Schubert F minor Fantasy for piano duet, a work I know well...I was quite unable to do so”, he wrote in a personal essay published last year in Brain that melded his own neurological symptoms and recovery with the history of the field. McDonald is survived by his partner of 25 years, Stanley Hamilton.
Haemoglobin concentrations in chronic kidney disease

We extend Robert Steinbrook’s Comment (Dec 23/30, p 2191)1 on two studies published in the New England Journal of Medicine that assessed haemoglobin concentrations in chronic kidney disease (CKD),1,3 and suggest that the data necessitate a prompt warning. Nephrologists have long wondered why some patients with CKD develop adverse cardiovascular events when anaemia is corrected. In haemodynamic studies, our group showed that an increase in the haematocrit resulted from pre-existing hypertension.4,5 The cardiac index especially in those with pre-existing anaemia is corrected. In haemodynamic studies published in the Journal of Medicine 2006; 368: 2191-93.


Effect of smoking on lifestyle interventions to prevent diabetes

Jaana Lindström and colleagues (Nov 11, p 1673)1 report valuable and encouraging results which show that active intervention directed to adjust diet and physical activity substantially suppresses the development of diabetes in patients with impaired glucose tolerance.

Lindström and colleagues note that the incidence of diabetes was possibly reduced by the intended effect of the intervention on diet and physical activity; however, it is still possible that the lifestyle modifications that accompanied the intervention, or indeed the baseline lifestyle of the participants, had a substantial role in the findings. Smoking, which was not addressed in the study, has consistently been shown to be associated with an increased incidence of diabetes in prospective studies.2-4 Furthermore, in a large-scale prospective study,5 lifestyle intervention suppressed the development of diabetes in non-smokers, but not in smokers. Conversely, smoking cessation can counteract the beneficial effect of lifestyle modification by increasing weight.6

These findings indicate that smoking is one of the essential factors to consider in lifestyle interventions against diabetes.

We declare that we have no conflict of interest.

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Authors’ reply

Takeharu Koga and colleagues raise an important issue. Smoking is a well recognised health hazard, and interventions against smoking are highly warranted. Smoking (and smoking cessation) can interfere with the efficacy of lifestyle interventions aimed at prevention of type 2 diabetes, as discussed by one of us (JT) in an editorial1 related to the study by Davey Smith and co-workers.

In the Finnish Diabetes Prevention Study (DPS), smoking was uncommon: only 6% of participants...
were regular smokers at the beginning of the study. Therefore, it is not likely that smoking status had any effect on the observations as a whole. Owing to the low numbers, subgroup analyses by smoking are not rational.

Two-thirds of the DPS participants were middle-aged women, among whom smoking is relatively uncommon. A low prevalence of smoking might be a marker of health-consciousness among the volunteers willing to participate in the DPS. In future programmes for the prevention of chronic diseases, the focus of lifestyle interventions might need to be adjusted according to smoking status.

Additionally, because atherosclerotic vascular diseases are the most common cause of death among people with different degrees of glucose abnormality, stopping smoking should always be one of the main goals in prevention strategies dealing with these high-risk groups.

We declare that we have no conflict of interest.

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Methadone and QTc prolongation

Mori Krantz and Philip Mehler (Aug 12, p 556) write about preventable cardiac risks of methadone treatment. They state: "In 1973, clinicians in New York sought an explanation for a perceived increase in the risk of sudden death in heroin addicts, even in those successfully treated with methadone." We have re-read this reference (one of us, BS, was co-author) and find no reference to unexplained deaths in methadone patients. Of more importance, however, is that the patients in the methadone group were all using several other drugs in addition to heroin for at least 3 days before the cardiography. There was no group in that study that was only using methadone. The frequency of QTc prolongation was 18% in those using heroin versus 34% in those misusing several drugs while on methadone maintenance. We could find no other series of unexplained deaths of addicts in treatment at that time, nor in the decades since.

After widespread use throughout the world, often under close medical supervision, it is hard to accept that a serious side-effect would be entirely overlooked. Most of the small number of reported torsades cases have involved other risk factors or doses averaging nearly 400 mg daily for pain management—ie, more than four times the average used in addiction treatment.

Krantz and Mehler’s implication that high doses of methadone should be avoided could paradoxically lead to more cocaine use and other high-risk behaviour, far outweighing any possible cardiac side-effect.

It seems more reasonable to monitor the changes in QT intervals when the need for high doses arises, especially in circumstances where multiple drugs are needed to control pain, depression, or other complex disorders.

We declare that we have no conflict of interest.

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Authors’ reply

We thank Andrew Byrne and Barry Stimmel for their insightful comments. However, we stand by our contention that sudden death is not a rarity among heroin addicts, whether treated with methadone or not. Therefore, we feel this is worthy of further investigation, given a report of rising mortality attributed to methadone.

Regarding the 1973 study by Lipski and Stimmel, we agree that there is a confounding effect of poly-drug abuse on the QTc interval that cannot be adjudicated in a post-hoc review of this study. Nonetheless, the fact that clinically important QTc prolongation was nearly twice as common among patients receiving methadone (proven by urine toxicology) than those who were methadone-naive is uncanny.

We concur with Byrne and Stimmel that electrocardiographic monitoring seems most appropriate for patients in whom the methadone dose is being escalated and among those on multiple QTc-prolonging drugs. Moreover, we also wholeheartedly agree that high-dose methadone is very effective in reducing illicit drug use. However, we believe that a high-dose methadone strategy has a clear safety trade-off. Our field has moved dramatically towards higher methadone doses over the past decade. In our methadone maintenance treatment practice in Denver, CO,
USA, 30–60 mg/day is an infrequently prescribed dose, whereas doses over 100 mg/day are now the norm. It is with consternation that we acknowledge the escalation of dosing standards as our best explanation for the increase in morbidity and mortality among methadone-treated patients. Indeed, these very concerns regarding high-dose methadone are expressed by the manufacturer in a just-released black box warning label.1

We declare that we have no conflict of interest.

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Acute myeloid leukaemia

In their review, Elihu Estey and Hartmut Döhner (Nov 25, p 1894)1 cite the 1999 paper by Gundestrup and Storm,2 reporting a 5·1-fold increased incidence of acute myeloid leukaemia in 3000 Danish male cockpit crews, a finding arbitrarily attributed to increased cosmic ray exposure. However, in 2003, Pukkala and colleagues showed in the largest study published to date that the incidence of acute myeloid leukaemia was not significantly higher than that of the general population in a cohort of 10 000 North European airline pilots who had served more than 20 years. The only cancers whose incidence has been found consistently increased in airline crew involve the skin.1

A more proven environmental risk factor for radiation-induced acute myeloid leukaemia is indoor radon exposure; cigarette smoking is another risk factor not cited in their review.5

I declare that I have no conflict of interest.

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Human papillomavirus vaccine policy

Your Editorial on human papilloma-virus (HPV) vaccination (Oct 7, p 1212)4 is disastrous for public health. Your message—that the EU is misguidedly dragging its feet over compulsory vaccination—is what the manufacturers want us to believe. But it is wrong.

You say we must eradicate HPV infection, irrespective of cost or collateral damage. This is rubbish, our aim must be to reduce illness caused by HPV infection, and the prime ill effect is cervical cancer. Countries with high mortality and no screening can achieve major gain from vaccination. But rushed introduction in Europe will worsen HPV-related illness by undermining existing screening and leaving women less protected than now.

In November, 2005, a meeting in London, UK, brought experts from all fields to consider the needs of National Health Service (NHS) research and policy. The conclusions were: women are well served by the NHS screening programme, which meets exacting standards1 and is averting 80% of deaths;2 if and when we have vaccine evidence on long-term disease

Barriers against STDs: what about planned pregnancy?

We welcome Anne Philpott and colleagues’ proposal that barriers against sexually transmitted diseases should be designed to promote sexual pleasure (Dec 2, p 2028).1 We agree that the uptake and consistency of use of such barriers, and hence their effectiveness, would be thereby enhanced. This is surely a concern to be kept in mind by those who design physical and chemical barriers. Also, those who aim to dispense them to potential users have to work within the cultural constraints of the society to maximise their pleasurable use.

An issue no less fundamental and in need of attention, however, is that for many young women and men, conception is also an integral part of sexual relationships. Fertility is not only desirable but essential to the maintenance of the community. There are many individuals who will accept neither physical barriers such as condoms, nor microbicides that are contraceptive, even if the risk of infection is reported to be high.

Perhaps these concerns seem obvious; nevertheless, Philpott and colleagues’ publication, and we hope ours too, go beyond the laboratory considerations that too often seem to take priority in prevention of HIV.

We declare that we have no conflict of interest.

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The printed journal includes an image merely for illustration
Correspondence

outcomes, and in all risk groups, then we can model the effect of a range of vaccination and screening combinations and implement accordingly; but on current evidence, adding vaccination for UK teenagers will more than double the cost of our cervical cancer control programme for little or no gain.

The manufacturers know this, so to sell vaccination in countries such as the UK they are busily branding HPV as a new disease, undermining national policymaking by running promotional “stakeholder” meetings in every locality, planting press stories to create a smoke screen—implying that the real barrier to protecting our daughters is unjustified prudishness—and securing promotional articles in prestigious journals such as The Lancet.1 Rushed policymaking will have disastrous consequences; we must use these vaccines wisely.

I am Public Health Lead for cervical screening for a population of a million in and around Bristol, UK, and work as a consultant to the UK National Screening Programmes.

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UNFPA’s country office in Guatemala used a form of interest-group analysis to plan and facilitate the adoption of that country’s first social development and population law in 2001.2 UNFPA’s Strategic Planning Office, with six country offices, has introduced interest-group analysis to scan the environment and engage with key players who influence the implementation of goals agreed at the International Conference on Population and Development (ICPD) in 1994. The approach has been applied to issues including early marriage and gender-based violence. In short, UNFPA, as the agency primarily responsible for sexual and reproductive health policy, is doing what Buse and colleagues recommend.

The process has emphasised that goals agreed at ICPD often stay locked within national policies and laws, without a tangible connection to implementation and local impact. We have learned that technical approaches alone are not enough to shape policy and produce results. We are also learning that UNFPA needs to engage with people beyond our “usual” partners and widen our circle of alliances.

This introduction of interest-group analysis is being guided by the experiences of using political analysis in health-policy reform, with support from Michael Reich at Harvard University.3,4 Additionally, we are using a software tool for political analysis developed by Reich and by David Cooper.5 UNFPA country offices have found this approach very useful. We are now working towards institutionalising it.

We declare that we have no conflict of interest.

*Brendan O’Brien, Mandeep Janeja, Anila Gopalakrishnan

Applied interest-group analysis in reproductive health policy

We fully agree with the Viewpoint by Kent Buse and colleagues (Dec 9, p 2101)1 about the need for agencies working in sexual and reproductive health policy to engage in applied political analysis as part of their core activities. We would like to draw your attention to the work of the United Nation Population Fund (UNFPA).

Richard Horton (Dec 2, p 1949)6 proclaims a new discipline to have been born in comparative health-systems studies. He also notes that “there are very few scientific studies that have analysed the interaction between the politics of a governing party and the health of populations... What has never been done is to examine the detailed mechanics of health policymaking”.

This statement is true only to some extent. In fact there are a lot of such publications; however, most of them have aroused little interest internationally (and therefore were published in national [non-English] journals) or have been seen as a matter for social scientists rather than medical ones. The past decade has seen great advances in the development of political analysis techniques.3–4

Until recently, the methods used in studies of health politics looked very suspicious to evidence-oriented medical reviewers. Now the situation is changing. The stone that the builders rejected has been made the cornerstone.

I declare that I have no conflict of interest.

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A focus on trees will miss the forest

Although the neglected disease community has proposed “a synergistic approach to disease control” (Nov 4, p 1547), it ignores the progress made on reduction of these diseases, and the substantial investments by public and private sources to address them. The approach would have carried more clinical weight had WHO not previously recommended a limitation on basic testing for HIV/AIDS owing to its cost in resource-limited settings.

In the WHO Health Report of 2000, the number of disability-adjusted life-years for tropical diseases was 0.9% of the total, and global mortality was 0.3%. The WHO Health Report for 2002 showed a 0.1% mortality rate for trypanosomiasis and leishmaniasis and zero for the remaining tropical diseases. There was a striking decrease in mortality from schistosomiasis, which WHO recorded at 200 000 in 1995.

GlaxoSmithKline has built a new research facility in Spain, dedicated to diseases identified by WHO as “neglected”. Novartis developed a Tropical Disease Research Institute in Singapore, targeting dengue, malaria, and tuberculosis. In October, Pfizer announced a collaborative effort with WHO’s Special Programme for Research and Training in Tropical Diseases (TDR). This will give TDR access to Pfizer’s library of medical compounds—the world’s largest. Since TDR became operational in 1977, it has expended US$1 billion on research into neglected diseases.

Mark Dybul has reason to question an approach that expensively duplicates existing efforts. Rather than integrate PEPFAR resources with those of WHO’s new Department of Control of Neglected Tropical Diseases, WHO ought to set the example by integrating this activity with its extant TDR Programme.

I declare that I have no conflict of interest.

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In praise of Rockefeller

In your Editorial about the possible withdrawal of public health programmes at the Rockefeller Foundation (Nov 11, p 1623), you praise the foundation’s long-term and high-quality influence. I would like to add something from my perspective as a public-health academic and clinician.

Chile is acknowledged to have an outstanding health situation for a less-to-mid-developed country. The influence of the Rockefeller Foundation started as early as 1930, with several generations of trainees at the schools of public health in the USA. Among them was the outstanding character of Abraham Horwitz, Director of the Pan American Health Organization for 20 years. The creation of the first Chilean School of Public Health in 1943 was a joint venture of Universidad de Chile and the Rockefeller Foundation. This school was the centre of reform for all Latin America’s health systems for decades. Our “Rockefeller Boys” were key in the institutional development that pushed for the National Health Service in 1952 and all its positive related outcomes.

I have been asked to assess two of the most successful Rockefeller Foundation health programmes: National Epidemiology Boards in 1994 and the International Clinical Epidemiology Network (INCLEN) in 1999. This last effort was done in collaboration with that renowned hero of international health, Halfdahn Mahler. For INCLEN our conclusion was that it had been, and still is, one of the strongest antecedents of the evidence-based medicine movement and the revival of scientific medicine.

So my public request to the Foundation: don’t give up on your public health projects. You might not be as rich as other players but you have the tradition, the quality, and the credibility.

I declare that I have no conflict of interest.

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When the book is wrong

A 38-year-old woman, who had received a kidney transplant 4 years previously, was admitted to the intensive care unit for severe pneumocystis pneumonia. The first-line therapy was intravenous co-trimoxazole (trimethoprim/sulfamethoxazole). However, after 10 days, she developed confluent exanthema of the trunk and co-trimoxazole was suspected as the cause. A cutaneous biopsy confirmed the clinical suspicion. Co-trimoxazole was stopped and the eruption progressively disappeared.

Intravenous pentamidine (Pentacarinat was proposed as an alternative because it is the second-
line therapy approved by the Belgian version of the “Sanford Guide to antimicrobial therapy 2005–2006” for severe pneumocystosis. However, the proposal was rejected in accordance with a note in the Belgian Pentacarinat prescribing information (Sanofi-Aventis) that Pentacarinat is contraindicated if sulphonamide hypersensitivity is suspected. This note also appears in the 23rd edition of a Compendium whose publication is supervised by the government.

The combination of clindamycin and primaquine, the third alternative treatment recommended by the Sanford Guide, was started. But after 48 h, the patient developed primaquine-induced methaemoglobinemia and the treatment was stopped. At this point, no alternative treatment could be given for this severe pneumocystosis.

Since no other international drugs database mentioned pentamidine’s contraindication if sulphonamide hypersensitivity was suspected, we contacted Sanofi-Aventis Belgium for an additional explanation. We were told that the notice had been written on governmental instruction. We therefore questioned the Belgian Ministry of Social Affairs, Health and Environment, but no medical evidence for the instruction could be provided. We therefore commenced intravenous pentamidine treatment, and the patient was discharged from the intensive-care unit after 21 days.

As a result of our investigation, the drug information notice will be modified as soon as possible by the Belgian Ministry of Social Affairs, Health and Environment and by Sanofi-Aventis Belgium. This case report emphasises the fact that even an official book can contain some mistakes: keeping a critical mind remains essential.

We thank François Gemenne for correction of the text. We declare that we have no conflict of interest.

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Homeland security reaches the anus

I wish to bring to your attention difficulties one of my patients recently encountered when entering the USA. He is a 48-year-old man with a fistula-in-ano managed with a long-term seton to control perianal sepsis.

A seton consists of a length of suture material knotted to form a loop which lies in the fistula track. It passes through the fistula, out of the external opening beside the anus, into the anus, and re-enters the fistula through the internal opening. Various different materials can be used; in this case the seton was made of a turquoise braided synthetic suture. Many fistulas are treated with setons in the short term, and, in those that are high or associated with Crohn’s disease, this management can be long-term.

On arrival in New York in August, 2006, for a holiday, the patient was interrogated by immigration officials, then examined and searched. The presence of the seton gave rise to much concern, I assume because of a suspicion that a drug package or terrorist weapon was in some way attached to it. A rectal examination was done, during which the examining official pulled very hard on the seton, causing severe pain, but fortunately not damaging the anal sphincter muscles encircled by it.

The patient now requires an examination under general anaesthetic to insert a replacement.

I thought I should highlight this rather bizarre manifestation of “homeland security” because I suspect that it might become a more frequent problem. I suggest that any patient with a seton who is planning to travel to the USA or any other country where they are likely to be searched in this manner should carry a letter from their specialist explaining the nature of their condition and treatment.

I declare that I have no conflict of interest.

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Kolbe AR, Hudson RA. Human rights abuse and other criminal violations in Port-au-Prince, Haiti: a random survey of households. Lancet 2006; 368: 864–73—In this Article (Sept 2, 2006), the conflict of interest statement should have included: “Athena Kolbe has also written under the name Lyn Duff. Lyn Duff is cited in references 2 and 19.”
Targeted reinnervation for enhanced prosthetic arm function in a woman with a proximal amputation: a case study

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Summary

Background The function of current artificial arms is limited by inadequate control methods. We developed a technique that used nerve transfers to muscle to develop new electromyogram control signals and nerve transfers to skin, to provide a pathway for cutaneous sensory feedback to the missing hand.

Methods We did targeted reinnervation surgery on a woman with a left arm amputation at the humeral neck. The ulnar, median, musculocutaneous, and distal radial nerves were transferred to separate segments of her pectoral and serratus muscles. Two sensory nerves were cut and the distal ends were anastomosed to the ulnar and median nerves. After full recovery the patient was fit with a new prosthesis using the additional targeted muscle reinnervation sites. Functional testing was done and sensation in the reinnervated skin was quantified.

Findings The patient described the control as intuitive; she thought about using her hand or elbow and the prosthesis responded appropriately. Functional testing showed substantial improvement: mean scores in the blocks and box test increased from 4·0 (SD 1·0) with the conventional prosthesis to 15·6 (1·5) with the new prosthesis. Assessment of Motor and Process Skills test scores increased from 0·30 to 1·98 for motor skills and from 0·90 to 1·98 for process skills. The denervated anterior chest skin was reinnervated by both the ulnar and median nerves; the patient felt that her hand was being touched when this chest skin was touched, with near-normal thresholds in all sensory modalities.

Interpretation Targeted reinnervation improved prosthetic function and ease of use in this patient. Targeted sensory reinnervation provides a potential pathway for meaningful sensory feedback.

Introduction

Improving the function of artificial arms remains a challenge, especially for amputations at the elbow or higher, where the disability is greatest. Motorised hooks, hands, wrists, and elbows are available, but existing methods of control are inadequate. Currently, most powered artificial limbs are controlled with the surface electromyogram (myoelectric signals) from a remaining pair of agonist-antagonist muscles in the amputated limb. This method allows only a single motion to be controlled at a time; operation of the prosthetic elbow, wrist, and hand, or hook must be done sequentially. Furthermore, current methods of myoelectric control do not have a natural feel because proximal muscle functions (eg, shoulder, bicep, or triceps muscles) are not normally used to direct wrist or hand movements. Thus, these methods are frustratingly slow and awkward. Furthermore, current prostheses have no intrinsic sense of touch and provide little sensory feedback to the user. They are instead operated only with visual feedback.

We developed a new biological neural machine interface for individuals with amputations, called targeted reinnervation. Targeted muscle reinnervation (TMR) uses the residual nerves from an amputated limb and transfers them onto alternative muscle groups that are not biomechanically functional since they are no longer attached to the missing arm. During the nerve transfer procedure, target muscles are denervated so that they can be reinnervated by the residual arm nerves that previously travelled to the arm before amputation. The reinnervated muscles then serve as biological amplifiers of the amputated arm motor commands. Subcutaneous tissue is removed so that surface myoelectric signals are optimised for power and focal recording. TMR thus provides physiologically appropriate electromyogram control signals that are related to previous functions of the lost arm. For example, transferring the median nerve to a segment of pectoralis muscle provides a hand-close myoelectric signal. The patient thinks about closing his or her hand and the median nerve reinnervated segment of the pectoralis muscle contracts. The myoelectric signal from this reinnervated muscle segment is then used to provide a control input to close the motorised hand. By transferring multiple nerves, TMR myoelectric signals allow intuitive, simultaneous control of multiple joints in an advanced prosthesis. TMR was first done in a man with bilateral shoulder disarticulation, increasing his performance on standardised function tests by as much as 250%. Two men with long transhumeral amputations had successful targeted reinnervation surgery with similar functional results. Surgery was unsuccessful in a fourth man, because of nerve injuries discovered during the surgery.

Similarly, targeted sensory reinnervation (TSR) might potentially be used to provide the amputee a sense of touch in the missing limb. With this technique, a segment of skin near or overlying the TMR site is denervated and the regenerating afferent nerve fibres...
from the residual hand nerves are enabled to reinnervate this area of skin. As a result, when this skin is touched, the amputee feels as if their hand is being touched. We call this transfer sensation, and it is an exciting mechanism to potentially provide meaningful sensation to the amputee. For example, sensors in the prosthetic hand could quantify pressure, temperature, and texture of objects, and actuators over the reinnervated skin could apply proportional pressure, thermal, and shear stimuli back to the skin of the TSR site, so that the amputee seems to feel what he or she is touching. TSR developed unexpectedly in our first patient. By removing subcutaneous fat, his skin was denervated and afferent nerve fibres regenerated through his pectoral muscles to reinnervate his chest skin.

After the initial success with our first male patient we sought to improve our techniques in subsequent surgeries and address new challenges for female patients. Specifically, we would not be able to remove much subcutaneous tissue in female patients (ie, give them a mastectomy) to optimise surface myoelectric recordings as we did in the male patient. For this reason, surgical techniques were developed to work above and to the side of the breast. Additionally, a new technique was developed to purposefully apply targeted sensory reinnervation without subcutaneous tissue removal. We describe the application of targeted muscle and sensory reinnervation in a young woman with a very proximal transhumeral amputation.

**Methods**

**Patient**

The patient was a 24-year-old woman who had a traumatic transhumeral amputation in May, 2004, due to a motorcycle accident. She had severe phantom limb pain (9 out of 10 Likert scale) that abated with treatment over 6 months. Since only 3 cm of her humerus remained, the patient was fitted with a shoulder disarticulation level prosthesis. She received her first conventional myoelectric prosthesis in October, 2004, in a different city; the device
consisted of a passive shoulder, a motorised elbow, a passive wrist rotator and a motorised hand. She used myoelectric signals from her pectoral and remnant triceps muscles to sequentially operate the prosthetic elbow and hand. She was trained to use the device in weekly occupation therapy sessions that lasted 3 months, starting in January, 2005.

Procedures
Targeted reinnervation surgery was done in August, 2005, with ethics committee approval and written informed consent from the patient. The risks of the procedure included permanent paralysis of the target muscles, recurrence of phantom limb pain, and development of painful neuromas, in addition to standard risks of elective surgery. Surgery was done under general anaesthesia and without muscle relaxation (figures 1–6). The patient’s previous amputation incision was reopened. The musculocutaneous, median, ulnar, and radial nerves were all identified by their branching pattern and cut back to normal appearing fascicles. A branch of the radial nerve leading to a triceps remnant was identified using a nerve stimulator and carefully preserved. All fat and scar tissue over the remnant triceps muscle was excised to optimise the surface myoelectric signal of this muscle.

Inspection of the inferior aspect of the clavicular head of the pectoralis revealed two separate motor nerves entering this muscle segment. Two large (1·5 mm diameter) motor nerves were found innervating the sternal head of the pectoralis major, and the motor nerve to the pectoralis minor was also identified. These motor nerve branches were all divided a few mm from where the motor nerve

Figure 3: Coaptation of nerves to pectoralis major
(1) Ulnar nerve. (2) Median nerve. (3) Coaptation of musculocutaneous nerve to clavicular head of pectoralis major. (4) Coaptation of median nerve to sternal portion of pectoralis major. (5) Coaptation of musculocutaneous nerve to clavicular head of pectoralis major.

Figure 4: Healthy fascicles of ulnar nerve

Figure 5: End-to-side neurorrhaphy of intercostal brachial cutaneous nerve coapted to median nerve

Figure 6: Final appearance
Lower incision marks area from which fat was removed from over serratus muscle.
intercostobrachial cutaneous nerve was cut and the distal end was coapted to the side of the median nerve. The supraclavicular cutaneous nerve was cut and the distal segment was coapted to the side of the ulnar nerve. The anterior was divided and the distal segment was coapted to the radial nerve.

(A) Targeted muscle reinnervation. The musculocutaneous, ulnar, and median nerves were transferred to separate segments of the pectoralis major muscle. The long thoracic nerve innervating the inferior three slips of serratus anterior was divided and the distal segment was coapted to the radial nerve.

We then did four brachial plexus nerve transfers (figure 7A). The ulnar nerve was sewn to the motor nerve of the medial half of the clavicular head of the pectoralis major and the musculocutaneous nerve was sewn to the lateral motor nerve of the same muscle segment. The median nerve was divided in half lengthwise along its inner epineurium, and the split nerve endings were coapted to each of the two motor nerves of the sternal head of the pectoralis major. These large brachial plexus level nerves completely covered the areas where the small motor nerves entered the muscle segments. The radial nerve was sewn end-to-end to the long thoracic nerve for reinnervation of the distal slips of the serratus anterior muscle.

We did two sensory nerve transfers (figure 7B). The supraclavicular sensory nerve was located through a separate 3-cm transverse incision in the neck. This sensory nerve was divided and the proximal end entered the muscle segments. The proximal ends of these nerves were resected and mobilised away from the chest wall so that they could not reinnervate the target muscles.

When the patient was enrolled into our study in May, 2005, functional testing was done with her conventional myoelectric prosthesis control. At this time, she had had the prosthesis for 8 months, and had been regularly using it for 5 months. A box and blocks test was done, in which the patient moves 2.5-cm square blocks from one box, over a 10-cm wall, and into another box. The test was modified slightly, allowing the patient 2 min, instead of 1 min, to move blocks. The patient was allowed to practise each test for several minutes until she felt comfortable with the task. She then did the task three times with rest breaks of several minutes in between. The Assessment of Motor and Process Skills (AMPS) test was done by an occupational therapist certified in this validated, single-subject testing method. For testing with the patient’s conventional prosthesis, the two tasks were: preparation of a peanut butter and jelly sandwich, including gathering items, preparing, cutting the sandwich in half, serving, cleaning up, and returning items to appropriate storage; and ironing a shirt, including setting up an ironing board, hanging the shirt on a hanger, safely storing the iron, and folding up the board. The patient was also asked to keep a diary of how much she used her prosthesis, recording changes in sensation, and documenting her impressions.

After the experimental surgery, the patient was instructed to try to use all aspects of her missing arm (elbow, wrist, hand, and fingers) daily in an attempt to activate pathways and strengthen muscle as soon as reinnervation occurred. In March, 2006, she was brought to our facility for 2 weeks to fit her with the new experimental prosthesis, train her in its use, and participate in studies. We did extensive surface electromyogram testing. A grid of 128 monopolar surface electrodes was placed over the muscles of interest in the patient’s anterior chest, lateral chest, and shoulder. Monopolar myoelectric signals were recorded as the patient attempted to open her hand, close her hand, flex her elbow, and extend her elbow, following a video demonstration. Ten trials of each movement were recorded with a BioSemi Active II system (BioSemi, Amsterdam, www.thelancet.com Vol 369 February 3, 2007 374
Netherlands) sampled at 2 kHz. The spatial electromyogram activity for each movement was characterised by contour plots where the average root mean square value of each channel’s electromyogram was represented by different colours. Surface electrodes were mounted in the patient’s prosthetic socket at the points corresponding to the maximum surface amplitude for each elbow and hand movement. During this 2-week period, the patient had training every day with the experimental prosthesis. On completion of this fitting and training period she went home and used her prosthesis for 5 weeks. She then returned to our facility for 1 week of testing and other experiments. The blocks and box test was repeated. The AMPs test was repeated with two different tasks: preparation of a grilled cheese sandwich, including preparation in a pan on the stove using butter, cutting the sandwich in half, and serving it with a beverage, opening and closing the container, returning items to the refrigerator, and cleaning of surfaces; and preparation and serving of a tossed salad with four ingredients, including peeling and slicing, getting out items and returning them to the refrigerator, pouring dressing, covering and storing leftovers, and cleaning up. The patient’s subjective opinions of the new prosthesis were also obtained.

In the assessment of sensory reinnervation, the patient was asked to point to the areas of her chest where the transfer sensation for individual digits was most prominent. The positions of the points were recorded on a schematic diagram of her chest with a representative grid. The character of the sensory reinnervation was quantified for each type of sensory percept. Light touch thresholds were determined with Semmes-Weinstein monofilaments (North Coast Medical, Morgan Hill, CA, USA).9 Sharp and dull sensibility was determined at 20 selected points distributed across the transfer site with a hand-held neurotip neurometer (Owen Mumford, Marietta, GA, USA). Ability to detect vibration was assessed by pressing a C128 tuning fork to various points on the chest. Temperature thresholds were assessed at two positions over the transfer site with a TSA II NeuroSensory Analyzer (Medoc, Ramat-Yishai, Israel).9 The patient’s normal contralateral chest and right thenar eminence served as control sites.

Role of the funding source
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 access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Postoperatively, the patient’s phantom limb pain returned to a lesser degree (6 out of 10 Likert scale) but it resolved.
with treatment within 4 weeks. No other complications occurred. The surgery caused no disfigurement (figure 8). An area 11 cm wide by 9 cm high became insensate on the patient's anterior superior chest (figure 8). On her lateral chest wall, only a narrow band around her surgical wound site became numb.

The patient had the first indication of muscle reinnervation about 3 months after the surgery. She could feel the muscles of her chest twitching when she tried to close her hand or bend her elbow. By 5 months, strong muscle contractions could be seen and palpated. Extensive electromyogram testing was done 6 months after surgery following full muscle reinnervation; signals were recorded from all the nerve transfer sites (figure 9). A new experimental prosthesis was made (figure 10) consisting of a motorised elbow with a computerised arm controller (Liberating Technologies, Holliston, MA, USA), a motorised wrist rotator, and a motorised hand (Otto Bock,

Figure 9: Map of surface electromyogram amplitude for four different movements

A Placement of electrodes
B Elbow flexion
C Elbow extension
D Hand closure
E Hand opening

These contour plots were built using monopolar high density surface electromyogram recordings. Distinct surface electromyogram distributions are evident for different movements.
Minneapolis, MN, USA). The prosthesis had passive shoulder components. The computerised arm was programmed to use the myoelectric inputs from the TMR muscles to control the motorised hand and elbow. Two pressure-sensitive pads were mounted in the patient’s socket that she used to control her motorised wrist, allowing independent, proportional, simultaneous control of all three joints (table 1).

With training, the patient became proficient in use of the prosthetic within a few days. She was able to operate the hand, wrist, and elbow simultaneously. She reported that operation of the hand and elbow was very intuitive: when she thought of opening the hand, closing the hand, bending the elbow, or straightening the elbow, the prosthesis responded accordingly. The patient was able to operate the wrist rotator with the pressure sensitive buttons at the same time as moving the hand and elbow; however, she rarely did so, because the cognitive burden of controlling all three joints simultaneously was high.

At the time of pre-operative testing the patient had been using her conventional prosthesis for 7 months. Testing with her conventional prosthesis showed poor function, as is typical with this level of amputation (table 2). Her functional outcomes were improved in all areas 7 weeks after beginning the fitting and training of the TMR-controlled experimental prosthesis. Webmovie 1 shows the patient undertaking the blocks and box test (left side is with conventional myoelectric control; right side is using TMR controlled prosthesis); she was almost four times as fast with TMR control, compared with the conventional prosthesis. AMPS testing showed substantial improvement in both motor and process scores. Webmovie 2 shows the patient undertaking daily living tasks with the experimental prosthesis.

The patient was very satisfied with the cosmetic result of the surgery and enthusiastic about the improvement in her limb control. Although she initially tried to use her original conventional prosthesis on a regular basis, she said that it was very frustrating and difficult to operate. Her use of the conventional prosthesis decreased to only 1–2 times per month, when the device was worn mainly for cosmetic reasons. She reported that her experimental prosthesis was much easier and more natural to use than was the conventional prosthesis. She described operation of her hand and elbow as: “I just think about moving my hand and elbow and they move.” Perhaps her most telling statement was: “My original prosthesis wasn’t worth wearing—this one is.” At time of writing the patient used her new TMR prosthesis for an average of 4–5 h a day (up to 16 h), 5–6 days per week for many functional tasks including cooking, putting on makeup, carrying things, eating, house cleaning and laundry, as well as for cosmetic purposes.

The patient had the first indication of sensory reinnervation at 3 months after the surgery. She reported a tingling sensation in her missing hand when her anterior
chest was touched. By 5 months, any stimulus applied to the previously insensate anterior chest skin was perceived as being in her missing hand. After about 6 months, she developed a relatively faint percept of her middle finger on the lateral chest wall.

The supraclavicular cutaneous nerve was anastomosed end-to-side to the ulnar nerve and a percept of the fourth and fifth fingers was expected in the reinnervated anterior chest skin. However, the anterior chest skin was clearly reinnervated by both median and ulnar afferents. The perceptive fields of touch were quite complex; when the patient was touched at a single point she often perceived sensation in contiguous or disjoint areas of different digits and her palm. Figure 11 shows the spots that the patient identified as the primary points where she perceived sensation in just one digit.

All modalities of cutaneous sensation were present; however, the percept of tingling in response to touch of the target skin persisted (rather than a more normal pressure sensation). The lowest threshold at which light touch could be perceived in the reinnervated region was 0·4 g; the thresholds at most points in this area were under 4 g, compared with a threshold of 0·4 g at the same location on the right side and a light-touch threshold of 0·16 g on the right index finger. With increased pressure the patient felt an increased intensity of the tingling sensation—ie, she was able to feel graded pressure. She had appropriate thresholds for warm and cold sensation within her reinnervated region. The average threshold for perception of cold was 29·1°C in her reinnervation area, 29·9°C on the intact contralateral chest, and 31·3°C in her right palm, indicating that sensitivity to cold was slightly increased in the reinnervated skin. The average threshold for perception of warmth was 35·2°C in the reinnervated region, 34·7°C on the contralateral chest, and 33·2°C in the right hand, indicating that sensitivity to an increase in temperature was slightly reduced in the reinnervated skin. At 19 of the 20 selected points across the transfer site, the patient was able to correctly differentiate between sharp and dull sensation, and was also able to perceive vibration in the reinnervated skin. Stimulation of each of the aforementioned types of percept modalities within the reinnervation region was interpreted by the patient as occurring in her missing hand.

**Discussion**

Targeted reinnervation surgery was successful in this young woman. Four independent myoelectric sites were created that allowed improved control of a motorised artificial arm. Transfer sensation also developed; when the patient was touched on her reinnervated chest skin, she perceived the sensation to be in her missing hand.

A great need exists for neural-machine interfaces that can enable people with disabilities to interact with their environment. An effective interface should extract neural command signals to operate devices that overcome a person’s motor impairment, provide sensory feedback to the person with a disability, or both. Research in brain-machine interfacing is developing new communication and control technology for people with severe motor disorders such as paralysis, stroke, cerebral palsy, and spinal cord injury. The possibilities of extracting information from the peripheral nervous system with nerve-cuff electrodes, sieve electrodes, and penetrating arrays have also been examined. To date, the cochlear implant is the most clinically successful neural-machine interface, and has improved the hearing of thousands of people by interfacing with the auditory neural system.

Targeted reinnervation is a new neural-machine interface for individuals with amputations. TMR rewires peripheral nerves and uses available surface muscles as biological amplifiers to develop rich new sources of motor command signals. After TMR our patient found that her prosthesis was much easier and more natural to use, because she was using physiologically appropriate neural pathways to operate her artificial arm. The function of her prosthesis improved substantially, as shown by an increase in speed and efficiency of motion. This system has other distinct advantages: it is relatively simple to implement; no hardware is implanted in the body that could break, necessitating additional surgery; and the technique can be used with existing myoelectric prosthetic technology.

Our patient tried to use her conventional prosthesis for several months, but became frustrated with the device and then wore it rarely. This problem is typical of shoulder disarticulation amputees, since the prostheses have such limited function and are quite heavy (our patient’s prostheses weighed just over 6 kg) and the harnessing is uncomfortable. The improved control led to improved satisfaction and wear time—the new device had similar weight and harnessing. The 4–5 h of use per day by the patient is judged to be heavy use for a unilateral proximal amputee. However, the prosthesis is still a tool that the patient uses when needed and takes off for comfort. Hopefully, improvements in arm prostheses will make
them lighter and more comfortable, thus increasing the time for which they can be comfortably worn.

We faced a substantial challenge with this patient, in that her breast covered much of the primary target muscle—her pectoralis major muscle. It was helpful that a remnant of her humerus preserved the insertion of the pectoralis, holding the sternal head in its normal anatomical position, up and across the chest, allowing electromyogram detection over at least the upper portion of the muscle. With a complete shoulder disarticulation, the pectoralis retracts medially and inferiorly, thus less muscle would have remained above the breast. The long thoracic nerve and distal serratus anterior muscle were successfully used to develop an additional surface electromyogram control site not covered by the breast.

In this study, we used a commercially available prosthesis with simple algorithms based on the magnitude of the surface electromyogram to control only the elbow and a one degree-of-freedom hand. However, the residual nerves of the arm contain all the control commands for complex movement of the elbow, wrist, thumb, and fingers. Much of this information is transferred to the TMR muscle; thus the potential exists for further improvement in control, dexterity, and function of artificial arms. Advanced signal processing algorithms have been used to extract more information from the residual limbs in transradial amputees, showing improved, intuitive control of wrist rotation, wrist flexion, and hand movements. Research is in progress to clinically implement these algorithms in advanced artificial arms that promise further improvement in control and function. Another developing technology that could benefit TMR is implantable myoelectric systems. Telemetry of intramuscular myoelectric signals could increase access to muscles under subcutaneous fat, breast tissue, and deeper muscles. They might improve information content and stability, compared with surface myoelectric signals, and increase the robustness of this neural-machine interface.

In this study we showed that targeted sensory reinnervation can be purposefully implemented to provide a discrete region of transfer sensation—ie, a sensation of touch in the missing limb. The target skin is an excellent transducer for cutaneous sensory input into the nervous system. We hypothesise that the skin provided the environment for the amputated afferent axons to find appropriate end organs that yielded appropriate sensory perception. This patient’s transfer sensation had high fidelity, in that all the cutaneous sensory modalities were present and the thresholds of perception were close to normal.

The clinical implications of TSR are exciting. The potential exists to provide meaningful light touch, graded pressure, texture, edge detection, and thermal feedback to amputees in an intuitive manner. For the patient, there is much to be gained with even a single point of pressure feedback. For example, the perception of simply touching an object can provide goal confirmation in grasping, and graded force feedback relates to how hard the user is squeezing an object; both have great functional value. This patient had a somatotopic organisation, in that different regions of the TSR skin felt like different fingers or her thumb. This occurrence might allow useful sensory feedback for multiple regions of the hand; sensors could be placed in each prosthetic digit and have the sensory feedback applied to the corresponding regions of reinnervated skin. Perhaps the most important aspect of TSR is psychological. Enabling patients a perception of feeling what they are touching could help them to incorporate their prosthesis into their self image in a more positive manner, and to better connect with their physical and social environments.

The sensory somatotopic organisation that developed differed from what we expected. In surgery, the distal segment of the intercostobrachial nerve was transferred to the median nerve and median sensation was anticipated on the lateral chest. Only a faint median percept developed, probably because the skin innervated by the intercostobrachial nerve was amputated with the arm leaving nothing for the median afferents to reinnervate. The distal segment of the supraclavicular nerve was transferred to the ulnar nerve, and ulnar sensation alone was expected on the anterior chest. However, a strong percept and large area of median nerve reinnervation were noted. The robustness of the median nerve sensory reinnervation was surprising. The median nerve afferents had to regenerate through the pectoralis major muscle and through a layer of subcutaneous tissue that was more than 1 cm thick while in competition with the regenerating ulnar afferents. Further study is clearly needed to better understand what guides, promotes, or impedes sensory axon regeneration. Research is also needed to assess the skin-receptor densities and receptor types and to characterise afferent-receptor interaction in this hyper-reinnervation model, in which a large excess of sensory afferents are competing to reinnervate a limited skin region.

The primary sensory cortex is able to undergo substantial change after amputation and nerve transfer. Neural plasticity could be detrimental to the outcome of the TSR if the sensory cortex was to integrate the hand percepts into a chest body image. However, this problem has not happened in 4 years with our first patient or in 1 year with this second patient. Additionally, the motor pathways seem to be equally robust. In fact, targeted reinnervation shows the endurance of dormant central pathways. The time of complete non-use for these central pathways was at least 18 months in this patient (time from amputation to reinnervation), yet motor commands were readily elicited and complex transfer sensation developed. However, whether longer periods of dormancy might affect the viability of these pathways is unclear. Another interesting possibility associated with neural plasticity is that the sensory cortex might develop a more functional somatosensory representation of the TSR site with use and...
time. For example, repeatedly touching a spot of reinnervated skin that contains some thumb afferents in correlation to touching an object with the prosthetic thumb might cause the brain to interpret that skin spot more clearly as representing a thumb.

A key question for the application of targeted reinnervation is how long do amputated nerves remain viable? Voluntary signals can be recorded from motoneurons many years after amputation and stimulating a nerve decades after amputation will produce a perception of sensation in the missing limb. Some axons are lost with time, but estimates of the time taken vary greatly. Furthermore, targeted reinnervation uses hyper-reinnervation of the target muscle and skin. The proportion of viable axons that are needed is unknown, but a large excess of both motor and sensory axons are transferred. The procedure can probably be undertaken successfully many years after the initial amputation.

This patient and our other three patients represent early application of targeted reinnervation technique. Whether the improved function is enough to keep these patients wearing their devices in years to come, or whether they adapt to their new control even better and show greater functional gains, remains to be seen. Long-term follow-up is also needed to see how our patient’s transfer sensation evolves. We need to ascertain whether the sensation persists unchanged or whether the character, localisation, and somatotopic organisation of the sensation are altered with time and use.

Contributors

T Kuiken participated in the all aspects of this article, including project management, surgery, data collection, and manuscript writing. L Miller, R Lipschutz, and B Lock participated in fitting of the prosthetic limb, data collection, and manuscript writing. G Dumanian participated in the patient’s training, data collection, and manuscript writing. P Marasco participated in data collection and manuscript writing. G Dumanian participated in the surgery, data collection, and manuscript writing. P Zhou participated in collection and analysis of electromyogram data. All authors saw and approved the final manuscript.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgments

This work was done in collaboration with Liberating Technologies, a company that manufactures and distributes prosthetic components. As a fee-for-service, they sold us the Boston Digital Elbow and modified the company that manufactures and distributes prosthetic components. As a result, we have no conflict of interest.

References

Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis

Arintaya Phrommintikul, Steven Joseph Haas, Maros Elsik, Henry Krum

Summary

Background Recombinant human erythropoietin is commonly used for treatment of anaemia. Our aim was to determine whether targeting different haemoglobin concentrations with such treatment is associated with altered all-cause mortality and cardiovascular events in patients with anaemia caused by chronic kidney disease.

Methods We did a meta-analysis of randomised controlled clinical trials that were identified in medical databases and trial registration websites. Trials were eligible for inclusion if they assessed the effects of targeting different haemoglobin concentrations in patients with anaemia caused by chronic disease who were randomly assigned to treatment with recombinant human erythropoietin, recruited at least 100 patients, and had a minimum follow-up of 12 weeks.

Findings We analysed nine randomised controlled trials that enrolled 5143 patients. There was a significantly higher risk of all-cause mortality (risk ratio 1.17, 95% CI 1.01–1.35; p=0.031) and arteriovenous access thrombosis (1.34, 1.16–1.54; p=0.0001) in the higher haemoglobin target group than in the lower haemoglobin target group in the fixed effects model without heterogeneity between studies. There was a significantly higher risk of poorly controlled blood pressure (1.27, 1.08–1.50; p=0.004) in the higher haemoglobin target group than in the lower target haemoglobin group with the fixed effects model; however, this was not significant in the random effects model (1.31, 0.97–1.78; p=0.075). The incidence of myocardial infarction was much the same in the two groups.

Interpretation To target higher haemoglobin concentrations when treating patients with anaemia caused by chronic kidney disease with recombinant human erythropoietin puts such patients at increased risk of death. Current guidelines do not include an upper limit for the target haemoglobin concentration; such an upper limit should be considered in future recommendations.

Introduction

Anaemia is commonly seen in individuals with chronic kidney disease.1 A reduction in haemoglobin concentrations in these patients has been shown to be associated with impairment in quality of life, reduced energy, neurocognitive decline, decreased exercise capacity, and increased mortality.2,3 The cause of anaemia in such individuals is mainly related to a deficiency in the synthesis of endogenous erythropoietin.4 Therefore, the use of recombinant human erythropoietin represents a logical and commonly used treatment for this disorder. At present, such treatments include erythropoiesis-stimulating agents such as epoetin alfa and beta as well as the analogue of recombinant human erythropoietin, darbepoetin alfa.

Use of recombinant human erythropoietin to treat anaemia caused by chronic kidney disease has been found in some small mechanistic studies to be associated with improvements in muscle strength,5 exercise capacity,6 fatigue,7 neurocognitive function,8 and depression.9 However, considerable controversy exists with regard to the concentration of haemoglobin at which patients should begin treatment with recombinant human erythropoietin as well as the haemoglobin concentration that should be aimed for to increase benefits to a maximum and to reduce potential adverse effects to a minimum. These adverse effects include the development or worsening of systemic hypertension, site access thrombosis in dialysis patients with arteriovenous shunts, and the apparent potential for increased cardiovascular events.10–12 The publication of two major studies of recombinant human erythropoietin in chronic kidney disease—Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta (CREATE)13 and Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR)14—has raised further the possibility that this treatment might be associated with an increase in cardiovascular events in those individuals in whom a higher haemoglobin concentration is aimed for.

Our aim was to do a meta-analysis of all available data to determine whether targeting different haemoglobin concentrations when treating anaemic patients with chronic kidney disease with erythropoiesis-stimulating agents is associated with altered all-cause mortality and cardiovascular events.

Methods

Search strategy and selection criteria

Randomised controlled clinical trials were identified via MEDLINE (source PubMed, 1966 to November, 2006), EMBASE (1974 to November, 2006), the Cochrane Controlled Clinical Trials Register Database (through November, 2006), the Cochrane Renal Group Specialised Register of Randomized Controlled Trials (through www.thelancet.com  Vol 369  February 3, 2007 381
November, 2006), and the ClinicalTrials.gov website. All searches included the keywords and corresponding MeSH terms for erythropoietin, darbepoetin, kidney disease, renal disease, and randomised controlled trial. Manual reference checking of the bibliographies of all retrieved articles was also done. To identify studies reported only at scientific meetings, we searched—both manually and electronically—the abstracts of annual scientific sessions of the American Society of Nephrology, European Renal Association-European Dialysis and Transplantation Association (ERA-EDTA), and the International Society of Nephrology from 2000 to November, 2006.

Studies were assessed for data quality and validity by consensus between two investigators (AP and ME). Formal data analysis was done in a blinded manner by another investigator (SJH), in accordance with Quality of Reporting of Meta-analyses recommendations.15

Prospective randomised controlled trials done in adults that were published in English were considered for inclusion in this meta-analysis. Studies were included if they assessed the effects of targeting different haemoglobin concentrations when treating patients with anaemia caused by chronic kidney disease with erythropoiesis-stimulating agents. Potential therapies used to achieve target haemoglobin concentrations were epoetin alfa, epoetin beta, darbepoetin, or placebo. Studies with fewer than 100 patients or with a duration of treatment and follow-up of less than 12 weeks were excluded. Trials with very low concentrations of haemoglobin at baseline (<80 g/L) were excluded from the main analysis, but were used in sensitivity analyses.

### Data extraction and quality assessment

Trials were assessed by two independent reviewers (AP and ME), who extracted data on patient characteristics, type and mode of erythropoiesis-stimulating agents, method of dialysis, co-intervention, and outcomes. Outcomes assessed were all-cause mortality, myocardial infarction, changes in blood pressure, arteriovenous access thrombosis, and

---

**Table 1: Design of included trials**

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Method of allocation</th>
<th>Outcome assessors masked?</th>
<th>Adjudication of adverse events</th>
<th>Intention-to-treat analysis?</th>
<th>Number of patients lost to follow-up</th>
<th>Early termination?</th>
<th>Study chair/design</th>
<th>Control of database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besarab et al11</td>
<td>Open label</td>
<td>Yes</td>
<td>Investigators</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>Foley et al12</td>
<td>Open label</td>
<td>Yes</td>
<td>..</td>
<td>Yes</td>
<td>No</td>
<td>Author</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>Furuland et al13</td>
<td>Open label</td>
<td>..</td>
<td>Central coordinator</td>
<td>Yes</td>
<td>0</td>
<td>No†</td>
<td>..</td>
<td></td>
</tr>
<tr>
<td>Roger et al14</td>
<td>Open label</td>
<td>..</td>
<td>..</td>
<td>Yes</td>
<td>1 (low haemoglobin)</td>
<td>No</td>
<td>Author</td>
<td></td>
</tr>
<tr>
<td>Parfrey et al15</td>
<td>Double blind</td>
<td>..</td>
<td>..</td>
<td>Yes</td>
<td>2 (1 high, 1 low haemoglobin)</td>
<td>No</td>
<td>Author</td>
<td></td>
</tr>
<tr>
<td>Levin et al16</td>
<td>Open label</td>
<td>..</td>
<td>..</td>
<td>Yes</td>
<td>2 (low haemoglobin)</td>
<td>No</td>
<td>Author</td>
<td></td>
</tr>
<tr>
<td>Rossert et al17</td>
<td>Open label</td>
<td>..</td>
<td>..</td>
<td>Study site investigators</td>
<td>Yes</td>
<td>Yes</td>
<td>Author</td>
<td></td>
</tr>
<tr>
<td>Singh et al18</td>
<td>Open label</td>
<td>..</td>
<td>Central committee</td>
<td>Yes</td>
<td>Yes, number not stated</td>
<td>No†</td>
<td>Authors and sponsor</td>
<td></td>
</tr>
<tr>
<td>Druke et al19</td>
<td>Open label</td>
<td>..</td>
<td>Central committee</td>
<td>Yes</td>
<td>0</td>
<td>No</td>
<td>Authors and sponsor</td>
<td></td>
</tr>
</tbody>
</table>

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*Thrombovascular events and vascular access thrombosis. †Amended by addition of exclusion criteria. ‡Amended by change of target haemoglobin concentrations.
### Table 2: Characteristics of trials included in meta-analysis

<table>
<thead>
<tr>
<th>n</th>
<th>Age (years)*</th>
<th>Sex†</th>
<th>Diabetes mellitus‡</th>
<th>CKD caused by diabetes mellitus</th>
<th>Stage of kidney disease§</th>
<th>Renal function¶</th>
<th>Dialysis</th>
<th>Number starting dialysis during study</th>
<th>Hypertension (%) at baseline</th>
<th>Cardiac inclusion criteria</th>
<th>Type of ESA and mode of delivery</th>
<th>Mean dose of ESA (U/week)</th>
<th>Mean study duration including follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Epoetin alfa, SC/IV</td>
<td>420 (350–520)</td>
<td>140 (90–175)</td>
</tr>
<tr>
<td>Besarab et al 21</td>
<td>1233</td>
<td>65 (12)</td>
<td>61 (12)</td>
<td>309 (9%)</td>
<td>295 (52%)</td>
<td>334 (54%)</td>
<td>357 (38%)</td>
<td>359 (41%)</td>
<td>283 (46%)</td>
<td>5</td>
<td>NA</td>
<td>HD</td>
<td>NA</td>
</tr>
<tr>
<td>Foley et al 21</td>
<td>146</td>
<td>62 (58–66)</td>
<td>**</td>
<td>62 (57–67)</td>
<td>**</td>
<td>31 (79%)</td>
<td>**</td>
<td>28 (76%)</td>
<td>**</td>
<td>NA</td>
<td>NA</td>
<td>14 (36%)</td>
<td>9 (24%)</td>
</tr>
<tr>
<td>Furuland et al 23</td>
<td>416</td>
<td>63 (12)</td>
<td>**</td>
<td>63 (14)</td>
<td>**</td>
<td>345 (67%)</td>
<td>**</td>
<td>126 (62%)</td>
<td>**</td>
<td>41 (19%)</td>
<td>40 (20%)</td>
<td>37 (17%)</td>
<td>32 (16%)</td>
</tr>
<tr>
<td>Roger et al 14</td>
<td>155</td>
<td>53 (14)</td>
<td>M</td>
<td>54 (12)</td>
<td>M</td>
<td>38 (51%)</td>
<td>M</td>
<td>18 (24%)</td>
<td>M</td>
<td>26 (33%)</td>
<td>NA</td>
<td>NA</td>
<td>3–4</td>
</tr>
<tr>
<td>Parfrey et al 23</td>
<td>596</td>
<td>52 (15 6)</td>
<td>49 (15 2)</td>
<td>178 (60%)</td>
<td>180 (60%)</td>
<td>NA</td>
<td>NA</td>
<td>56 (19%)</td>
<td>51 (17%)</td>
<td>5</td>
<td>NA</td>
<td>HD</td>
<td>NA</td>
</tr>
<tr>
<td>Levin et al 21</td>
<td>172</td>
<td>56 (14 9)</td>
<td>57 (14 9)</td>
<td>55 (70.5%)</td>
<td>52 (70.3%)</td>
<td>32 (41%)</td>
<td>26 (35.1%)</td>
<td>25 (32.1%)</td>
<td>22 (29.7%)</td>
<td>2–4</td>
<td>15–79</td>
<td>None</td>
<td>7HD</td>
</tr>
<tr>
<td>Rossert et al 27</td>
<td>390</td>
<td>58 (13 6)</td>
<td>57 (13 6)</td>
<td>113 (8.8%)</td>
<td>118 (61%)</td>
<td>67 (34%)</td>
<td>68 (35%)</td>
<td>51 (17%)</td>
<td>49 (26%)</td>
<td>3–4</td>
<td>25–60</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Singh et al 28</td>
<td>1432</td>
<td>66 (13 4)</td>
<td>66.3 (13 5)</td>
<td>313 (43.8%)</td>
<td>329 (45.5%)</td>
<td>NA</td>
<td>NA</td>
<td>335 (48.6%)</td>
<td>364 (50.8%)</td>
<td>3–4</td>
<td>15–50</td>
<td>None</td>
<td>155</td>
</tr>
<tr>
<td>Druke et al 29</td>
<td>603</td>
<td>59 (13 7)</td>
<td>58 (13 7)</td>
<td>171 (57%)</td>
<td>154 (51%)</td>
<td>80 (27%)</td>
<td>77 (25%)</td>
<td>61 (20%)</td>
<td>63 (21%)</td>
<td>3–4</td>
<td>15–35</td>
<td>None</td>
<td>137</td>
</tr>
</tbody>
</table>

BP=blood pressure. CHF=congestive heart failure. DBP=diastolic blood pressure. ESA=erythropoiesis-stimulating agents. F=female. HD=haemodialysis. IHD=ischaemic heart disease. IV=intravenous. LVD=left ventricular disease. LVH=left ventricular hypertrophy. M=male. NA=not available. PD=peritoneal dialysis. SC=subcutaneous. *Data are mean (SD) or mean (95% CI). †Data are number of men (%). ‡Data are n (%); numbers are back-calculated from percentage in Besarab et al,21 Singh et al,14 Parfrey et al,25 and Furuland et al.23 §On the basis of the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative clinical practice guidelines. ¶Glomerular filtration rate (mL per min per 1·73 m2). ||Mean (95% CI) in U/kg/week. **Data for LVD group, mean (95% CI); in LVH group, 62 (57–67) in high group vs 60 (56–66) in low group. ††Data for LVD group, in LVH group, 15 (47%) in high group vs 15 (48%) in low group. †‡Data for LVH group, in high group vs 15 (26%) in high group vs 11 (31%) in low group. §§Data are mean (95% CI) for LVD group, in high (HV) vs low haemoglobin (19·058 ± 8·993). ¶¶Predialysis: 36 patients in high haemoglobin group vs 36 in low haemoglobin group. ¶¶¶Predialysis: 236 ± 140 in high and low haemoglobin group. ¶¶¶¶Basel: 155 ± 136; PD: 23 ± 23. ||||Based on the number of patients that received anti-hypertensive therapy. ***Data shown in predialysis group as U/kg/week (high haemoglobin 19 ± 8·993). §§§Data are median (range). ¶¶¶Significantly different (p<0·03) between the high haemoglobin group and the low haemoglobin group.
The Roger et al trial is not reported because there were no deaths in either group.

Table 3: Baseline, target, and achieved haemoglobin concentrations in included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline, target, achieved haemoglobin concentration (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besarab et al</td>
<td>90–110 (M), 100–120 (F)</td>
</tr>
<tr>
<td>Foley et al</td>
<td>90–110</td>
</tr>
<tr>
<td>Furuland et al</td>
<td>90–120</td>
</tr>
<tr>
<td>Roger et al</td>
<td>110–130 (M), 100–120 (F)</td>
</tr>
<tr>
<td>Parfrey et al</td>
<td>80–120</td>
</tr>
<tr>
<td>Levin et al</td>
<td>110–135</td>
</tr>
<tr>
<td>Rossett et al</td>
<td>&lt;130 (M), 125 (F)</td>
</tr>
<tr>
<td>Singh et al</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Druke et al</td>
<td>110–125</td>
</tr>
</tbody>
</table>

Risk ratio (95% CI) Weight (%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk ratio 95% CI</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besarab et al</td>
<td>1.21 (1.02–1.45)</td>
<td>57.9</td>
</tr>
<tr>
<td>Foley et al</td>
<td>1.33 (0.31–5.75)</td>
<td>1.1</td>
</tr>
<tr>
<td>Furuland et al</td>
<td>0.99 (0.61–1.62)</td>
<td>10.1</td>
</tr>
<tr>
<td>Levin et al</td>
<td>0.34 (0.04–3.22)</td>
<td>1.1</td>
</tr>
<tr>
<td>Parfrey et al</td>
<td>0.66 (0.33–1.39)</td>
<td>7.2</td>
</tr>
<tr>
<td>Druke et al</td>
<td>1.48 (0.87–2.52)</td>
<td>7.6</td>
</tr>
<tr>
<td>Rossett et al</td>
<td>0.17 (0.02–3.37)</td>
<td>2.2</td>
</tr>
<tr>
<td>Singh et al</td>
<td>1.45 (0.96–2.19)</td>
<td>13.0</td>
</tr>
<tr>
<td>Overall</td>
<td>1.17 (0.98–1.39)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2: Risk of all-cause mortality in the higher haemoglobin target group compared with the lower haemoglobin target group (fixed effects analysis)

The Roger et al trial is not reported because there were no deaths in either group.

See Online for weboappendix.

The quality of trials was assessed with standard criteria for allocation concealment, analysis by intention-to-treat, completeness of study and follow-up, adjudication of adverse events, study chair and design, funding source, and data-base controller.

Statistical analysis

Risk ratios (RR) with 95% CI of outcomes were derived from every study. Results were pooled with Stata version 8.2 with both the Mantel-Haenszel fixed effects model and the DerSimonian and Laird random effects model for dichotomous outcomes. In the Mantel-Haenszel model, we used Stata to calculate a weighting for every study in accordance with the number of events that occurred in every study to form an average overall outcome statistic and 95% CI. The DerSimonian and Laird model also considered any observed variability between the studies included in the analysis. Heterogeneity between studies was analysed with χ² and I² statistics. Significance was tested with the fixed effects model, unless heterogeneity was shown, in which case the random effects model was used. Statistical significance was set at the 0.05 level on the basis of two-way Z-tests and the 0.1 level of χ² tests.

Role of the funding source

There was no source of external funding for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 255 potentially eligible articles, 246 of which were excluded (figure 1). Nine trials with 5143 patients met the specified criteria. Table 1 shows the description of the trials; table 2 shows the characteristics of these trials. Briefly, the trials differed in terms of the population studied, duration of intervention, and primary outcomes. The number of patients in each study ranged from 146 to 1432. All studies were done in patients with moderately to severely reduced glomerular filtration rate or kidney failure, except that by Levin and colleagues, which also included patients with mildly reduced glomerular filtration rates. Age was fairly homogeneous, ranging between 50 to 65 years. Participants were mainly men, with the exception of Singh and colleagues’ study and those by Besarab and colleagues and Roger and co-workers (webappendix). Duration of follow-up ranged from 12 to 48 months. Two studies were terminated prematurely because of safety issues. Besarab and colleagues halted their study after an interim analysis raised concerns about safety, whereas Rossett and co-workers terminated their study after two cases of red cell aplasia. Singh and colleagues’ study was terminated because of the unlikelihood of showing a benefit in the higher haemoglobin target group. The studies differed in terms of cardiac co-morbidities in the recruited patients (table 2). Besarab and colleagues and Singh and co-workers both enrolled a higher proportion of diabetic patients than did the other trials. Table 3 shows the target and achieved haemoglobin concentrations in the trials. Reporting of cardiovascular outcomes and criteria for defining such outcomes (especially hypertension and left ventricular mass) varied between the trials. A detailed discussion of the differences between the included trials, can be found in the weboappendix.

Four trials comparing recombinant human erythropoietin with placebo were excluded because of very low

See Online for weboappendix.
haemoglobin concentrations at baseline, with the achieved haemoglobin concentration in the placebo group (about 70–80 g/L) being considerably lower than the currently recommended target.13,14,21,24–27 No difference was seen in the effect of recombinant human erythropoietin to aim for a high haemoglobin concentration, another that targeted a low haemoglobin concentration, and a placebo group—was excluded since the number of patients in the two active treatment groups did not meet the minimum patient number inclusion criteria.13 The effect of addition of these five excluded trials28–31,33 on the outcomes assessed in the meta-analysis was examined in sensitivity analyses.

The risk of all-cause mortality was significantly higher in the higher haemoglobin target group (RR 1·17, 95% CI 1·01–1·35; p=0·031; figure 2) than in the lower haemoglobin target group. This effect was dominated by Besarab and colleagues’ study,21 which contributed about 58% of the weight. There was no significant heterogeneity between the trials (heterogeneity $\chi^2$ 9·59, p=0·07, $I^2$=27%; figure 2).

A subgroup analysis was done with the studies that included patients with chronic kidney disease both predialysis13,21,24–27 and undergoing dialysis.21–23,25 RR of all-cause mortality was 1·33 (95% CI 0·98–1·81; p=0·067) in those not receiving dialysis and 1·11 (0·94–1·31; p=0·22) in the dialysis subgroup. A sensitivity analysis including the five trials that were excluded from the main analysis because baseline haemoglobin concentrations were too low, resulted in a RR for all-cause mortality of 1·14 (0·99–1·32; p=0·07).

Seven studies provided data on myocardial infarction.13,14,21,24–27 No difference was seen in the effect of recombinant human erythropoietin on myocardial infarction between the two groups (0·98, 0·73–1·31; p=0·88; figure 3). Again, this effect was dominated by Besarab and colleagues’ study,21 which contributed about 49% of the weight. There was no heterogeneity between the trials (heterogeneity $\chi^2$ 1·42, p=0·965, $I^2$=0%; figure 3). A subgroup analysis done with the predialysis patients13,14,21,24–27 resulted in an RR of 0·90 (95% CI 0·58–1·41; p=0·66) between the two haemoglobin target groups. We were not able to analyse this outcome in the haemodialysis subgroup because relevant data were available in only two trials. A sensitivity analysis, which included the two trials that were excluded from the main analysis in which myocardial infarction was reported,13,14 resulted in an RR of 0·97 (95% CI 0·72–1·30; p=0·82).

The risk of poorly controlled blood pressure was significantly higher in the higher haemoglobin target group than it was in the lower haemoglobin target group (RR 1·27, 95% CI 1·08–1·50; p=0·004; figure 4) with the fixed effects model. There was no heterogeneity across the trials with $\chi^2$ 0·58, p=0·419, $I^2$=0%; figure 4). The effect was not significant when a random effects model was used (RR 1·31, 95% CI 0·97–1·75; p=0·075), with the analysis widening the CI by placing a higher weighting on the study by Rossert and colleagues,27 which had just over half the number of patients of each of the trials by Parfrey and colleagues and Druke and co-workers.13,25 A sensitivity analysis, which included the four excluded trials that had reported poorly controlled blood pressure28–31 introduced significant heterogeneity ($\chi^2$ 16·94, p=0·018) with an RR of 1·42 (95% CI 1·22–1·66; p<0·0001) with the fixed effects model and 1·62 (1·16–2·26; p=0·005) with the random effects model.

We analysed data from four studies with haemodialysis patients13,21,24,25 and two studies in patients who began haemodialysis during the study.13,24 There was a significantly higher risk of arteriovenous access thrombosis in the higher haemoglobin target group than in the lower haemoglobin target group (RR 1·34, 95% CI 1·16–1·54; p=0·0001; figure 5). Besarab and colleagues’ study
Discussion

Our results show an increase in the risk of all-cause mortality in anaemic patients with chronic kidney disease in whom a higher haemoglobin target (in the normal physiological range) is aimed for with treatment with recombinant human erythropoietin. Such patients are also at an increased risk of arteriovenous access thrombosis and poorly controlled hypertension, which could contribute to the increased risk of mortality. Furthermore, there seems to be no beneficial effect on left ventricular mass index over the study period between the higher and the lower haemoglobin groups in each individual study. We were unable to do a formal meta-analysis for the effect of erythropoiesis-stimulating agents on left ventricular mass because of differences in the presentation of data. However, there was no difference in the change of left ventricular mass index over the study period between the higher and the lower haemoglobin groups. Furthermore, whether the increased risk of mortality noted in the higher haemoglobin target group in this meta-analysis relates to the achieved higher haemoglobin per se or to the means by which this was achieved—ie, higher haemoglobin concentrations due to the use of (in most cases) higher doses of erythropoiesis-stimulating agents interacting with erythropoietin receptors—is unclear. Recombinant human erythropoietin not only increases blood viscosity as a result of increased erythrocyte mass but also increases thrombotic risk via increased inflammation and anti-fibrinolytic activity, which can occur irrespective of haemoglobin concentration. Other possible mechanisms are stimulation of vascular growth and the dysregulation of production and responsiveness of vasoactive factors. Of interest is that Levin and colleagues and Rossert and co-workers used lower mean doses of recombinant human erythropoietin in the high haemoglobin group than did the other studies, and a trend toward fewer deaths was seen in these groups than in the other studies.

Sensitivity analyses showed that the inclusion of trials that began at very low haemoglobin concentrations somewhat attenuated the excess of deaths recorded with higher haemoglobin targets in individual studies. However, this finding is not surprising, since the use of recombinant human erythropoietin in these excluded studies raised very low haemoglobin concentrations to levels much the same as those in the lower haemoglobin target concentration groups in our main analysis.

Epidemiological studies of patients with chronic kidney disease have shown increased mortality at lower haemoglobin concentrations. However, such studies could be confounded by several forms of bias, including treatment-by-indication bias in the presence of co-morbid disease. Previous systematic reviews and meta-analyses of randomised controlled trials have been limited with regard to the risks and benefits of therapy with recombinant human erythropoietin, in particular by fewer trials and patients able to contribute to such analyses. Thus such analyses are underpowered to comprehensively address risks at higher haemoglobin target concentrations with these agents. Furthermore, questions have been raised with regard to the methods used (eg, combining observational studies—including registry data—with data from randomised controlled trials) as well as the source of funding of some earlier studies.

Our findings have several implications for ongoing clinical research. There remains a paucity of evidence regarding the optimum haemoglobin target concentration in anaemic patients with chronic kidney disease. The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) will partly address this issue. The effect of darbepoetin versus placebo on mortality and non-fatal cardiovascular events (ie, myocardial infarction, myocardial events. This contention is lent support by considerable mechanistic data; however, the risk of myocardial infarction seemed to be much the same in the two haemoglobin target groups. Furthermore, whether the increased risk of mortality noted in the higher haemoglobin target group in this meta-analysis relates to the achieved higher haemoglobin per se or to the means by which this was achieved—ie, higher haemoglobin concentrations due to the use of (in most cases) higher doses of erythropoiesis-stimulating agents interacting with erythropoietin receptors—is unclear. Recombinant human erythropoietin not only increases blood viscosity as a result of increased erythrocyte mass but also increases thrombotic risk via increased inflammation and anti-fibrinolytic activity, which can occur irrespective of haemoglobin concentration. Other possible mechanisms are stimulation of vascular growth and the dysregulation of production and responsiveness of vasoactive factors. Of interest is that Levin and colleagues and Rossert and co-workers used lower mean doses of recombinant human erythropoietin in the high haemoglobin group than did the other studies, and a trend toward fewer deaths was seen in these groups than in the other studies.

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ischaemia, stroke, and heart failure) in anaemic (ie, haemoglobin concentration <110 g/L) patients with chronic kidney disease and diabetes is currently being explored in this study, which involves 4000 patients. Interestingly, the target haemoglobin concentration of 130 g/L for the darbepoetin group is in the range of that achieved in the higher haemoglobin group used here (ie, 120–140 g/L), and will prospectively address whether this concentration might be too high for such patients, as suggested by our results.

Our observations have implications for other disease states that are associated with low haemoglobin concentrations. In particular, studies of recombinant erythropoietin (or erythropoiesis-stimulating agents) have begun in patients with chronic heart failure who also have low haemoglobin concentrations caused by multiple mechanisms, including impaired erythropoiesis. The largest of such studies—the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF) trial46—also has a target haemoglobin concentration in the same range as the higher haemoglobin target concentrations in the studies assessed here. RED-HF has a primary endpoint of all-cause death and hospitalisation due to heart failure, and will therefore contribute important information with regard to target haemoglobin concentrations in a separate but overlapping disease process to that of chronic kidney disease.

Of interest is that the active erythropoiesis-stimulating agent in both RED-HF and TREAT is darbepoetin. Whether our findings can be extrapolated to this agent is unclear, since no long-term trial data regarding its use and safety in patients with chronic kidney disease were able to contribute to our analysis.

Our meta-analysis has several limitations, related both to meta-analyses in general and to this study in particular. Meta-analyses are not a substitute for a properly done, adequately powered randomised controlled trial. However, to appropriately address all-cause mortality outcomes in this patient population, a commitment to a massive trial would be required and is unlikely to occur. Thus, well-conducted meta-analyses are of considerable importance in addressing these clinical questions. Furthermore, all meta-analyses are affected by the variation in reporting methods used by different investigators. An inconsistency in key definitions and reporting style—eg, with respect to blood pressure and what is meant by uncontrolled hypertension—has the potential to affect the integrity and validity of the presented data. Such an inconsistency was also evident with respect to reported changes in left ventricular mass, which prevented us from doing a meta-analysis for this outcome. Similarly, the various composite endpoints reported by studies were not able to be combined formally because of inconsistencies in endpoint components.

Bias towards reporting of positive trials can also affect the findings of meta-analyses. We have sought to minimise publication bias by ensuring that our literature search was as rigorous as possible, in accordance with recommendations by experts in analyses of this nature.2,47 Additionally, heterogeneity in outcomes should also be taken into account when interpreting the results of meta-analyses. However, there was, in general, very little heterogeneity in the outcomes examined here. Issues specific to the agent studied—eg, masking both patient and investigator to a clearly identifiable injectable agent—could be relevant to the internal validity of blinded randomised controlled trials and thus of this meta-analysis.

Pooling of studies that involved patients on dialysis with studies that included patients who are deemed to be predialysis could also be a source of bias. However, we feel that the combined data is the best possible summation of the current database regarding this issue. This is supported by both the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) clinical practice guidelines12 and the ERA-EDTA guidelines,17 which used combinations of these studies in the development of their recommendations. Our subgroup analyses, which assessed predialysis and dialysis patients with chronic kidney disease separately, supports this contention, with generally concordant results in both subgroups.

Our results raise important questions with regard to the appropriateness of current target haemoglobin concentrations in anaemic patients with chronic kidney disease who are being treated with recombinant human erythropoietin. Current guidelines12,13 for anaemia management in chronic kidney disease recommend the maintenance of haemoglobin concentrations at 110 g/L or more, which is based mainly on evidence of benefit with regard to some quality-of-life measures. However, although the 2006 NKF-KDOQI clinical practice guidelines suggest that there is little evidence of benefit of maintaining haemoglobin concentrations above 130 g/L, they do not specifically recommend any strict upper limit of target haemoglobin concentration for anaemic patients with chronic kidney disease being treated with recombinant human erythropoietin.19 This meta-analysis shows an excess risk of major adverse events—including death—when haemoglobin is raised to 120–160 g/L in such individuals. Although such a concentration of haemoglobin is within the normal physiological range, any putative clinical benefits seem to come at the expense of reduced survival in these patients. Therefore, an upper limit for target haemoglobin concentrations should be considered in future revisions of guideline recommendations.

References


231–35.


Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis

Anushua Sinha, Orin Levine, Maria D Knoll, Farzana Muhhib, Tracy A Lieu

Summary

Background Routine vaccination of infants against Streptococcus pneumoniae (pneumococcus) needs substantial investment by governments and charitable organisations. Policymakers need information about the projected health benefits, costs, and cost-effectiveness of vaccination when considering these investments. Our aim was to incorporate these data into an economic analysis of pneumococcal vaccination of infants in countries eligible for financial support from the Global Alliance for Vaccines & Immunization (GAVI).

Methods We constructed a decision analysis model to compare pneumococcal vaccination of infants aged 6, 10, and 14 weeks with no vaccination in the 72 countries that were eligible as of 2005. We used published and unpublished data to estimate child mortality, effectiveness of pneumococcal conjugate vaccine, and immunisation rates.

Findings Pneumococcal vaccination at the rate of diptheria–tetanus–pertussis vaccine coverage was projected to prevent 262 000 deaths per year (7%) in children aged 3–29 months in the 72 developing countries studied, thus averting 8·34 million disability-adjusted life years (DALYs) yearly. If every child could be reached, up to 407 000 deaths per year would be prevented. At a vaccine cost of International $5 per dose, vaccination would have a net cost of $838 million, a cost of $100 per DALY averted. Vaccination at this price was projected to be highly cost-effective in 68 of 72 countries when each country’s per head gross domestic product per DALY averted was used as a benchmark.

Interpretation At a vaccine cost of between $1 and $5 per dose, purchase and accelerated uptake of pneumococcal vaccine in the world’s poorest countries is projected to substantially reduce childhood mortality and to be highly cost-effective.

Introduction Vaccination of infants in the world’s poorest countries against Streptococcus pneumoniae (pneumococcus) has the potential to prevent many deaths, but would need substantial funding. Pneumonia and other respiratory infections cause about 2 million child deaths yearly, nearly all in developing countries.1 Most pneumonia deaths are believed to be due to bacterial pneumonia,2 and S pneumoniae is the most common cause of bacterial pneumonia in infants and young children.3 Additionally, pneumococcus often causes otitis media, bacteraemia, sepsis, and meningitis in early childhood. Experience with other vaccines suggests that, without substantial global investment and coordinated effort, a conjugated pneumococcal vaccine is unlikely to reach children in developing countries during the next decade.4 Multilateral organisations, including the Global Alliance for Vaccines and Immunization (GAVI), have taken an increasingly important role in stimulating access to vaccines in poor countries.5-7

To decide whether and where to support introduction of pneumococcal vaccine, national and global policymakers need detailed information for justification of this investment. Previous studies of this topic,8-10 done before pneumococcal conjugate vaccine was available, do not have information from an important vaccine efficacy trial in The Gambia.11 Our aim was to incorporate these data into an economic analysis of pneumococcal vaccination of infants in GAVI-eligible countries (as of 2005) using a model applicable to many of the pneumococcal conjugated vaccine products in development. We did a decision analysis to generate global and country-specific information about the projected benefits, costs, and cost-effectiveness of pneumococcal vaccination in developing countries.

Methods

Study design

We constructed a decision analysis model using standard methods12 to assess lives saved, disability-adjusted life years (DALYs) averted, costs, and cost-effectiveness of pneumococcal conjugate vaccination of infants in the

Panel: GAVI eligible countries (2005)

Articles

world’s poorest countries. These outcomes were assessed for each of the 72 countries that were eligible for GAVI support (panel)—countries with gross national income less than US $1000 per head and meeting other pre-specified criteria. A total of 76·9 million babies are born yearly in these GAVI-eligible countries. An expert panel with five members was convened and advised us on model structure and model inputs.

The decision tree (figure 1) included two strategies: vaccine purchase and provision, in which pneumococcal vaccine was purchased and provided to countries, via GAVI financial support, beginning in 2006; or no vaccine. No vaccine assumed that there would be no uptake of the vaccine, on the basis of previous experience in GAVI-eligible countries.6 In the GAVI financial support strategy, all children born were assigned a probability of death that depended on whether or not the child received the vaccine and on vaccine effectiveness against all-cause mortality. The death of a child resulted in the accrual of DALYs and death-related costs. Prevention of death by vaccination averted both DALYs and death-related costs. The vaccination programme resulted in costs related to purchase of vaccine and to programme administration.

We chose this model structure because data for childhood mortality and vaccination rates are available for all countries in this analysis. Data for intermediate outcomes, such as the incidence of pneumococcal infection or the distribution of pneumococcal serotypes, are available only from a few countries and are of variable quality. Hence, these outcomes were not incorporated into this model.

The set of assumptions used to do the primary analysis is termed the base-case analysis (table 1). Our base-case estimated vaccine effects on mortality alone; it was conservative in that it did not provide vaccination credit for reduction of non-fatal disease (eg, pneumonia needing hospital admission). The base-case analysis also did not assume any herd immunity effects—ie, protection of unvaccinated children or adults due to other individuals in the population being vaccinated.

We assumed that vaccine would be given according to the recommended schedule for diptheria–tetanus–pertussis vaccines in GAVI-eligible countries (6, 10, and 14 weeks of age), and that vaccination rates in individual countries would be equal to the proportion of children reported to receive three doses of diphtheria–tetanus–pertussis vaccine in that country in 2003 (DTP3 rate).8

### Table 1: Model assumptions for countries eligible for support from the Global Alliance for Vaccines and Immunization, by under-5 mortality rate per 1000 births

<table>
<thead>
<tr>
<th>Probability of dying between age 3 and 29 months</th>
<th>Vaccine effectiveness against all-cause mortality*</th>
<th>Vaccine efficacy against all-cause mortality†</th>
<th>Vaccination coverage rate</th>
<th>DALYs averted per death averted</th>
<th>Vaccine cost per dose‡</th>
<th>Vaccine programme cost per dose‡</th>
<th>Cost of treating fatal disease‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;150</td>
<td>10.2%</td>
<td>7.4</td>
<td>7.3%</td>
<td>60%</td>
<td>30.8</td>
<td>5</td>
<td>0.34</td>
</tr>
<tr>
<td>100–149</td>
<td>5.6%</td>
<td>7.4</td>
<td>13.1%</td>
<td>68%</td>
<td>32.0</td>
<td>5</td>
<td>0.43</td>
</tr>
<tr>
<td>25–99</td>
<td>3.0%</td>
<td>3.7</td>
<td>30.9%</td>
<td>86%</td>
<td>33.1</td>
<td>5</td>
<td>0.45</td>
</tr>
<tr>
<td>&lt;25</td>
<td>0.4%</td>
<td>0.1</td>
<td>3.2%</td>
<td>87%</td>
<td>32.3</td>
<td>5</td>
<td>0.84</td>
</tr>
<tr>
<td>Range used in sensitivity analyses</td>
<td>75–125% base-case value</td>
<td>3–16%</td>
<td>Base-case value to 100%</td>
<td>Base-case value to 3.4</td>
<td>1–10</td>
<td>1–5 times base-case value</td>
<td>0.1 to 10 times base-case value</td>
</tr>
</tbody>
</table>

* = number of deaths prevented per 1000 children. † = % reduction in deaths. ‡ = International $.
Estimates of pneumococcal vaccine efficacy were available from several large, randomised controlled trials. Our analyses were based on the results of the trial done in The Gambia, because that study setting most closely resembled that of other GAVI-eligible countries. The Gambian trial is also unusual in that it provides an estimate of the efficacy of pneumococcal vaccination for prevention of all-cause child mortality.

In the trial, children were vaccinated through the existing Gambian expanded programme on immunisation at ages of 6, 10, and 14 weeks. Events were recorded between age 3 and 29 months. The vaccine's efficacy for prevention of culture-confirmed invasive pneumococcal disease caused by vaccine serotypes was 77%, and vaccine serotypes accounted for 65% of invasive pneumococcal disease in the control group. Overall, a 50% reduction in culture-proven invasive pneumococcal disease was seen. 330 of 8189 children randomised to receive pneumococcal vaccine and 389 of the 8151 randomised to receive placebo died, which is an absolute reduction of 7.4 deaths prevented per 1000 vaccinated children during the period of observation.

We assumed that pneumococcal conjugate vaccine would be given in the same schedule as that used in the trial, and that vaccine would prevent deaths only between ages 3 and 29 months, the period observed in the trial. To extrapolate trial results to other countries, we assumed that vaccine efficacy against all-cause mortality would be greatest in those countries with high mortality rates in children aged under 5 years and lowest in countries with low mortality rates in this age group. This assumption was based on the finding that the proportion of childhood deaths caused by acute respiratory infection increases as mortality rate in children aged under 5 years increases, suggesting that the burden of pneumococcal disease, a common cause of acute respiratory infections could be highest in countries with highest child mortality.

In countries with mortality rates in children under the age of 5 years greater than that seen in the Gambian trial population (99 per 1000 livebirths), we assumed that vaccine efficacy against mortality would be capped at 7.4 deaths prevented per 1000 children. In countries with very high mortality rates in children aged under 5 years, this cap resulted in a low percentage reduction in deaths. Conversely, the projected vaccine efficacy against mortality was adjusted downwards from 7.4 per 1000 for any country with infant mortality rates less than or equal to 99 per 1000, on the basis of the ratio of the mortality rate in a specific country to that of the Gambian trial population. Unlike vaccine trials, in this analysis variations in vaccine efficacy mirror variations in the underlying risk of pneumococcal mortality in individual countries—not inherent variations in the biological activity of the vaccine. The probability of death between 3 and 29 months of age was derived from neonatal mortality data and standard life tables. We converted rates to probabilities using an exponential cumulative incidence function. All costs are shown in International $ valued as for 2000, adjusted for purchasing power parity. The price at which vaccine will be available to GAVI or to developing countries is unknown. Our base-case used $5 per vaccine dose, under the assumption that the two-tiered pricing scheme used in international public vaccine markets will apply to pneumococcal vaccine. Vaccine programme costs were estimated under the assumption that pneumococcal vaccination would be incorporated into routine vaccine administration during infancy. Vaccine programme costs were derived from country-level financial sustainability plans data provided to GAVI by seven GAVI-eligible countries, and ranged between $0.27 and $0.97 per dose. These costs accounted for all non-vaccine costs (capital, transport, medical staff, injection supplies, training, and other expenses) for immunisations delivered via the expanded programme on immunisation.

The cost of a death preventable by pneumococcal vaccination was assumed to be equal to the cost of a case of pneumonia treated in hospital. Direct medical costs included days in hospital, medical staff time, diagnostic tests, and medications. Direct non-medical costs included transportation to health-care facilities and parent or caregiver time spent caring for a sick child. The costs of hospital days and medical staff time were derived from a set of WHO regional standard unit costs developed by choosing interventions that are cost effective (WHO-CHOICE) project. We assumed that 85% of hospital care was delivered in secondary facilities and 15% in tertiary facilities. WHO-CHOICE costs were applied to all countries on the basis of WHO region and were adjusted by ratios of public to private health care payment and urban to rural population.

The costs of diagnostic tests, medications, transportation, and parent time were derived from a detailed study of resource use in childhood pneumococcal disease done in India for the Children’s Vaccine Initiative (A Krishnan, personal communication). These costs were extrapolated to other countries, weighting costs by per head gross domestic product and ratios of public to private health care payment and urban to rural population.

Analyses
The base-case analysis estimated deaths averted by vaccination. Deaths averted were converted into years of life lost and DALYs, a standard measure used by WHO and World Bank in quantifying societal burden of disease. We used standard methods and assumptions, including age weighting in estimating DALYs. DALYs averted were based on estimates of life expectancy at age 1 year from standard life tables. In secondary analysis, vaccine was also given credit for averting non-fatal pneumococcal meningitis, some of which could have resulted in permanent disability. Rates of meningitis-related permanent disability were taken...
Standard disability weights for sequelae (deafness, seizure disorder, motor deficit, and mental retardation) were applied. The base-case analysis was done from a societal perspective, including all direct medical and non-medical costs borne by GAVI, governments, and families. Health outcomes and costs were discounted at 3% per year. We estimated cost-effectiveness ratios for all countries based on the formula: Cost-effectiveness ratio = (vaccine programme costs – cost of deaths averted) / (DALYs averted). The cost-effectiveness ratio numerator and denominator were calculated by multiplying probabilities in the decision tree by values for costs and DALYs, with standard decision analytical methods.

As a standard for comparison, we used WHO’s thresholds of cost-effective interventions. Interventions with cost-effectiveness ratios of less than three times the gross domestic product per head are cost effective, and those with cost-effectiveness ratios below gross-domestic product per head are highly cost effective.

To test the robustness of model results, we varied the assumptions over a plausible range in sensitivity analyses. We also varied assumptions using Monte Carlo probabilistic sensitivity analysis. In the probabilistic sensitivity analysis, each assumption was assigned a range of values it could have and a frequency distribution over that range. Values for each assumption were randomly drawn from their distributions, and the model was run 10 000 times with these probability-sampled sets of assumptions. These methods and distributions are described in more detail in the webappendix.

Analyses were done with DATAPró software, release 11 (TreeAge Inc, Williamstown, MA) and Microsoft Excel (Microsoft Corp, Redmond, WA).

Role of the funding source
GAVI provided data on vaccine programme costs for seven GAVI-eligible countries but had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results
In the 72 GAVI-eligible countries, we projected that without pneumococcal vaccination, there would be 3.79 million deaths of children aged 3–29 months yearly. Pneumococcal vaccination was projected to prevent 262 000 of these deaths (7%) and avert 8.34 million DALYs annually if delivered at coverage rates similar to those for DTP3 (table 2). The greatest numbers of deaths could be averted in countries with both large birth cohorts and high childhood mortality. In India, Pakistan, Ethiopia, Tanzania, and Nigeria, 139 000 deaths could be averted, accounting for 53% of all deaths that could be averted in all GAVI-eligible countries.

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### Table 2: Projected outcomes of pneumococcal conjugate vaccination in 72 low-income countries, by under-5 mortality rate per 1000 births

<table>
<thead>
<tr>
<th>Under-5 mortality rate per 1000 births</th>
<th>Number of countries</th>
<th>Vaccine costs*</th>
<th>Savings from medical care averted*</th>
<th>Net costs*</th>
<th>Lives saved†</th>
<th>DALYs averted‡</th>
<th>Cost per life saved§</th>
<th>$ per DALY averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>25</td>
<td>178</td>
<td>11 6</td>
<td>167</td>
<td>75 000 (4%)</td>
<td>23</td>
<td>2 2200</td>
<td>74</td>
</tr>
<tr>
<td>High</td>
<td>100-149</td>
<td>20</td>
<td>196</td>
<td>14 6</td>
<td>181</td>
<td>82 000 (9%)</td>
<td>2 6</td>
<td>2 2200</td>
</tr>
<tr>
<td>Medium</td>
<td>25-99</td>
<td>23</td>
<td>493</td>
<td>18 0</td>
<td>475</td>
<td>105 000 (10%)</td>
<td>3 5</td>
<td>4 500</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;25</td>
<td>4</td>
<td>15</td>
<td>0.02</td>
<td>15</td>
<td>86 (3%)</td>
<td>0.03</td>
<td>125 000</td>
</tr>
<tr>
<td>All countries pooled analysis</td>
<td></td>
<td>882</td>
<td>44 3</td>
<td>838</td>
<td>262 000 (7%)</td>
<td>8 3</td>
<td>3 2200</td>
<td>100</td>
</tr>
</tbody>
</table>

*=$, millions. †=% of deaths averted shown in parentheses. ‡=millions. §=$.

### Figure 2: Tornado diagram summarising one-way sensitivity analyses

Termini of bars represent cost-effectiveness ratios at the low and high assumption values shown to the right of the graph. Longer bars represent assumptions to which the model is more sensitive. BC=base-case value. DTP3=diphtheria—pertussis—polio vaccine. DALYs=disability-adjusted life years.
If all 72 GAVI-eligible countries were to undertake pneumococcal vaccination at current DTP3 rates, 160·5 million doses of vaccine would be needed per year. Total vaccine programme costs would be about $882 million per year, including $802 million for vaccine purchase and $79·8 million for other vaccine programme costs, including administration, supplies, and additional medical staff time.

In our base-case analysis, which did not provide the vaccine programme credit for reduction of non-fatal disease, vaccination would avert direct medical and non-medical costs of $44·3 million in disease costs due to mortality. The net programme costs (vaccine programme costs minus disease costs) were $838 million. We used a human capital approach and gross national income per head as the value of a year’s lost productivity to estimate that $2·71 billion would be saved by averting 262 000 child deaths yearly. (This estimate was not used in cost-effectiveness calculations because the cost-effectiveness ratios already accounted for productivity losses as DALYs.)

In a secondary analysis in which vaccination was assumed to reduce hospital admission rates, vaccination would avert $233 million annually in disease costs, resulting in net programme costs of $649 million per year.

Pneumococcal vaccination would cost $100 per DALY averted, on the basis of pooling costs and health outcomes for all 72 countries. The median country-level cost-effectiveness ratio was $75 per DALY averted (range, $56 in Azerbaijan to $14800 in Cuba). At a vaccine price of $5 per dose, pneumococcal vaccination was projected to be cost-effective for 71 of the 72 (99%) countries, and highly cost-effective for 68 (94%) countries. At $2·50 per dose, pneumococcal vaccine was highly cost-effective in all countries apart from Cuba. Vaccination was not cost-saving over the vaccine cost range ($1 to $10 per dose) analysed.

Vaccination was very cost effective in countries with mortality rates in children aged under 5 years of more than 100 deaths per 1000 births. For example, cost-effectiveness ratios in Laos, Cambodia, and Haiti were $67 per DALY averted. Conversely, countries with mortality rates in children under 5 of less than or equal to 25 per 1000 births had the highest cost-effectiveness ratios. For example, cost-effectiveness ratios in Georgia, Sri Lanka, and Ukraine were $3433, $4211, and $5754 per DALY averted, respectively.

The projected cost-effectiveness of vaccination was most sensitive to estimates of vaccine efficacy against all-cause mortality and vaccine cost (figure 2). In countries with low childhood mortality, vaccine-dose cost was the main determinant of cost-effectiveness, but in countries with intermediate or high childhood mortality, both vaccine cost and efficacy had equal effect.

Results were moderately sensitive to the mortality rate, vaccine programme cost, and disease cost. Disease and vaccine programme costs were varied over wide ranges. When vaccine programme costs were increased five-fold from the country-specific base-case estimate, the cost-effectiveness ratio was $139 per DALY averted. When we reduced disease costs to a tenth of the country-specific base case estimate, the pooled cost-effectiveness ratio was $105 per DALY averted. Results were insensitive to vaccination rate.

The sensitivity of the analysis to vaccine efficacy was dependent on the price at which vaccine was offered (figure 3). At $1 per dose, the analysis was insensitive to vaccine efficacy. At this dose cost, conjugated pneumococcal vaccine remained a very cost-effective...
intervention across all vaccine efficacies, with a cost-effectiveness ratio of $15–$101 per DALY. However, at $10 per dose, the analysis became fairly sensitive to vaccine efficacy, suggesting vaccine cost has a substantial influence on the overall analysis.

In the probabilistic sensitivity analysis, the number of DALYs averted by vaccination ranged from 3 million to 21 million DALYs and the net costs ranged from $491 million to $1320 million (figure 4). The cost-effectiveness ratio ranged from $31 to $286 per DALY averted, with a credible range (2.5–97.5 percentile) of $57–$185 per DALY averted. In all 10 000 simulations of the model, all estimates of costs and DALYs averted were greater than 0—ie, vaccination was neither cost-saving (net cost < 0) nor detrimental to health outcome (DALYs <0). Quantitative estimates of sensitivity made with Spearman’s correlation coefficients identified vaccine efficacy against all-cause mortality and cost as the most important drivers of cost-effectiveness. The correlation coefficient for vaccine efficacy against all-cause mortality was -0.87 and was 0.37 for vaccine dose cost.

Access to vaccine and risk of mortality can vary by family income. Poorer children within a country could be at greater risk of dying and might be less likely to be vaccinated than rich children in the same country. Therefore, we did a secondary analysis, in which risk of death increased and vaccination rates decreased in lower income strata within each GAVI-eligible country. In this analysis, vaccine was least cost-effective in the higher income strata within a country, because of low mortality rates and high vaccine costs due to high vaccination rates. The converse was true in lower income strata within a country, with high mortality rates and low costs due to low vaccination rates. When pooled across all income strata, the effects of income stratification were slight, with a pooled cost-effectiveness ratio across all 72 GAVI-eligible countries of $101 per DALY averted.

In a separate analysis incorporating non-fatal disease, we assumed that vaccine prevented 7% of outpatient pneumonias, 35% of pneumonias that resulted in hospital admission, and 22% of pneumococcal meningitis that needed treatment in hospital. Under these assumptions, 1–16 million potential hospital admissions were averted. Cost-effectiveness ratios in countries with infant mortality rates of less than 25, 25–99, 100–149, and greater than or equal to 150 were $3532, $112, $56, and $60, respectively. The pooled cost-effectiveness ratio was $80 per DALY averted.

**Discussion**

At current vaccination rates, pneumococcal vaccination in GAVI-eligible countries could prevent 262 000 deaths yearly in children aged 3–29 months old, or about 7% of all potential deaths in this age group. Furthermore, at a price of $5 per dose, pneumococcal vaccine would be a highly cost-effective purchase in 68 of the 72 GAVI-eligible countries, on the basis of WHO standards for assessment of the economic value of health interventions. If vaccination coverage rates in these countries were 100%, 40 700 child deaths would be prevented every year.

Our analysis incorporated data from a clinical trial of conjugated pneumococcal vaccine. This trial benefited from a location and clinical setting that closely resemble typical conditions in many GAVI-eligible countries, compared with conditions at the sites of earlier trials, such as the USA, Finland, or urban South Africa. Our study focused on developing countries that are a policy priority, where GAVI has a commitment to promoting childhood immunisation and the introduction of selected new vaccines to childhood immunisation schedules.

Decisions about the introduction of conjugated pneumococcal vaccine in some of these countries will probably be made in the near future. Traditionally, new, expensive vaccines such as Haemophilus influenzae type b and hepatitis B have been slow to reach national immunisation programmes in poor countries, in part because of their cost. However, innovative financing mechanisms, such as advance purchase commitments and international financing facilities, are under consideration for the purchase and provision of conjugated pneumococcal vaccine to accelerate their adoption by GAVI-eligible countries. This analysis lends weight to the assertion that such an investment would prove lifesaving and very cost effective in most of these countries.

Our results are in accord with earlier analyses of vaccines for developing countries that suggested that pneumococcal vaccination would have a cost-effectiveness ratio of $70 per quality-adjusted life-year or $58–$117 per life-year saved. The earlier studies had drawbacks in that they were done before the availability of new conjugate vaccines and did not have effectiveness data for either mortality or hospital admissions from studies like the Gambian trial. Our study concurs with the evidence that purchase and provision of pneumococcal conjugate vaccine for infants in the developing world is likely to be a highly cost-effective health investment.

This study’s primary result—that pneumococcal conjugate vaccine will prevent deaths and will be highly cost effective at $5 a dose—was robust when assumptions were varied in sensitivity analyses. Cost-effectiveness was driven by vaccine cost and vaccine efficacy and was less sensitive to all other assumptions.

Our primary analysis was conservative in several ways. It did not give vaccination credit for prevention of non-fatal disease. However, the sensitivity analysis that assumed that pneumococcal vaccination would prevent some hospital admissions suggested that this effect could potentially avert large numbers of such admissions and their costs. This finding is especially relevant for countries with well developed health care infrastructures and reduced child mortality rates. In these countries, the potential to avert morbidity could prove important.
in making the decision whether or not to introduce vaccine.

This analysis did not give vaccination credit for herd immunity protection. In the USA, routine pneumococcal vaccination of infants has led to large decreases in invasive pneumococcal disease in unvaccinated children and adults.29–32 However, whether developing countries, in which patterns of interaction and exposure differ, would show herd immunity effects of a similar magnitude is unclear. We also did not account for potential increases in disease caused by serotypes not covered by the vaccine or changes in the most common serotypes to those not covered by the vaccine, which could potentially degrade vaccine efficacy over time.33

The price at which pneumococcal conjugate vaccine will be offered to developing countries is unknown. However, a two-tiered pricing system has long been applied to vaccine prices in international public markets.34 We assumed that the same tiered pricing structure that results in lower costs for the eight antigens used in The Gambia would apply to pneumococcal conjugate vaccine as well. The base-case value used, $5 per dose, is a much higher price than those paid by UNICEF for diphtheria–tetanus–pertussis–H influenzae vaccine ($2–80) or hepatitis B vaccine ($0–62).35 Forecasts produced for GAVI’s PneumoADIP suggest production will be adequate to meet demand if this vaccine is added to immunisation schedules in GAVI-eligible countries.

The broad scope of this analysis needed a streamlined approach. The model was based on simple assumptions for which the best data exist, including the probability of death and vaccine efficacy against death. Our primary analysis did not attempt to estimate the reductions in the incidence of specific pneumococcal diseases such as pneumonia or meningitis. Our model was not dependent on pneumococcal serotype distribution, which varies between countries. Because our model does not need data for serotype distribution or the antigens used, our approach could be applied to all candidate pneumococcal conjugate vaccines with similar efficacies against mortality in developing world settings. However, the effect of pneumococcal vaccination will be dependent in part on the overlap between pneumococcal serotypes included in the vaccine and the local serotype distribution of disease-causing pneumococcal strains. At national level, local or regional data for pneumococcal disease burden and serotype distribution, as well as HIV prevalence (which modulates vaccine efficacy)36 will be useful in further refining the expected cost-effectiveness of vaccination.

Decisions about purchase and provision of pneumococcal vaccine will be dependent on many factors in addition to cost-effectiveness, which include affordability, sustainability, opportunity costs, and programme capacity. However, the public health rationale for introduction of pneumococcal vaccination in poor countries is clearly based on the benefits recorded in recent trials. As this study makes evident, the economic argument for purchase of this vaccine in the developing world is equally compelling.

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

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Contributors
A Sinha, O Levine, M D Knoll, and T A Lieu designed the study. Data collection was done by A Sinha, MD Knoll, F Muhib, and T A Lieu. Data were analysed by A Sinha, F Muhib, M D Knoll, and T A Lieu and were interpreted by A Sinha, O Levine, M D Knoll, and T A Lieu. The manuscript was written by A Sinha, M D Knoll, and T A Lieu and was edited by O Levine. All authors were involved in the decision to submit the manuscript for publication.

References


Wilson’s disease
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Progressive hepatolenticular degeneration, or Wilson’s disease, is a genetic disorder of copper metabolism. Knowledge of the clinical presentations and treatment of the disease are important both to the generalist and to specialists in gastroenterology and hepatology, neurology, psychiatry, and paediatrics. Wilson’s disease invariably results in severe disability and death if untreated. The diagnosis is easily overlooked but if discovered early, effective treatments are available that will prevent or reverse many manifestations of this disorder. Studies have identified the role of copper in disease pathogenesis and clinical, biochemical, and genetic markers that can be useful in diagnosis. There are several chelating agents and zinc salts for medical therapy. Liver transplantation corrects the underlying pathophysiology and can be lifesaving. The discovery of the Wilson’s disease gene has opened up a new molecular diagnostic approach, and could form the basis of future gene therapy.

Wilson’s disease is a rare autosomal recessive genetic disorder of copper metabolism, which is characterised by hepatic and neurological disease. The disease affects between one in 30 000 and one in 100 000 individuals, and was first described as a syndrome by Kinnier Wilson in 1912. The past two decades have seen major advances in our understanding of the pathogenesis, cellular biology, and molecular genetics of the disease. Most symptoms first appear in the second and third decades of life. In affected individuals, there is accumulation of excess copper in the liver caused by reduced excretion of copper in bile. The great danger is that Wilson’s disease is progressive, can remain undiagnosed, and is thought to be fatal if not treated.

Hepatic pathology
In the early stages of the disease, diffuse cytoplasmic copper accumulation can be seen only by special immunohistochemical stains for detecting copper, which are not routinely available. This early accumulation of copper is associated with macrosteatosis, microsteatosis, and glycogenated nuclei which are features that can be seen in various other disorders—eg, nonalcoholic steatohepatitis. The ultrastructural abnormalities range from enlargement and separation of the mitochondrial inner and outer membranes, with widening of the intercristal spaces, to increases in the density and granularity of the matrix, or the occurrence of large vacuoles. In the absence of cholestasis, these changes are regarded as pathognomonic of Wilson’s disease. Ultrastructural analysis might be useful for helping to distinguish between heterozygous carriers and patients.

The initial stages of Wilson’s disease progress to an intermediate stage, which is characterised by perportal inflammation, mononuclear cellular infiltrates, erosion of the limiting plate, lobular necrosis, and bridging fibrosis, and these features are indistinguishable from those of autoimmune hepatitis. Mallory bodies can be seen in up to 50% of biopsy specimens. Cirrhosis almost invariably follows with either a micronodular or a mixed macronodular–micronodular histological pattern. In patients with fulminant hepatic failure, parenchymal apoptosis, necrosis, and collapse might predominate, often with a background of cirrhosis. There are rare reports of older individuals, who present with the disease but do not seem to have liver cirrhosis, although they have neurological disease.

Molecular pathogenesis
The gene responsible for Wilson’s disease (on chromosome 13) was identified almost simultaneously by three separate laboratories. The gene (ATP7B) is highly expressed in the liver, kidney, and placenta. ATP7B encodes a transmembrane protein ATPase (ATP7B), which functions as a copper-dependent P-type ATPase. The ATP7B transporter has dual synthetic and excretory roles, functioning in the transport of copper into the trans-Golgi compartment, for incorporation into the plasma protein ceruloplasmin, and into the bile, for excretion of excess stores. Defective ATP7B function results in hepatic copper accumulation, which leads to the hepatic and neurological features of Wilson’s disease.

Search strategy and selection criteria
We searched the MEDLINE database from January, 1966, to June, 2006, for specific topics in relation to the search terms “Wilson disease” or “Wilson’s disease” in combination with the terms “genetic”, “liver disease”, “neurology”, and “psychiatric”. We largely selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy, and selected those we judged relevant. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar. We prioritised articles published in high-quality journals, natural history studies, and randomised controlled trials. Personal knowledge and clinical experience was used to complete the review, where gaps in knowledge still remain.
Healthy function of ATP7B includes trafficking of the protein between different cellular compartments in response to copper. Studies of polarised HepG2 hepatoma cells cultured in low-copper medium (<1 μM) showed ATP7B localised to the trans-Golgi network. The addition of copper resulted in the redistribution of ATP7B to vesicles and then to vacuoles. This effect is reminiscent of patterns of ATP7B immunohistochemistry seen in human liver, showing punctate immunoreactivity within hepatocytes and staining of the apical membrane, adjacent to the bile canaliculi. Copper-induced trafficking of ATP7B can therefore show the transitions in its cellular role. In low and normal copper states, ATP7B is present in the trans-Golgi network, and is important in the biosynthesis of holocaeruloplasmin. When excess copper is present, the protein moves towards the canicular aspect of the hepatocyte, where it takes on an excretory role in promoting biliary copper excretion.

Mutation of the protein ATP7B can interrupt its normal cellular processing. The most common ATP7B mutation found in patients of European origin is the histidine to glutamate substitution at aminoacid 1069 (H1069Q). In the hepatocytes of patients with Wilson’s disease homozygous for H1069Q, ATP7B was mislocalised to the endoplasmic reticulum consistent with a failure of the mutant protein to undergo normal trafficking to its usual resident position in the trans-Golgi network. By use of baculovirus to express wild-type and mutant ATP7B in insect SF9 cells, the H1069Q mutation was shown not to result in major misfolding, but the normal catalytic phosphorylation of ATP7B by adenosine triphosphate (ATP) was substantially decreased. Histidine 1069 is needed for the correct orientation of ATP in the ATP7B catalytic site before ATP hydrolysis.

In the human hepatocyte, ATP7B represents one step in the network of copper metabolism pathways that are increasingly being characterised at molecular level (figure 1). Dietary copper is absorbed in the stomach and duodenum and transported via the portal vein to the liver, which is the main organ responsible for copper homoeostasis. Copper is taken up into the hepatocyte via copper transporter 1 (CTR1) on the sinusoidal aspect of the hepatocyte. In mice, CTR1 is essential for healthy development and is thought to be the main mechanism for uptake of copper into mammalian cells. Knockout of the CTR1 gene results in embryonic lethality. In the cytoplasm, glutathione and metallothionein proteins are important scavengers, protecting the cell from copper’s toxic effects. A specific copper chaperone, ATOX1, delivers copper to the Wilson’s disease protein, ATP7B, by copper-dependent protein-protein interaction. ATP7B brings about transport of copper into the trans-Golgi and holo-caeruloplasmin and, under conditions of copper loading, into vesicles for export of copper into bile.

The biliary excretion process includes another protein, COMMD1 (originally called MURR1), which interacts directly with ATP7B. Mutation of COMMD1 causes the copper toxicosis of Bedlington terriers—an autosomal recessive disorder that involves hepatic copper overload and deficient biliary copper excretion. However, sequencing and haplotype analysis reported no evidence to implicate the COMMD1 protein in copper-storage disorders of undefined aetiology in human beings. The copper metabolism pathway has been found to regulate the metabolism of chemotherapeutic drugs containing platinum—e.g., cisplatin. CTR1 has been identified as the uptake mechanism for entry of these agents into tumour cells, and the copper-transporters ATP7A and ATP7B regulate their efflux. Thus, understanding the copper transport pathway could provide insight into the development of resistance to these anticancer agents.

Clinical applications of Wilson’s disease genetics

The Human Genome Organisation (HUGO) database for Wilson’s disease lists roughly 300 different mutations described in the disease, which are distributed across the ATP7B gene. As a result, the distribution of ATP7B genotypes is complex and most patients are compound heterozygotes, having two different mutations of the ATP7B gene. In general, a few mutations predominate, depending on the population tested. Therefore, in molecular diagnosis, selected exons are chosen for initial screening according to the population group. Vrabelova and colleagues reported that screening of five prevalent mutations in patients from the Czech Republic and Slovakia detected 70% of Wilson’s disease mutant alleles.

The H1069Q mutation represents 37–63% of mutations in studies of white populations. Other mutations are prevalent in non-European populations and in isolated ethnic groups. In Chinese patients, H1069Q seems to be absent, but R778L has been reported to represent 34–38% of mutations. In a study of Indian patients with the disease, neither H1069Q nor R778L was detected.
Saudi Arabian patients, a founder effect was detected, with a predominant 4193delC mutation present in many members of one tribe. Prevalent disease mutations have also been detected in isolated populations, including Iceland and Gran Canaria (one of the Canary Islands).

The homozygous H1069Q genotype has been detected frequently in several studies of white patients with Wilson's disease, and has therefore been widely used as a model to investigate possible genotype-phenotype relations. Although an association has not been universally reported, homozygous H1069Q has been associated with late onset and neurological disease in several studies, including a meta-analysis of 577 patients.

Wilson's disease is an autosomal recessive disorder, which means that there is a 25% chance that a sibling of the index case has Wilson's disease. Once homozygous or compound heterozygous mutations in ATP7B have been established in the index patient, then mutation detection is valuable in family screening. The same genotype in asymptomatic family members confirms diagnosis of the disease, thus allowing early treatment before the onset of complications. In family members in whom clinical and biochemical features are uncertain, the demonstration of either heterozygous (carrier) or wild-type gene sequence prevents unnecessary treatment.

If the index patient has a secure diagnosis of Wilson's disease on the basis of clinical and biochemical evidence but testing for ATP7B mutations is not available, family screening can be done by haplotype analysis of polymorphic markers flanking the disease gene. In this instance, the rare possibility of recombination events (typically between 0.5 and 5% of cases) needs to be considered. The rate of recombination is dependent on which flanking markers are studied.

Genetic testing for ATP7B mutations can be valuable to confirm a diagnosis of Wilson's disease, especially when presentation is unusual. This situation has been drawn attention to by the molecular confirmation of early-onset hepatic disease in a 3-year-old child. Mutation analysis has also confirmed late-onset disease, including the case of two siblings in their 70s—the oldest reported patients so far at time of diagnosis.

ATP7B mutation analysis makes an important contribution to clinical practice. Unfortunately, systematic genetic testing for Wilson's disease is still difficult and fairly expensive because of many different mutations, the occurrence of regulatory mutations in non-coding sequence, the large size of the gene that spans around 80 kb, and the restrictions of present methods. However, technical advances allowing high-throughput screening could be applied to the disease. This new apparatus can sequence six million base pairs of DNA per hour with an accuracy greater than 99%. Such advances might permit specialised laboratories to sequence the entire genomic Wilson's disease gene from patients, including not only the translated exons, but also the important non-coding sequences that are not normally investigated, to detect all mutations.

**Clinical manifestations and range of disease**

The clinical range of Wilson's disease is wide, and knowledge of the various disease presentations is important (panel 1). In broad terms, patients can present acutely with liver failure, haemolysis, or both, or more chronically with liver disease, neurological disease, or both.

Patients who first present with neurological or psychiatric signs tend to be older than those with hepatic features alone. Most patients with CNS involvement are believed to have liver disease at the time of presentation but they are often not symptomatic from their liver disease. However, hepatic histology is not generally available for these patients because the diagnosis is usually established on the basis of Kayser-Fleischer (K-F) rings (an ophthalmic manifestation of the disease) and decreased caeruloplasmin concentrations.

**Hepatic disease**

Wilson's disease can present as fulminant hepatic failure—ie, worsening coagulopathy and encephalopathy with an associated Coombs negative haemolytic anaemia.
renal failure, and substantially increased serum and urinary concentrations of copper. Around 5% of patients present in this manner with most patients being in the second decade of life, when K-F rings might not yet be apparent. Almost all patients are already cirrhotic, though some might show evidence of massive necrosis with only bridging fibrosis, which clearly would progress to cirrhosis with time. Concentrations of serum alkaline phosphatase are frequently depressed, and this feature has led to the finding that a ratio of alkaline phosphatase concentration (IU/L) to bilirubin concentration (mg/dL) of less than two might be diagnostic of Wilsonian concentration (IU/L) to bilirubin concentration (mg/dL) has led to the finding that a ratio of alkaline phosphatase concentration (IU/L) to bilirubin concentration (mg/dL) of less than two might be diagnostic of Wilsonian fulminant hepatitis. Transient low-grade haemolysis can take place even when liver disease is not clinically evident.

The clinical picture can be similar to other forms of chronic hepatitis, which emphasises the need to screen such patients for Wilson’s disease. In patients presenting with liver disease, neurological features (if they occur) usually do so 2–5 years later.

**Cirrhosis**

The patient might present with insidious cirrhosis. Clinical features of this disease include spider naevi, splenomegaly, portal hypertension, and ascites. In some patients cirrhosis is well compensated. All young patients with unexplained chronic liver disease, with or without cirrhosis, should be screened for Wilson’s disease.

Hepatocellular carcinoma is rarely associated with Wilson’s disease, but may occur in the setting of cirrhosis and chronic inflammation. 11 cases have been reported thus far, and it is thought that men with longstanding treated Wilson’s disease have the greater risk of developing hepatocellular carcinoma.

**Eye changes**

Ophthalmic findings include K-F rings (figure 2) and sunflower cataracts. Both findings are reversible with medical therapy or after liver transplantation. The reappearance of either of these eye changes in a medically treated patient suggests non-compliance with therapy.

K-F rings are most apparent at the periphery of the cornea. They are caused by the granular deposition of copper on the inner surface of the cornea in Descemet’s membrane. The upper pole is affected first. The rings have a golden brown appearance. Although sometimes visible to the naked eye, slit lamp examination is necessary to confirm the presence or absence of K-F rings. Rings indistinguishable from K-F rings have also been seen in other forms of chronic liver diseases, especially longlasting cholestasis and cryptogenic cirrhosis.

Sunflower cataracts are brilliantly multicoloured and are visible only by slit-lamp examination. They do not impair vision. Other less common findings include night blindness, exotropic strabismus, optic neuritis, and optic disc pallor.

**Neurological and neuropsychiatric disease**

Neurological and neuropsychiatric signs are the presenting features in 40–50% of patients with Wilson’s disease. The neurological abnormalities can be classified as: (a) an akinetic-rigid syndrome similar to Parkinson’s disease, (b) pseudosclerosis dominated by tremor, (c) ataxia, and (d) a dystonic syndrome. Subtle signs can appear before the characteristic neurological features, including changes in behaviour, deterioration of school work, or an inability to carry out activities that need good hand-eye coordination. Handwriting might deteriorate and micrographia—as in Parkinson’s disease—could develop. Other common neurological findings include tremor, lack of motor coordination, drooling, dysarthria, dystonia, and spasticity. Migraine, headaches, and insomnia have also been reported, although seizures could be more common. Along with behavioural changes, other psychiatric manifestations include depression, anxiety, and frank psychosis.

Advances in neuroimaging have helped to improve our understanding of the pathophysiology of Wilson’s disease. Structural brain MRI in patients with the disease has shown widespread lesions in the putamen, globus pallidus, caudate, thalamus, midbrain, pons, and cerebellum as well as cortical atrophy and white matter changes. In general, these lesions show high-signal intensity on T2 weighted images and low-intensity on T1 scan. Although MRI changes are present in many Wilson’s disease patients, even patients without neurological symptoms, these changes tend to be more severe and widespread in patients with neurological Wilson’s disease. Proton-density MRI sequences seem to be especially sensitive in showing the extent of the neuropathology. Histologically, there is an increase in astrocytes within the grey matter, associated with swollen glia, liquefaction, and appearances of spongiform degeneration. Neuronal loss is often accompanied by gliosis and active glial fibrillary protein. The characteristic astrocytes are Alzheimer type 1 and 2 cells. Opalski cells are distinctive for Wilson’s disease, and these are fairly large (up to 35 μm in diameter), with fine granular

**Figure 2: Kayser-Fleischer (K-F) ring**

There is a brown discolouration at the outer margin of the cornea because of the deposition of copper in Descemet’s membrane. Here it is clearly seen against the light green iris. Slit lamp examination is required for secure detection.
cytoplasm and slightly abnormal nuclei (single or multiple). These cells are thought to originate from degenerating astrocytes.76

Cognitive dysfunction in patients with Wilson’s disease can accompany neurological deficits, often in the absence of detectable cortical association or hepatic encephalopathy, which lends support to the importance of pathological changes in basal ganglia as the primary cause of cognitive deficits in the disease.67

Neurological assessment should be undertaken on all patients with Wilson’s disease. Patients with obvious symptoms or signs should be seen by a neurologist or movement disorder specialist before treatment. A specific rating scale (based on that for Huntington’s disease) has been used in clinical trials to assess patients78—but however, this scale has never been tested outside of this research setting.

Other changes

Pathological changes of bone and periarticular abnormalities have been recorded to account for osteomalacia, osteoporosis, spontaneous fractures, adult rickets, osteoarthrosis, osteochondritis dissecans, chronodocalcinosis, subchondral cyst formation, and azure lunulae of the fingernails.69 The knee joints and spine are the most common sites for skeletal and articular abnormalities.70 Myocardial copper accumulation can cause cardiomyopathy and arrhythmias, although these are clinically rare.71 Other rare extrahepatic manifestations include hypoparathyroidism,72/74 infertility, repeated miscarriages,73–75 and renal abnormalities,78,79 including aminoaciduria and nephrocalcinosis.

Estabishing a diagnosis

There is no one test for the diagnosis of Wilson’s disease (panel 2). The diagnostic challenge is that the symptoms are often non-specific and the disease affects many different organ systems, which results in confusion with other disorders. The diagnosis is easy to establish in individuals with neurological symptoms, K-F rings, and a low caeruloplasmin concentration. The absence of K-F rings does not necessarily exclude the possibility of this disease but in patients with predominantly neurological disease, K-F rings are absent in only 2% or less of cases. In patients with liver disease as the presenting feature, the diagnosis can be more difficult. Molecular analysis of ATP7B mutations, (if available), can potentially be diagnostic. However, this method is expensive, and will not necessarily detect all disease producing mutations.

To help with diagnosis, Ferenci and co-workers80 proposed a scoring system. Clinical, biochemical, and histological features were allocated a score and the total accumulated score indicated the possibility of the patient having Wilson’s disease. Although helpful if a diagnosis of the disease is being considered, this proposed scoring system has not been assessed prospectively.

Roberts and Schils88 provide formal guidelines for current diagnostic approaches and treatment. These guidelines were prepared for the American Association for the Study of Liver Diseases and provide specific recommendations on the basis of previous published work and the researchers’ experience in caring for paediatric and adult patients with Wilson’s disease.

Serum aminotransferase activity is generally abnormal in this disease except at a very early stage. For many individuals, the degree of raised aminotransferase activity might be mild and does not necessarily reflect the severity of the liver disease.

Caeruloplasmin

A caeruloplasmin concentration of less than 0·2 g/L (normal laboratory range 0·2 to 0·5 g/L), has been regarded to be consistent with Wilson’s disease and diagnostic in association with K-F rings. Up to 95% of homozygotes and 20% of asymptomatic heterozygotes have serum caeruloplasmin values less than 0·2 g/L. 5% of homozygotes, and in some studies up to 50% of affected individuals with severe decompensated liver disease, have normal caeruloplasmin concentrations.82

One explanation for this finding is that caeruloplasmin is an acute-phase reactant and concentrations can be raised into the normal range by inflammation. Conversely, low concentrations of caeruloplasmin can be seen in hypoproteinaemic states. Low concentrations also occur in Menke’s disease and acaeruloplasminemia—both of which are very rare disorders.83

Hepatic copper

The normal copper content of liver is less than 55 μg/g dry weight. Accurate analysis needs an adequate sample of liver (at least 1 cm of a 1-6 mm diameter core). A hepatic copper concentration greater than 250 μg/g dry weight is usual in homozygous Wilson’s disease and with some caveats remains the best biochemical test for the disease. Measurement of copper content in liver is the most important diagnostic test in patients in whom other data are suggestive but not diagnostic of disease.
Diagnosis is sometimes only considered retrospectively, after liver biopsy has been done. Under these circumstances, liver biopsy specimens can be retrieved from paraffin blocks for quantitative copper measurement. However, the sensitivity and specificity of this test have never been clearly established.

Thus, liver copper content is an important indicator of disease, although a value below 250 μg/g dry weight does not exclude the possibility of disease. Specimens with extensive fibrosis and few parenchymal cells can provide copper concentrations that are falsely low. Furthermore, greatly increased hepatic copper concentrations can be seen in long-term cholestasis. Therefore, the results of the hepatic copper concentration estimation should be taken in the context of the histological, clinical, and biochemical data.83

**Urinary excretion of copper**

Urinary copper is derived from the so-called free (non-caeruloplasmin-bound) copper circulating in plasma. In Wilson’s disease, the 24-h urinary copper excretion is increased, and the concentration taken as suggestive of disease is greater than 100 μg per 24 h (>1.6 μmol/24 h). The reference limits for normal 24-h excretion of copper vary between laboratories, with many taking 40 μg per 24 h (0.6 μmol/24 h) as the upper limit of normal. This limit seems to be a better threshold for diagnosis because testing sensitivity is increased. Results can be difficult to assess unless strict precautions are taken. Wide-necked bottles with copper-free disposable polyethylene liners have been recommended.

Interpretation of 24-h urinary copper excretion can be difficult because of an overlap with results in other types of liver disease, especially severe liver injury. Heterozygotes could also have intermediate levels for 24-h copper excretion. Urinary copper excretion with penicillamine administration can also be a useful diagnostic adjunctive test. This test has only been standardised in the paediatric population, in whom 500 mg of d-penicillamine was given orally at the beginning and again 12 h later during 24-h urine collection. Copper excretion greater than 25 μmol per 24 h (1600 μg copper/24 h) was regarded as diagnostic for paediatric Wilson’s disease.89 In adults and heterozygote carriers, the predictive value and usefulness of using penicillamine in testing is unknown.

**Family screening**

First-degree relatives must be screened for Wilson’s disease. The probability of finding a homozygote in siblings is 25% and in the children is roughly 0.5%. Liver function tests, serum copper and caeruloplasmin concentration, and urinary copper analysis are done for relatives. If necessary, investigations should be extended to test for K-F rings. 24-h urinary copper might be difficult to interpret in Wilson’s disease heterozygotes.

The diagnosis could remain contentious when individuals without K-F rings have a low caeruloplasmin concentration. These individuals might need a liver biopsy for hepatic copper quantification to eliminate the diagnosis. Molecular genetic analysis is becoming more widely available and is useful for families in whom both mutations have been detected in the index patient, allowing molecular analysis for the same mutations in siblings.

Haplotyping analysis of markers around the ATP7B gene on chromosome 13 has been used in families to establish whether siblings of affected individuals have inherited the same pair of chromosomes. This approach would be useful when it has not been possible to detect both mutations in the index case by mutation analysis.

**Treatment**

The drug treatment of Wilson’s disease is based on the use of copper chelators to promote copper excretion from the body, or zinc to reduce copper absorption, or both. Liver transplantation is successful for patients with liver failure that is unresponsive to medical treatment. Wilson’s disease was progressive and fatal until 1951, when the first chelating agent dimercaprol given intramuscularly was used. In 1956, John Walshe reported the clinical benefit of the orally active chelator penicillamine, which revolutionised treatment of the disease. However, some patients did not tolerate penicillamine, and in 1969, trientine was introduced as an alternative chelator. These two agents have remained the mainstay of chelation treatment for patients with Wilson’s disease. Ammonium tetrathiomolybdate, used by veterinarians for treating copper poisoning in animals, is another chelator, which is under assessment in the USA for treatment of patients with neurological Wilson’s disease. This chelator remains an investigational drug, not yet available in the UK nor outside clinical trials in the USA. Zinc was first used in treatment in the early 1960s and has been studied in the USA particularly, gaining recognition for asymptomatic and presumptomatic patients and as maintenance therapy after an initial period of treatment with a chelator.

Historically, penicillamine has been the treatment of choice, on the basis of clinical data and many years of experience. However, side-effects and neurological deterioration in some patients after starting treatment have led to the suggestion that trientine is an effective and safer alternative initial therapy. A randomised double blind study showing trientine with ammonium tetrathiomolybdate in patients with neurological presentation found that tetrathiomolybdate might be better than trientine. No randomised trials exist in patients with liver disease. After initial chelation therapy, usually until clinical improvement had been noted, the choice for maintenance therapy is between reduction in the dose of chelator or zinc monotherapy.

The best therapeutic approach remains controversial and there is no universally accepted regimen (panel 3). We have to emphasise two aspects of care to optimise
clinical outcome—first, proper monitoring of patients and second, support to ensure compliance with whichever regimen is used. Compliance is a problem for patients, because they find it difficult to take life-long treatment when they feel healthy.

Penicillamine
Penicillamine is cysteine, doubly substituted with methyl groups. A free sulphhydryl group acts as the copper-chelator. Total bioavailability after oral administration is 40–70%. More than 80% of penicillamine excretion is in urine, with chelated copper. Penicillamine can also induce metallothionein, a cysteine-rich protein that is an endogenous chelator of metals. Thus, penicillamine enhances urinary copper excretion but can also lead to the sequestration of free intracellular copper.

The initial dose of penicillamine is 1000–1500 mg per day in two to four divided doses. The treatment is best taken 1 h before or 2 h after food. Absorption might only be 50% if it is taken with a meal. The use of lower initial doses, 250–500 mg per day, increasing over a few weeks, can increase tolerance to the drug. Regular monitoring of full blood count and urinary protein (using dipsticks) can increase tolerance to the drug. Early side-effects in the first 1–3 weeks include sensitivity reactions with fever, rash, lymphadenopathy, neutropenia, thrombocytopenia, and proteinuria. If these adverse effects are noticed, then penicillamine should be stopped and an alternative treatment used. Later side-effects include nephrotoxicity (a lupus-like syndrome) and bone marrow suppression (eg, thrombocytopenia and aplasia). Skin complications have arisen with long-term use of penicillamine, including progeriatric changes (with long-term doses greater than 1000 mg per day), elastosis perforans serpiginosa, and aphthous stomatitis. Furthermore, penicillamine can affect pyridoxine metabolism, and this vitamin (vitamin B6) should therefore be given (50 mg weekly) to children, pregnant women, and patients with malnutrition or an intercurrent illness. The clinical benefit of penicillamine in Wilson’s disease is well documented. In patients with severe liver disease—eg, patients with high bilirubin or low albumin concentrations, prolonged prothrombin time, ascites, or high Child-Turcott score—hepatic function usually improves. In those who deteriorate, either the penicillamine dose can be increased for a trial period or the patient listed for urgent liver transplantation. In patients with neurological disease, gradual clinical and cerebral MRI improvement is well documented.

However, the side-effects and the initial neurological deterioration, reported in 20–50% of patients with a neurological presentation and which in some cases cannot be reversed, have led to other agents being considered for first-line treatment.

Trientine
As evidence grows for the effectiveness of trientine, with fewer side-effects arising than with penicillamine, trientine is now regarded as an accepted alternative to penicillamine for initial treatment of Wilson’s disease. Trientine has a polyamine structure, which chelates copper by the formation of stable complexes with the four constituent nitrogens in a planar ring. Although commonly regarded as a weaker chelator of copper than penicillamine, there is still some debate—it could be that these two chelators mobilise different pools of body copper. The initial dose is 1200–1800 mg per day in two to three divided doses. Maintenance therapy is 900–1200 mg per day. As in the case of penicillamine, the timing of oral administration in relation to food is important.

Trientine is becoming recognised as an effective initial treatment since there are few reported side-effects—pancytopenia occurs rarely and hypersensitivity reactions and renal effects have not been reported. Sideroblastic anaemia and hepatic siderosis can occur if copper deficiency develops because of excessive treatment. The frequency of neurological deterioration is thought to be less with trientine than with penicillamine, but could still arise. Data for patients with severe liver disease have been reported. Askari and colleagues studied nine adults with severe liver disease identified over a 10 year period, who received initial treatment with trientine (1000 mg/day) and zinc (150 mg/day). Only one patient had hepatic encephalopathy. One patient developed mild neurological symptoms and was given ammonium tetrathiomolybdate and zinc after 2 weeks of the original treatment. In the eight patients receiving trientine and zinc, the combination was given for at least 4 months and then maintenance zinc treatment was used. Over the first 12 months of treatment, prothrombin time and raised bilirubin and albumin concentrations returned to normal, and ascites disappeared. Benefit was maintained over 12 months to 14 years of follow-up. These are encouraging data. The
European database, EuroWilson, set-up for newly diagnosed patients with Wilson’s disease, might add information regarding the effectiveness of penicillamine and trientine for patients with severe hepatic presentation.

**Ammonium tetrathiomolybdate**

Ammonium tetrathiomolybdate forms a complex with copper and protein. Taken with meals, the drug forms complexes with copper in the food and that secreted into the intestine, thus preventing absorption. Taken between meals, the drug is absorbed and complexes copper in the blood with albumin. This complex is metabolised by the liver and excreted in bile. A randomised trial compared the efficacy of ammonium tetrathiomolybdate in patients with neurological Wilson’s disease with that of trientine (both groups also received zinc). In the ammonium tetrathiomolybdate group, one of 27 patients had neurological deterioration, compared with five of 27 patients in the trientine group. Anaemia or leucopenia occurred in three patients in the ammonium tetrathiomolybdate group, and four patients had increased aminotransferase concentration, although these side-effects resolved on dose reduction.

**Zinc**

Zinc induces intestinal metallothionein, which preferentially binds to copper within the duodenal enterocyte. Copper absorption into the circulation is reduced, and copper is lost when the enterocyte is shed during normal cell turnover. Without normal absorption but with continuing copper losses there is a negative copper balance. Furthermore zinc can induce copper-binding metallothionein in hepatocytes, thereby reducing the damaging effects of free copper.

The dose of zinc for adults is 150 mg per day of elemental zinc given in three doses. Food interferes with absorption but patients vary in their ability to comply with the recommended separation from food. However, if this recommendation is difficult for the patient the dose can be adjusted. Dyspepsia can be a troublesome side-effect, and changing the formulation (to acetate, sulphate, or gluconate) and timing of administration can help.

Zinc has been used successfully in asymptomatic or presymptomatic affected family members of individuals with Wilson’s disease. Czlonkowska and co-workers reported that zinc is equally as effective as penicillamine in a group of patients predominantly with neurological disease, with a follow-up of 12 years. In patients with severe hepatic disease, maintenance therapy with zinc was effective after an initial period of treatment with trientine and zinc (given at separate times).

**Present choice of medical treatment**

Virtually all the data on the treatment options are from clinical series of patients rather than randomised studies, which makes definitive recommendations difficult. Moreover, clinical deterioration has been reported or alluded to in reviews for all treatment methods, showing that none is totally effective or reliable. Variables confounding outcome include the clinical phase and pattern of disease when treatment starts and patients’ compliance with treatment.

We can conclude that treatment for Wilson’s disease is generally very effective. Although many physicians still use penicillamine as the first choice chelator for symptomatic patients, data suggest that trientine is as effective and has fewer side-effects, especially in those with neurological onset. Combined treatment with zinc, separated appropriately from trientine, has been used without any disadvantage. For asymptomatic patients many will use this approach initially, although others judge that zinc therapy is sufficient. For maintenance therapy of patients who are initially symptomatic and have responded to chelator treatment, the dose of the chelator can be reduced or replaced with zinc. Clinical follow-up and monitoring of copper concentrations and excretion are essential, coupled with patients’ support to encourage compliance with which ever therapy is used.

The most difficult challenge is how to manage patients who deteriorate, despite what seems to be best possible therapy. Liver transplantation is available for hepatic disease, but for patients with neurological deterioration no such option is available. Studies that attempt to identify clinical features associated with neurological deterioration have identified possible brain MRI changes that need further assessment. Although some clinicians start with a lower dose of chelator and then increase the dose subsequently, currently there is no evidence that this approach reduces the risk of neurological deterioration. If neurological deterioration takes place, withdrawal of the chelator and then reintroduction of the chelator at low-dose with escalation has been reported with some benefit, but data supporting this approach are only anecdotal. The decision of whether to continue with the chosen treatment or change to or add another agent, or administer dimercaprol intramuscularly (despite associated discomfort and potential complications) is difficult even for clinicians with experience of treating Wilson’s disease. If ammonium tetrathiomolybdate were to become widely available, patients would have another potentially useful treatment option, and Brewer and colleagues suggest that this drug could have a lower risk of neurological deterioration.

**Other therapeutic agents**

Toxic concentrations of copper in the liver produce oxidant damage to mitochondria with lipid peroxidation, which can be reduced experimentally by vitamin E administration. Vitamin E concentrations may be low in patients with Wilson’s disease. However, there are no data to substantiate the administration of vitamin E in patients with disease, which is also the case for N-acetylcysteine.
Functional imaging can prove useful in treating patients, especially in exploring possibilities for new therapies. Magnetic resonance spectroscopy has shown reduced amounts of striatal N-acetylaspartate, a marker of neuronal health, in Wilson’s disease patients with neurological symptoms compared with those without disease.47 If this reduction is proven to be caused by reversible persistent neuronal dysfunction, it could provide a target for neuronal rescue therapy. Single-photon-emission computed tomography (SPECT) imaging has shown presynaptic and postsynaptic deficits in the dopaminergic system of patients with this disease.48 SPECT and positron-emission tomography might therefore have a role in identifying a subpopulation of patients with predominantly presynaptic dopaminergic deficits, who could be potential candidates for dopamine replacement therapy.47,48 There is no evidence for the potential role of functional neurosurgery in the management of neurological symptoms, including dystonia, in Wilson’s disease.

Diet
Some foods—eg, chocolate, liver, nuts, mushrooms, and shellfish—contain high concentrations of copper and in general are best avoided.

Monitoring of medical treatment
Patients on initial therapy should have follow-up appropriate to the severity of their neurological or hepatic features. Neurological assessment and monitoring of liver function tests should be done, and signs of hepatic decompensation assessed.

During chelation therapy, 24-h urinary copper excretion is measured and an output of 3–8 μmol per day (200–500 μg) denotes adequate treatment. Some experts recommend collection of urine after stopping chelator for 48 h (no chelator is taken on the third day), to assess the urinary copper excretion while off treatment. Which of these approaches is best is not known. During zinc therapy, 24-h copper excretion is also measured with a target of less than 2.0 μmol per day (less than 125 μg) to suggest satisfactory treatment. Urinary output of zinc is also measured to show whether sufficient zinc is being taken and absorbed, and to show patients’ compliance.

During all treatments, whether with a chelator or zinc, or both, an estimation of non-caeruloplasmin-bound (ie, so-called free) copper is made from the measurements of total copper and caeruloplasmin. However, caeruloplasmin is almost universally measured with an immunological rather than enzymatic assay, which challenges the accuracy of this assessment. The target is a non-caeruloplasmin-bound copper concentration of between 50 and 150 μg/L.

Liver transplantation for Wilson’s disease
The oldest Wilson’s disease patient to undergo a liver transplantation is now 30 years past his initial transplant.109 Although transplantation is an effective cure, there are risks associated with the procedure and the immunosuppressive therapy that follows.49 Ideally, family screening and development of efficient population screening for Wilson’s disease will eventually reduce the number of patients with this disorder requiring liver transplantation.

Liver transplantation is clearly indicated for patients with acute fulminant hepatic failure from Wilson’s disease. Fulminant hepatic failure describes the development of coagulopathy and encephalopathy as a result of acute hepatic deterioration within 8 weeks from the onset of illness. There are some reports of cure by medical therapy of rare patients who have acute liver disease and even haemolytic anaemia caused by Wilson’s disease.50 However, failure to act promptly to stabilise and transplant those with true fulminant failure is important to avoid progressive encephalopathy and cerebral oedema and multiorgan failure. Liver transplantation of these individuals can be achieved by a cadaveric donor or living donor transplant, even if the donor is a heterozygous carrier.

Liver transplantation is also indicated for patients with Wilson’s disease in whom medical therapy is ineffective, as defined by a failure to stabilise and prevent progressive hepatic insufficiency.51 These patients include those whose disease was discovered after manifestation of cirrhosis and severe hepatic insufficiency, and those who might have been successfully treated but discontinued their treatment and then deteriorated or developed some secondary liver injury, leading to worsening disease. This group includes a subset of patients, who have neurological and hepatic disease, but in whom hepatic symptoms are predominant. The difficulty is in how to define an adequate treatment trial for these patients and what constitutes a true failure of medical therapy. In view of the delay between the initiation of treatment and measurable objective laboratory response, often a gap of up to 6–8 weeks, the previous recommended interval for a medical trial was for 3 months’ time. Although this 3-month suggested trial is not absolute since some patients will deteriorate before this time has elapsed, careful monitoring is essential to detect these individuals for whom transplantation might be more urgently needed. If the patient stabilises in this time, there is hope for the long-term use of medical therapy and avoidance of liver transplantation.

In whom would liver transplantation for Wilson’s disease be medically futile? Individuals who are not suitable candidates for transplantation under any circumstances include those with liver failure, severe cerebral oedema, long-term reduction of cerebral perfusion pressure, active infections, malignancies, or those with severe psychiatric disease with suicidal ideation. Similarly, patients with severe long-standing neurological impairment from Wilson’s disease are unlikely to recover after transplantation. The failure of transplantation to
improve neurological disease and the increased frequency of post-transplant complications caused by calcineurin inhibitors used to prevent rejection are not routinely reported, but have occurred on both sides of the Atlantic (unpublished findings). In view of the acute shortage of donor organs and our growing waiting lists for liver transplant recipients, the use of an organ for liver disease that can be stabilised medically is not easily justified. This is especially true when the risk of potential worsening of neurological disease is uncertain.

A new factor in this dilemma has arisen, with the arrival of living-donor liver transplantation. This procedure removes the concern about misallocation of a donor organ from the public donor pool, but has different risks associated with the procedure for the donor and recipient. However, many treatment programmes that undertake this procedure insist that the same indications for deceased liver transplant be applied to those for living donor transplant to avoid undue risk to the donor and recipient.

Patients with less severe neurological impairment caused by Wilson’s disease present a unique dilemma with respect to treatment by liver transplantation. There are reports of improved neurological and psychiatric disease in patients with this disorder who had liver transplant for their liver disease, and in some patients for whom transplantation was undertaken for their neurological impairment. The decision of whether to choose transplantation rather than medical treatment is complicated because of the long period (up to 4 years) over which neurologically affected patients can improve while on medical therapy. The difficulty is that the time needed to find out whether medical treatment for neurological disease has failed, is probably longer than the window of opportunity for transplantation to prevent progression. This argument remains unresolved, and although we continue to transplant for liver disease as the primary indication, continued improvements in safety and management of transplant patients, and the growing use of living-donor liver transplants, will probably add impetus to this continued debate. The development of better prognostication for neurological progression or improvement of Wilson’s disease by MRI findings or other clinical or biochemical variables will help improve our ability to make treatment choices.

The future

Why is there a need for a cure for a disease that has available medical therapy? Patients faced with a lifelong need for medication and physicians faced with the results of non-adherence to therapy are the two main arguments.

Genetic therapy and hepatocyte transplantation represent future curative treatments for Wilson's disease, along with currently available liver transplantation. However, both cell and liver transplants need immunosuppression to maintain grafted cells. Future use of stem-cells, ex-vivo modification of cells by gene therapy, or better means of inducing immune tolerance might obviate the difficulty of immunosuppression and provide a cure for this disease by cell transplantation. With respect to gene therapy, we have learned from cell transplant studies in a rodent model for Wilson’s disease that not only can disease progression be prevented, but also that only 30–50% of the liver mass need be functionally healthy with respect to copper metabolism, to provide protection for the remaining liver cells. This finding suggests that gene therapy need not achieve 100% efficiency with respect to transduction of all of the hepatocytes. In preclinical studies the transduced ATP7B gene can result in expression and function in liver cells. Although there are still many hurdles to overcome in Wilson’s disease, present gene therapy trials and continuing research will hopefully achieve both the safety and effectiveness of gene transfer, and overcome hurdles to permit efficient transduction of even large genes, such as ATP7B.

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

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References:
**Sexual Dysfunction 1**

**Sexual sequelae of general medical disorders**

**Rosemary Basson, Willibrord Weijmar Schultz**

**Summary**

That sexual symptoms can signal serious underlying disease confirms the importance of sexual enquiry as an integral component of medical assessment. Data on sexual function are sparse in some medical specialties. However, increased scientific understanding of the central and peripheral physiology of sexual response could help to identify the pathophysiology of sexual dysfunction from disease and medical interventions, and also to ameliorate or prevent some dysfunctions. Many common general medical disorders have negative effects on desire, arousal, orgasm, ejaculation, and freedom from pain during sex. Chronic disease also interferes indirectly with sexual function, by altering relationships and self-image and causing fatigue, pain, disfigurement, and dependency. Current approaches to assessment of sexual dysfunction are based on models that combine psychological and biological aspects.

**Introduction**

Medical understanding of sexual responses has increased substantially in the past 15 years. Neurotransmitters and endothelial factors that mediate genital congestion have been identified—albeit with far more data in men than in women. More recently, brain imaging techniques have afforded a window on the neurological circuits that appraise and process sexual stimuli: the intricacies of the “gyrus fornicatus” (cingulate gyrus) discovered by anatomists a century ago are now being unravelled.

This sexual medicine series reviews the accumulating data on the comorbidity of sexual and other medical disorders. Diseases and medical interventions can directly interfere with central and peripheral sexual physiology. However, the traditional dualistic notion that sexual dysfunction has either psychological or organic origins has been replaced by an understanding that the two are inseparably combined. Psychological factors such as personality, coping style, and external stressors can modulate immune, inflammatory, endocrine, and neurological mechanisms. Furthermore, medical disease has psychological repercussions that could potentially disrupt physiology. Although in its early stages, functional brain imaging is beginning to clarify the modulation of sexual response by psychological and medical factors. Such factors can predispose to, precipitate, or maintain sexual dysfunction, and therefore they need to be considered.

We outline the general medical disorders and treatments that interfere with sexual motivation, desire, subjective arousal and excitement, orgasm, pleasure, and freedom from pain. We also discuss the physical response of genital congestion that is organised by the autonomic-nervous system. Two very common dysfunctions—vascular erectile dysfunction and dyspareunia from vulvar vestibulitis syndrome—are addressed in detail. The other two articles in this series review the sexual sequelae of specific neurological and endocrine disorders.

Data about the concurrence of sexual dysfunction with many medical disorders are scarce. Well-validated questionnaires about sexual dysfunction, tested in a range of languages, have only recently become available. Some questionnaires focus on genital issues rather than subjective responses even though, in both men and women, the two do not always correlate. Despite evidence to the contrary, the assumption that women regularly sense desire in between sexual experiences, as men do, is common. Some investigators advocate that validated diagnostic methods should be revised to more accurately correspond to contemporary ideas about the sexual responses of men and women, and to up-to-date definitions of women’s dysfunction (although these have yet been incorporated into official definitions of mental disorders). Many studies include only patients in stable relationships or those who are sexually active, and thus exclude those for whom sexual dysfunction has precluded sexual activities or relationships.

The available studies of the prevalence of dysfunctions are derived from clinical samples of widely varying size, with and without controls; the levels of evidence for treatment diverge widely. Throughout the series, we cite case-control prevalence studies and randomised controlled treatment trials, but where unavailable we refer to previous research, and reviewed the tables of contents of the major sexology journals.

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**Search strategy**

We searched the MEDLINE, EMBASE, LILACS, and PubMed databases (2000–present) using the key words “sexual function”, “sexual dysfunction”, “sexual dysfunction—psychological”, “dyspareunia”, “sexuality”, “sexual disorders”, “sexual behaviour”, “ejaculation disorders”, “orgasmic disorders”, “sexual desire disorders”, “sexual arousal disorders”, and “Peyronie’s disease” in combination with the diseases “hypertension”, “coronary artery disease”, “congestive cardiac failure”, “depression”, “diabetes”, “pituitary disease”, “multiple sclerosis”, “Parkinson’s disease”, “stroke”, “hyperlipidaemia”, “renal failure”, “adrenal disease”, “LUTS”, “sleep apnoea”, and “primary and secondary hypogonadism”. We confined our search to studies of sexual function and dysfunction in people and to studies published in English. We focused on evidence-based medicine, including reviews, randomised controlled trials, and clinical practice guidelines. The authors also referred to reports in their own databases, compiled in the process of previous research, and reviewed the tables of contents of the major sexology journals.
to treatment based on open-label studies or clinical experience (personal and from published work) and note the limitations of the evidence.

**Sexual function and dysfunction**

Sexual dysfunction can herald serious underlying disease. Onset of erectile dysfunction, the most common sexual disorder in older men, is seen as a pointer to generalised endothelial dysfunction, which invites assessment of cardiovascular health and, in particular, the health of coronary arteries. One study showed that, of 132 men who received coronary angiographies, 45% had a history of erectile dysfunction, which preceded the diagnosis of coronary artery disease in 58% of these men. In a retrospective cohort study of 26 000 men in good general health, with a mean age of 40 years, who were registered in an integrated health-information bank, and followed up for an average of 1 year, a two-fold increase in the risk of myocardial infarction was identified in the 13 000 men with erectile dysfunction at baseline. Endothelial dysfunction in the brachial arteries of men who are presumed to have vascular erectile dysfunction, but have no other evidence of cardiovascular disease, could identify those who are particularly at risk. A study screening for erectile dysfunction in a health centre showed undiagnosed diabetes, hypertension, and other comorbid disorders in a third of 125 affected men. Low sexual desire in combination with an abnormally low concentration of

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathophysiology of sexual dysfunction</th>
<th>Therapy and general comments</th>
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<tbody>
<tr>
<td>Depression: low desire in 50–60% untreated patients</td>
<td>Neurotransmitters of frontal limbic circuitry thought to be affected in depression. Indirect mechanism via sleep disturbance, low self image, despondency, withdrawal.</td>
<td>Bupropion, mirtazapine, moclobemide, tianeptine, or reboxetine could have fewer effects on sexual function.</td>
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<td>Coronary artery disease, myocardial infarction, or both: most patients reduce frequency of sexual activity, 50% to 54% do not resume.</td>
<td>Low motivation to trigger desire or act upon it because of fear of further MI.</td>
<td>Advise that risk is low and short-lasting: MI at age 50 yrs invokes increased risk from 10 to 20 chances in a million/h for 2 h after sex. Relative risk not increased if CAD already established. Advise that cardiovascular symptoms are very unlikely if no symptoms arise during exercise testing to 6 METS. Prescribe exercise.</td>
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<tr>
<td>Low motivation to trigger desire or act upon it because of fear of further MI.</td>
<td>Fear of using needed PDE5i in case of nitrates requirement.</td>
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<td>Concomitant depression in more than 50% of patients.</td>
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<tr>
<td>Testosterone replacement in 10 to 20% of men.</td>
<td>Testosterone treatment in men is of limited benefit, due partly to associated hyperprolactinaemia and anaemia.</td>
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<td>Low testosterone in men: Leydig cell dysfunction but rise in LH blunted. LH pulse amplitude decreased, GnRH pulsatility reduced.</td>
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<td>Anovulation, no LH surge (associated testosterone decrease has not been studied).</td>
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<td>High prolactin secretion is autonomous, and possibly stimulated by secondary hyperparathyroidism.</td>
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<td>Low zinc levels.</td>
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<td>Anaemia of renal failure.</td>
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<td>Anaemia from uraemic menorrhagia (amenorrhoea more common).</td>
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<td>Concomitant depression.</td>
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<tr>
<td>No desire triggered during sexual experience since outcome is repeatedly painful from oestrogen deficiency and associated dyspareunia.</td>
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<tr>
<td>In women: lower urinary tract symptoms including urinary incontinence. Odds ratio of 2 for stress incontinence.</td>
<td>Leakage of urine with penetration (or with orgasm) reduces sexual motivation.</td>
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<tr>
<td>Diabetes: prevalence of low desire in men and women with diabetes uncertain.</td>
<td>Patients report low desire with high glucose but data are sparse.</td>
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<tr>
<td>Hyperprolactinaemia.</td>
<td>Reduced GnRH pulses and low serum testosterone in men, but testosterone supplementation alone is of little benefit. Women also have reduced arousal and orgasm and increased dyspareunia, without change in other hormone levels.</td>
<td></td>
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<tr>
<td>In men: primary or secondary hypogonadism.</td>
<td>Lack of testosterone affects brain processing of sexual stimuli.</td>
<td>Address cause of secondary hypogonadism. Replace testosterone if no contraindication (eg, past history of prostate or breast cancer).</td>
</tr>
<tr>
<td>In women: bilateral oophorectomy.</td>
<td>Loss of ovarian testosterone and androstenedione (precursor of oestrogen and testosterone). Supplementation of oestrogen alone might not restore desire.</td>
<td>Sexual benefit has been shown in four 6 months’ parallel group RCTs of testosterone supplementation for oestrogenised, surgically menopausal women—but only from 300 µg and not 450 µg transdermal patch. No long-term safety data are available.</td>
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testosterone in the blood (hypotestosteronaemia) can signal innominately treatable disorders such as haemochromatosis or pituitary adenoma. Furthermore in women, disorders of mental health, especially depression, underlie the presentation of low desire in some 17–26% of cases.20 Various diseases interfere with sexual desire (table 1).27–64 as do some treatments; these range from the obvious (eg, bilateral oophorectomy or orchectomy) to the less obvious (eg, suppression of the hypothalamic pituitary axis by corticosteroids, which reduces production of adrenal prohormones such as androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate). A connection between low desire and depression is ubiquitous and for sex before the sexual encounter.

Disorders of sexual desire and sexual motivation

Hypoactive sexual desire

Men and women have multiple incentives and reasons for initiation of, or agreement to have, partnered sexual activity.13,21,25 One reason is to fulfill desire, or so-called sexual drive, which is typically sensed daily or more often by young and middle-aged men and by women who are in the early stages of sexual relationships, but infrequently in most middle-aged women, despite the fact that they report satisfactory sexual lives.32,33 Thus, the definition of hypoactive sexual desire in women is a subject of continuing debate.35 Past definitions have been more appropriate to male sexuality, with a focus on sexual thoughts, sexual fantasies, and desire for sex before the sexual encounter.

Various diseases interfere with sexual desire (table 1).27–64 as do some treatments; these range from the obvious (eg, bilateral oophorectomy or orchectomy) to the less obvious (eg, suppression of the hypothalamic pituitary axis by corticosteroids, which reduces production of adrenal prohormones such as androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate). A connection between low desire and depression is ubiquitous and for sex before the sexual encounter.

Reduced sexual motivation

Other than sexual desire, the reasons for engaging in partnered sex can include generation of emotional closeness, confirmation that an argument has been resolved, or reassurance of a loving relationship despite...
illness or disfigurement. In both men and women, motivation is influenced by many circumstantial factors such as interpersonal difficulties, low self-image, absence of needed sexual stimuli or sexual skills in either partner, or issues about privacy or safety. A difficult sexual response—ie, no arousal, no erection, or disinclination to engage in sexual behaviour—can be seen as simply adaptive, rather than dysfunctional. Factors that commonly interfere with sexual motivation and response should be assessed in the context of additional contributions from chronic illness.

Disorders of sexual response

Accepted models of human sexual response are circular, and consist of overlapping phases, in a variable order, with some responses more characteristic of one sex than the other. Men (commonly) and women (sometimes) have a sense of desire at the beginning of a sexual experience. Although this desire might be absent initially, a person can become motivated to sexually engage. Figure 1 shows that desire can be triggered later during the experience once the person is subjectively aroused, with the result that arousal and desire become indistinguishable.

Despite frequent absence of desire at the outset of sexual engagement, women can report satisfactory sexual outcomes. As a result, the definitions of sexual disorder and dysfunction for women have been revised. Lack of sexual desire at the beginning of a sexual experience is no longer always thought to indicate a hypoactive sexual-desire disorder. Rather, it is the recurrent and consistent incapacity to trigger any desire or arousal that constitutes disorder. Despite acknowledgment that men can also be sexually neutral at the beginning of an encounter, and become aroused into sexual desire, recommendations to revise the definition of male sexual-desire disorder have not yet been published. Diagnostic categories, for both men and women, refer to the different phases of sexual response, but now acknowledge that dysfunction in women typically affects all phases and in men less commonly. Traditionally, sexual disorders were diagnosed in the case of either personal or interpersonal distress in addition to the abnormal response. The latest revisions to definitions of women’s disorders add a descriptor for the degree of personal distress (whether none, mild, moderate, or severe) to a statement of the diagnosis.

Functional and dysfunctional arousal: genital studies

Sexual arousal consists of the mind’s processing of internal sexual stimuli (eg, fantasy) and external sexual stimuli, and their context. Psychological responses (cognitive, emotional, and motivational) are appraised, as are the reflexive changes within the autonomic nervous system. Healthy men can accurately assess their own genital engorgement, which correlates with subjective arousal and encourages further arousal (excitement). By contrast, the correlation between the subjective arousal of healthy women and measures of increased vaginal congestion is highly variable—as recorded by vaginal photoplethysmography or by ultrasound measures of clitoral blood flow. Similarly, the correlation between increases in clitoral volume, as measured by MRI, and women’s subjective arousal as they view erotic videos, and yet, simultaneous assessment of vaginal engorgement shows increases in vaginal congestion that are similar to those in control women. Research also suggests that triggers for women’s genital arousal might be less specific than men’s. Women, but not men, who watched visual stimuli

Figure 1: Circular model of human sexual response, showing cycle of overlapping phases. The sexual and nonsexual outcome influences future sexual motivation

Figure 2: Model of sexual arousal

ANS=autonomic nervous system. Brain areas activated during arousal to allow sexual feelings, to maintain focus on the sexual stimuli, to anticipate reward, to form a mental image of sexual behaviour, to limit actual behaviour despite arousal, and to elicit autonomic nervous system response of physical sexual arousal.
that was considered by these healthy volunteers to be sexual but not erotic or arousing (eg, videos of primates mating), had evidence of genital congestion as measured with vaginal and penile photoplethysmography.73

**Functional and dysfunctional arousal: brain imaging studies**

Functional brain imaging studies to delineate the neural circuits implicated in sexual arousal also attempt to explore differences between men and women and between people with and without sexual dysfunction. The use of PET for brain imaging of healthy people during visual sexual stimulation identifies a model of sexual arousal that includes complex brain circuitry, such as the cortical, limbic, and paralimbic regions that are known to be associated with cognition, motivation, and emotions, linking to changes within the autonomic nervous system.135 Figures 2 and 3 integrate these findings with the current model of triggered and initial desire and also with psychophysiological studies of subjective arousal and genital congestion.

In sexually healthy men, brain imaging in response to visual erotica shows robust correlation between subjective sexual arousal and activation in regions of the brain that organise the genital response.72 This correlation has not been reported in sexually healthy women.73 Moreover, we do not yet know which neural systems mediate arousal in women. In a recent study of 28 healthy men and women who watched erotic stimuli, subjective reports of arousal were similar, and many regions of the brain were activated in both men and women.74 However, in women this activation was no greater for sexually explicit stimuli than for scenes of warm but non-sexual interaction between couples.75 These neutral scenes still caused activation in the hypothalamus in men—perhaps in keeping with men’s tendency to interpret many stimuli as subtly (or at least potentially) sexual.74

**Overview of pathophysiology of deficient genital congestion**

Deficient genital congestion presents as erectile dysfunction in men. In women, a similar deficiency can present as dyspareunia, due to insufficient vaginal lubrication, or as genital arousal disorder. This disorder is defined as absence of vulval swelling or vaginal lubrication from any type of sexual stimulation, with reduced sexual sensations from caressing genitalia, yet with preservation of subjective sexual excitement from non-genital sexual stimuli.76

Genital congestion in response to sexual stimulation results from relaxation of vascular smooth muscle, with the result that arteries dilate, to fill the enlarging sinusoidal spaces within cavernous tissue of either the penis or the clitoral and bulbar tissue. Much more research has been done to investigate penile physiology than vulval physiology. The main neurotransmitter that mediates penile and clitoral smooth muscle relaxation is nitric oxide (NO), which is derived from autonomic nerves. Acetylcholine is released as a co-transmitter. Another source of NO is the endothelium—its release is evoked from postganglionic cholinergic nerves, shear stress, and substances such as oxygen in plasma. Nerve-derived NO is thought to initiate most smooth muscle relaxation, whereas endothelial NO contributes to maintenance of the relaxed state.75 Penile-resistance arteries relax by an additional endothelium-independent mechanism, which is attributed to a hyperpolarising factor, mediated by Ca2+ activated K+ channels. NO acts on guanyl cyclase to generate cyclic guanosine monophosphate (cGMP), and the subsequent cascade of dilator signals provide the basis for phosphodiesterase type 5 (PDE5) inhibition of cGMP by sildenafil, vardenafil, and tadalafil to ameliorate erectile dysfunction.77 Benefit from these medications is dependent on adequate sexual stimulation and on the retention of some capacity to generate endothelial and neurogenic NO. Once tissue expansion is sufficient, the veins that exit the trabecular tissue through the tough fibrous capsule are compressed, which prevents further escape of blood (veno-occlusion). Thus, in the penis, the high flow of the developing erection is converted to the low flow of a fully erect penis.

Veno-occlusion does not seem to be a key factor in female clitoral and bulbar response.78 Neurotransmission of vaginal muscle and vaginal vascular smooth-muscle is less clear; vasoactive intestinal peptide acts via cyclic adenosine monophosphate (cAMP) and is itself degraded by neutral endopeptidase. Increased blood flow through the vaginal submucosal plexus increases the formation of interstitial fluid, which percolates between vaginal epithelial cells into the lumen as sexual lubrication.

In both men and women, genital detumescence and decreased engorgement are mediated by adrenergic constriction of the inflow arteries, which decreases tissue...
pressure and facilitates egress of blood through the veins. Other factors associated with smooth-muscle constriction that maintains flaccidity and detumescence might include endothelin-1 and constrictor prostanoids, such as thromboxane A2 and angiotensin II. These excitatory substances cause intracellular free calcium to increase, which transiently activates calcium-calmodulin-dependent myosin light chain kinase, and initiates smooth-muscle contraction. Calcium sensitisation pathways then take over. One such pathway is associated with RhoA, a small G-protein that activates rho-kinase, which in turn inhibits myosin phosphatase, and thereby maintains contractile tone. The consensus is that the phasic contraction of penile smooth muscle is regulated by an increase in calcium and the tonic contraction is governed by calcium sensitisation pathways.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathophysiology of sexual dysfunction</th>
<th>Therapy and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease: prevalence of ED 44%-65%. 77</td>
<td>Endothelial dysfunction, structural atheromatous change, loss of smooth muscle from ischaemia, or cavernosal fibrosis—all leading to impaired venous occlusion.</td>
<td>Give PDE5is, assuming no nitrate therapy. Use caution with α blockers, hypotension, aortic stenosis, LV outflow obstruction, and unstable angina. 77-79 Avoid vardenafil with patients with congenital long QT and IA anti-arrhythmic drugs. 79 Recommend weight loss and exercise. 79 D1/D2 receptor agonist apomorphine stimulates erections centrally, and is available in Europe. Not contraindicated in presence of nitrates. Some benefit for mild ED. 79</td>
</tr>
<tr>
<td>Renal failure: prevalence 55%-85% in men with uraemia or on peritoneal dialysis, haemodialysis, or both, with further increase after transplantation. 80-82</td>
<td>Endothelial dysfunction from associated HT and DM. Reduced NO production associated with increased production of dimethyl arginine. 83 Structural changes in cavernosal smooth muscle. 84 Uraemia-associated reduced bioavailability of L-arginine, reduced NOS expression, quenching of NO by increased reactive oxygen species and inhibition of NOS. 85 ANS dysfunction associated with uraemia. 85 Penile artery occlusion associated with interruption of internal iliac for placement of pelvic kidney.</td>
<td>Antagonists of renin angiotensin system and calcium channel antagonists could potentially improve endothelial function, but have not been investigated in renal failure. Give PDE5is, which magnify action of remaining NO.</td>
</tr>
<tr>
<td>Lower urinary tract symptoms: odds ratio 2 to 7. 86</td>
<td>Increased smooth muscle tone from heightened sympathetic nervous system activity. Reduced NOS in cavernous nerves and nerves to bladder outlet. Increased smooth muscle Rho-kinase activity. Smooth muscle fibrosis from ischaemia.</td>
<td>Of the uroselective α blockers, alfuzoxin is associated with less ejaculatory dysfunction than tamsulosin. 87 Could possibly combine α blockers with PDE5is (other than vardenafil) — but no evidence from RCTs.</td>
</tr>
<tr>
<td>Cardiac failure: prevalence of ED is up to 80%. 88</td>
<td>Associated CAD, HT, or both.</td>
<td>Caution recommended with erectile enhancement because of risk of hypotension. 88 Preliminary evidence of benefit from PDE5is for exercise tolerance and reduction of endothelial dysfunction in patients with heart failure.</td>
</tr>
<tr>
<td>Hypertension: odds ratio 1.3 to 1.7 89-91</td>
<td>Endothelial dysfunction. Structural change reducing maximal flow.</td>
<td>Level 1 evidence of benefit from sildenafil if SSRI s are necessary and ED persists. 92 Calcium-channel blockers and angiotensin renin antagonists might improve endothelial function. 91 PDE5is are effective in 70% of men with hypertension; 91 however, use caution with α blockers, and note that vardenafil is contraindicated. 91</td>
</tr>
<tr>
<td>Diabetes: odds ratio 1.5 to 3.95 92-94</td>
<td>Reduced NOS activity is possibly because of overexpression of arginase. Lack of NADPH, which is an essential co-factor for NOS. Reduced NADPH also promotes smooth muscle contractility by increasing DAG and protein kinase C. Reduced endothelium-derived hyperpolarising factor. Increased oxygen free radicals including those from advanced glycosylation end-products quench released NO. 95</td>
<td>PDE5is are effective in about 56% of men with DM. 95 Future NO-releasing PDE5is could prove useful when endogenous NO is severely deficient. 95 Intracavernosal PGE1 is usually effective. Titrination to 20-40 μg typically needed because of vascular impairment.</td>
</tr>
<tr>
<td>Primary and secondary hypogonadism: low testosterone is responsible for just 4-5% of ED. Erections are still possible from visual stimuli. 95-97</td>
<td>Low testosterone reduces availability of NO. 95 Associated low desire limits focus on sexual stimuli.</td>
<td>Address cause of secondary low testosterone. Supplement if no contraindications.</td>
</tr>
<tr>
<td>Depression: ED present in 26-50% of untreated patients. 98-99</td>
<td>Neurotransmitters of frontal limbic circuitry thought to be affected in depression.</td>
<td>Effectively treating ED can encourage remission of depression. 99 ED improved with sildenafil in 50% of men vs 20% with continuous positive airway pressure—trials of combined treatment have been advocated. 99</td>
</tr>
<tr>
<td>Sleep apnoea: severe obstructive sleep apnoea independently associated with ED. 100</td>
<td>Possible dysfunction of ANS and endothelial dysfunction associated with nocturnal hypoaemia, nocturnal hypertension, and nocturnal over-activity of sympathetic nervous system.</td>
<td>PDE5is of benefit when some NO is still released from pelvic autonics in response to stimulation (ie, ineffective in non-nerve sparing pelvic cancer surgery; can enhance erections from psychological stimuli in men with complete SCI affecting lumbar sacral cord given intact thoracolumbar outflow). Intracavernosal PGE1 usually effective – use smallest dose eg. 2 μg and titrate in small increments to avoid priapism.</td>
</tr>
<tr>
<td>Neurological disease involving ANS (see accompanying paper on sex and neurological illness). 101</td>
<td>Interruption of central, spinal, and peripheral autonomic pathways.</td>
<td></td>
</tr>
</tbody>
</table>

(Continues on next page)
Odds ratios for comorbid disorders are 1.3–1.77 for various diseases are shown in table 2. Age-adjusted mechanisms of erectile dysfunction associated with diabetes, hyperlipidaemia, and smoking have been studied. The probable pathological and physiological syndromes; carcinoma in situ; penile cancer.


Table 2: Diseases and drugs associated with erectile dysfunction

<table>
<thead>
<tr>
<th>Medical disorder</th>
<th>Type of pain</th>
<th>Findings on physical examination</th>
<th>Therapeutic options and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peyronie’s disease</td>
<td>Pain on erection and difficulty with penetration.</td>
<td>Penile curvature due to the formation of a plaque of fibrous tissue.</td>
<td>Spontaneous improvement is likely. Patients should be advised to continue coital activity. No non-invasive treatments have been shown to help. Surgical correction should not be attempted for at least 12 months after onset or until symptoms have been stable for at least 3 and preferably 6 months.</td>
</tr>
<tr>
<td>Phimosis: usually idiopathic, but can be associated with candidosis</td>
<td>Penile pain, itching, or both; preputial ballooning during voiding; voiding pain; slow urinary stream; and urinary frequency</td>
<td>Inability to exteriorise the glans penis.</td>
<td>A normal state until age 5. Based on CE, later phimosis might be prevented by genital hygiene and gentle retraction of the foreskin without causing pain; moderately potent topical steroids might be beneficial. Otherwise surgery, such as preputial plasty (in which no skin is removed) or circumcision, might be necessary.</td>
</tr>
<tr>
<td>Priapism: sickle cell disease, thalassaemia major, leukaemia, erectile disorders, antidepressant drugs, antihypertensive drugs, recreational drugs, and malignancy</td>
<td>A persistent (and after a variable length of time, painful) unwanted erection that is not associated with sexual desire or sexual stimulation.</td>
<td>1. Low-flow, ischaemic or anoxic priapism. 2. High-flow well oxygenated priapism, in which pain is less of a feature. 3. Recurrent or stuttering priapism, usually high-flow but can become low-flow and anoxic. Frequently associated with sickle-cell disease.</td>
<td>1. In early stages, advise micturition, application of ice pack, cold showers; give analgesics or terbutaline for a pharmacologically prolonged erection. A low-flow ischaemic priapism requires urgent treatment to prevent muscle necrosis; aspiration of cavernous blood can confirm the diagnosis of a low-flow ischaemic priapism, relieves pain, and reduce pressure. If this treatment does not produce sufficient results after 10 minutes, an α-adrenoceptor antagonist should be injected. This should be repeated, and detumescence maintained, for 1 hour, followed by short surgery. 20% of men with a priapism lasting 24 hours do not regain the ability to have intercourse unless a penile prosthesis is implanted. 2. This disorder can resolve spontaneously; if not, selective embolisation with autologous blood clot or surgical ligation of a fistula is usually successful. 3. Use haemorrhagic management of sickle cell disease.</td>
</tr>
<tr>
<td>Dermatologic diseases, Sexually transmitted disease; Zoon’s balanitis, erosive lichen planus, lichen sclerosis; non-specific balanoposthitis, dysaesthesia syndrome; carcinoma in situ; penile cancer.</td>
<td>Pain on touch and penetration.</td>
<td>Visible symptoms, dysfunctional foreskin, or both.</td>
<td>Exclude sexually transmitted disease. Treat underlying disorder (see table 5). Based on CE, counsel couples about non-penetrative and safe sex. Also, give psychosexual support for sexual difficulties from limited skin contact, visible symptoms, disrupted self-image, inability to meet a partner, shame, or lack of confidence.</td>
</tr>
</tbody>
</table>

Injury. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant. TRUS=transrectal ultrasound. TURP=transurethral prostatectomy. UMNL=upper motor neuron lesion.

Table 4:

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Associated disease</th>
<th>Associated drugs</th>
<th>Therapy and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature ejaculation.</td>
<td>Prostatitis, epididymitis, urethritis, or SCI (rare).</td>
<td>Withdrawal from opiates, ephedrine, or trifluoperazine.</td>
<td>Give SSRIs, especially paroxetine (5-HT2C stimulation),120 with cognitive-behavioral techniques including stop-start and pubococcygeal muscle training based on CE.120</td>
</tr>
<tr>
<td>Delayed or absent ejaculation and orgasm.</td>
<td>SCI, especially if complete UMNL, MS, or very low testosterone.</td>
<td>SSRIs and antipsychotics.</td>
<td>Prescribe use of vibrator, with or without yohimbine, bupropion, buspirone, or cyproheptadine (based on CE). If fertility needed use vibrostimulation or electroejaculation,120 with attention to autonomic dysreflexia for lesions above T6. Give sildenafil to reverse SSRI-induced delay.120</td>
</tr>
<tr>
<td>Orgasm present, ejaculation absent.</td>
<td>Very low testosterone, damage to pelvic sympathetic nerves from RPND or pelvic surgery; SCI, MS, or diabetes.</td>
<td>Testosterone replacement if not contraindicated. Viberator with or without yohimbine, bupropion, buspirone, cyproheptadine (based on CE). If fertility needed: vibrostimulation or electroejaculation,120 with attention to autonomic dysreflexia for lesions above T6. Give sildenafil to reverse SSRI-induced delay.120</td>
<td></td>
</tr>
<tr>
<td>Retrograde ejaculation, confirmed by sperm in urine or TRUS showing open bladder neck at rest.</td>
<td>Diabetes, MS, TURP; bladder neck surgery; damage to pelvic sympathetic nerves from pelvic surgery; or RPND.</td>
<td>Thiazides, phenothiazines, s-blockers, or antipsychotics.</td>
<td>If fertility needed, give sympathomimetics (eg, TCAs or pseudoephedrine, based on CE). If unsuccessful, postorgasmic urine can be prepared for intrauterine insertion. Alkalisation of the urine is necessary.</td>
</tr>
<tr>
<td>Painful ejaculation.</td>
<td>Prostatitis (acute or chronic); epididymitis; urethritis; LUTS; post-traumatic urethral strictures, urinary tract stones.</td>
<td></td>
<td>Treat underlying disorder. Tamsulosin can be of benefit when underlying urological pathology is clearly identified,120 but not when absent.120</td>
</tr>
<tr>
<td>Low-volume ejaculate.</td>
<td>Low testosterone; urethral strictures, ejaculatory duct obstruction, or LUTS.</td>
<td>Tamsulosin or antiandrogens.</td>
<td>Treat underlying disorder. Could be caused by ageing.</td>
</tr>
<tr>
<td>Female orgasm delayed or absent.</td>
<td>SCI (especially complete UMNL), or MS. Low testosterone states or LUTS; (especially urge incontinence). Pelvic floor dysfunction.</td>
<td>Antipsychotics, SSRIs, and antiandrogens.</td>
<td>From risperidone but not olanzapine in small open label study. Increase stimulation (eg, stronger vibrator based on CE). Suppression effective in one of two RCTs for SSRI-induced delay.121 Surgical intervention is the definitive therapy for incontinence, but it was worsened sexual function in 71% of patients and improved sexual function in only 29%.121</td>
</tr>
<tr>
<td>Painful female orgasm.</td>
<td>Post menopause; IUD; pelvic inflammatory disease; endometriosis; pelvic floor dysfunction.</td>
<td></td>
<td>Postmenopausal oestrogen and progesterone (based on CE). Treat underlying disorder.</td>
</tr>
</tbody>
</table>

CE=clinical experience. IUD=intruterine device. LUTS=lower urinary tract symptoms. MS=multiple sclerosis. RCT=randomised controlled trial. RPND=retroperitoneal lymph node dissection. SCI=spinal cord injury. SSRI=selective serotonin reuptake inhibitor. TCA=tricyclic antidepressant. TRUS=transrectal ultrasound. TURP=transurethral prostatectomy. UMNL=upper motor neuron lesion.

Table 4: Diseases and drugs associated with dysfunction of orgasm and ejaculation
women’s persistent genital arousal syndrome, a recently recognised disorder that is somewhat similar, is intrusive, unwanted, persistent genital congestion with preorgasmic feelings, which is only slightly relieved by orgasm.  Neither medical susceptibility factors nor effective treatment are known.

**Orgasm dysfunction**

A full understanding of the physiology of orgasm in men and women remains unclear. Orgasm has been variously recognised disorder that is somewhat similar, is intrusive, unwanted, persistent genital congestion with preorgasmic feelings, which is only slightly relieved by orgasm.  Neither medical susceptibility factors nor effective treatment are known.

<table>
<thead>
<tr>
<th>Medical disorder</th>
<th>Type of dyspareunia</th>
<th>Findings on physical examination</th>
<th>Therapeutic options and general comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal atrophy: associated with renal failure, chemotheraphy-induced menopause, hypothalamic or pituitary disease, bilateral oophorectomy, or hyperprolactinemia.</td>
<td>Introtial pain and with penile-vaginal movement, Possible postcoital burning. Deeper dyspareunia when vaginal atrophy advanced.</td>
<td>Pallor, dryness, increased fragility and thinning of vullovaginal epithelium, vaginal shortening, loss of rujage, narrowing, or urethral caruncle.</td>
<td>Local oestrogen therapy is highly recommended. Low-dose estradiol by vaginal ring or tablet can be equally effective, but serum levels remain postmenopausal. Tibolone improves this disorder beyond placebo. Frequent sexual arousal and (if necessary) non-penetrative activity could promote genital health. Give dopaminergic drugs such as bromocriptine, cabergoline, or both to reduce prolactin; with surgery or radiation as appropriate.</td>
</tr>
<tr>
<td>Chronic (abdominal) pain; Endometriosis; Chronic PID; IBS; Crohn’s disease; Ulcerative colitis; Ovarian tumour; Abdominal wall pain.</td>
<td>Deep dyspareunia. IBS also associated with introital pain from comorbid VVS.</td>
<td>General tenderness to deep bimanual examination.</td>
<td>Sexual dysfunction is highly prevalent in such patients. Women report deep dyspareunia. Organical disorders should be treated accordingly but sexual dysfunction may still need to be specifically managed. Irrespective of the organic or functional nature of the pain, a history of possible negative sexual experiences should be elicited before any procedures or treatment.</td>
</tr>
<tr>
<td>Lower urinary tract symptoms (LUTS) with urinary incontinence.</td>
<td>Introtial and deep dyspareunia on vulvar burning after sexual intercourse.</td>
<td>Perineal and vulvar inflammation.</td>
<td>Voiding dysfunction, recurrent bacterial cystitis, hyperactive sexual desire, and sexual pain disorders are highly correlated. For recurrent cystitis give local OT, IV antibiotic self-treatment or prevention, and postcoital micturition (based on CE). In case of prolapse, surgical treatment can be curative but can also have undesired effects on sexual functioning.</td>
</tr>
<tr>
<td>Pelvic radiation.</td>
<td>Introtial and deep dyspareunia.</td>
<td>Thinning and fragility of vaginal epithelium, loss of elasticity, stenosis, or foreshortening.</td>
<td>Preventive measures, such as transposition of the ovaries to prevent ovarian failure. Therapeutic options based on CE include couple counselling about non-penetrative sex, topical oestrogen, lubricants, vaginal inserts, and vaginal reconstruction.</td>
</tr>
<tr>
<td>Chronic vulvovaginal candidiasis associated with diabetes and HIV.</td>
<td>Introtial dyspareunia and with penile-vaginal movement.</td>
<td>Elrhythmia, swelling of vulva, and thick clumpy white or pale yellow vaginal discharge.</td>
<td>Oral agents recommended for recurrent symptomatic candidiasis.</td>
</tr>
<tr>
<td>Vulvar vestibulitis syndrome (VVS) associated with IBS, fibromyalgia, interstitial cystitis (IC), and other pain syndromes.</td>
<td>Superficial vulvovaginal pain on (attempted) penetration, pain on non-penetrative vulvovaginal touching, postcoital burning, or burning from partner’s ejaculation fluid.</td>
<td>Variable erythema of the vestibule. Alldodynia typically located between 4 and 8 o’clock on the introitus, just exterior to the hymenal ring but can involve the skin around the openings of the Skene’s ducts or the whole introital rim. Hypertonic pelvic floor muscles. Pain with attempted digital or speculum entry.</td>
<td>Vaginal muscle EMG biofeedback with pelvic floor physical therapy and CRT have been shown to have clinical benefit, but evidence is limited. Based on CE treatment with topical oestrogen, cremolyn, xylocane, capsaicin, or botulinum toxin injections. Based on CE, and the not yet proven assumption that neuropathic pain is at least in part responsible for the pain of VVS, give TCAs or AEDs. For comorbid IC, DBPCTs have shown benefit of oral or intravesical pentosan polysulfate, intravesical dimethyl sulphoxide or resiniferatoxin (vallinoid). Based on CE, there may also be benefit from antihistamines, quercetin, intravesical heparin, lidocaine, or a combination. Excision of the affected regions (vestibulectomy, vestibuloplasty, or perineoplasty) can reduce pain in the short term but long term sexual outcome less clear.</td>
</tr>
<tr>
<td>Dysaesthetic vulvodynia.</td>
<td>Introtial dyspareunia, and with penile-vaginal movement.</td>
<td>None.</td>
<td>Vulvar burning and pain that causes sexual and psychological distress accompanied by the complete absence of any physical abnormality on examination, in biopsies or culture. Based on CE, TCAs or AEDs can be of partial benefit.</td>
</tr>
<tr>
<td>Genital mutilation.</td>
<td>Introtial pain and with penile-vaginal movement and deep dyspareunia.</td>
<td>Type I: all or part of the clitoris and its prepuce or skin excised. Type II: clitoris excised, labia minora partly or totally removed. Type III: all external genitalia excised, vaginal opening closed except for a matchtip-sized hole to allow urine and blood to escape.</td>
<td>Experienced by an estimated 130 million women, in particular from north Africa, the middle east, and southeast Asia. Based on CE, use a respectful approach and provide information about health consequences. Offer sexual counselling, psychotherapy, and support groups. Offer to repair the vulva, vagina, or both. Involve the partner, the family, or both in decisions. Clarify the legal and ethical responsibility of the physician, who must decline any request to restitch after childbirth. Offer specific management of sexual dysfunction as needed.</td>
</tr>
</tbody>
</table>

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fantasy, sexual dreams, and physical stimulation of other areas (eg, the nipple) can trigger orgasms in men and women. Women with complete spinal-cord injury above the spinal-cord level T10 can have orgasms from vibrostimulation of the cervix, possibly mediated by way of vagal afferents.122

Table 4 shows neurological disorders that delay or preclude orgasm in men and women.14 Damage to the pelvic autonomic plexuses (eg, from radical prostatectomy or radical hysterectomy) does not preclude orgasm. The necessary autonomic nerves probably travel with somatic fibres S2, S3, S4; there are branches from sympathetic ganglia to the union of S2, S3, S4 parasympathetic and somatic fibres proximal to the superior hypogastric plexus. Contrary to clinical impressions, weakening of the pelvic floor from vaginal deliveries is not correlated with sexual dysfunction.14 The most common drugs that impede orgasm are the selective serotonin reuptake inhibitors.

**Ejaculatory dysfunction**

Ejaculation consists of sympathetically mediated emission of seminal fluid into the posterior urethra and somatically mediated expulsion of the ejaculate. Animal studies have shown that dopamine facilitates ejaculation, and that serotonin facilitates ejaculation by way of 5-HT₄ receptors and inhibits it by way of 5-HT₂C receptors. Emission consists of contraction of the epididymis, vas deferens, seminal vesicles, and prostate, and closure of the bladder neck. Rhythmic contraction of the perineal muscles propels the ejaculate forward. Some medical disorders preclude ejaculation, orgasm, or both, as shown in table 4. About 20% of men with lower urinary tract symptoms (in the absence of infection) report painful ejaculation.150

**Chronic dyspareunia**

Prevalence figures for chronic dyspareunia vary from 6·5% to 40% in older women, and 14% to 34% in younger women.112,113 Dyspareunia in women frequently arises in the context of chronic disease (table 5), and in men is usually related to Peyronie’s disease (table 3). Irrespective of the associated chronic disease, the initial pathophysiological mechanisms of women’s dyspareunia are often unclear, but central and peripheral sensitisation of the nervous system might be the overriding process. Pain is normally reported when impulses reach the brain via A δ fibres or C-fibre nociceptive afferents. In chronic pain the threshold of nociceptors is reduced by the release of chemical inflammatory mediators into the tissue, which causes peripheral sensitisation. Nociceptors can become sensitised to weak, non-noxious stimuli, which results in allodynia, and to noxious stimuli, which results in the exaggerated pain response of hyperalgesia. Allodynia and hyperalgesia can also be due to central sensitisation, in which signals entering the central nervous system via non-nociceptive Aδ or C-fibre afferents are amplified abnormally, so that they evoke pain. The cause of the increased descending excitatory signals, decreased inhibitory signals, or both, which produce central sensitisation of dorsal horn cells, is unclear. We need to know whether psychological factors, such as the expectation of pain from a highly intimate behaviour (normally associated with pleasure and emotional release), have a role.

Vulvar vestibulitis syndrome is the most common subtype of chronic dyspareunia, and affects about 9% of women.151 Although reported predominantly in young, otherwise-healthy women, vulvar vestibulitis syndrome also affects older women, especially those diagnosed with other pain disorders such as fibromyalgia and irritable

### Table 5: Subtypes of chronic dyspareunia in women

<table>
<thead>
<tr>
<th>Dermatological diseases</th>
<th>Benign non-STD can be atopic eczema, contact dermatitis (including iatrogenic), lichen simplex, lichen sclerosis, lichen planus, psoriasis, hidradenoma, foxtail dermatitis, chronic vulvar gland infection, pediculosis pubis, pinworm infections, Behçet’s, aphthous ulcers, cicatricial pemphigoid, pyoderma gangrenosum, anorectal Crohn’s, burn, or trauma. STD can be HSV, syphilis, chancroid, lymphogranuloma venereum, granuloma inguinale, condylomata accuminata, or molluscum contagiosum. Neoplasia can be VIN, vulvar Paget’s, or melanoma.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ectropion</td>
<td>Recent studies have shown that dopamine facilitates ejaculation, and that serotonin facilitates this by way of 5-HT ₄ receptors and inhibits it by way of 5-HT ₂C receptors. Emission consists of contraction of the epididymis, vas deferens, seminal vesicles, and prostate, and closure of the bladder neck. Rhythmic contraction of the perineal muscles propels the ejaculate forward. Some medical disorders preclude ejaculation, orgasm, or both, as shown in table 4. About 20% of men with lower urinary tract symptoms (in the absence of infection) report painful ejaculation.150</td>
</tr>
<tr>
<td>Vaginal septum</td>
<td>Recent studies have shown that dopamine facilitates ejaculation, and that serotonin facilitates this by way of 5-HT ₄ receptors and inhibits it by way of 5-HT ₂C receptors. Emission consists of contraction of the epididymis, vas deferens, seminal vesicles, and prostate, and closure of the bladder neck. Rhythmic contraction of the perineal muscles propels the ejaculate forward. Some medical disorders preclude ejaculation, orgasm, or both, as shown in table 4. About 20% of men with lower urinary tract symptoms (in the absence of infection) report painful ejaculation.150</td>
</tr>
<tr>
<td>Vaginal agenesis</td>
<td>For a benign non-STD, based on CE,14 give corticosteroids (oral, topical, or injectable), immunosuppressive drugs (azathioprine, dapsone, tacrolimus, pemeirocin, thalidomide, or imfl iximab); immune augmentation drugs (imiquimod); surgery; behavioural and physical therapy; and biofeedback. Also offer psychosexual support for sexual problems resulting from limited skin contact, visible symptoms, disrupted self-image, inability to meet a partner, shame, lack of confidence, or a combination of these. For treatment options for STD consult Guidelines from ISTI, WHO and CDC USA.14–17 Asymptomatic shedding and further infection necessitate strong encouragement of protective measures and safe sex. For neoplasia attempt surgery, laser therapy with radiation, or chemotheraphy, as appropriate. Sexual activities do not stop for most couples. Based on CE, psychosexual counselling can be of benefit, in particular in the first year after treatment.150</td>
</tr>
<tr>
<td>Neurological disorders</td>
<td>Recent studies have shown that dopamine facilitates ejaculation, and that serotonin facilitates this by way of 5-HT ₄ receptors and inhibits it by way of 5-HT ₂C receptors. Emission consists of contraction of the epididymis, vas deferens, seminal vesicles, and prostate, and closure of the bladder neck. Rhythmic contraction of the perineal muscles propels the ejaculate forward. Some medical disorders preclude ejaculation, orgasm, or both, as shown in table 4. About 20% of men with lower urinary tract symptoms (in the absence of infection) report painful ejaculation.150</td>
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<td>Emotional disorders</td>
<td>Recent studies have shown that dopamine facilitates ejaculation, and that serotonin facilitates this by way of 5-HT ₄ receptors and inhibits it by way of 5-HT ₂C receptors. Emission consists of contraction of the epididymis, vas deferens, seminal vesicles, and prostate, and closure of the bladder neck. Rhythmic contraction of the perineal muscles propels the ejaculate forward. Some medical disorders preclude ejaculation, orgasm, or both, as shown in table 4. About 20% of men with lower urinary tract symptoms (in the absence of infection) report painful ejaculation.150</td>
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<td>Physical disorders</td>
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<tr>
<td>Gynaecological disorders</td>
<td>Recent studies have shown that dopamine facilitates ejaculation, and that serotonin facilitates this by way of 5-HT ₄ receptors and inhibits it by way of 5-HT ₂C receptors. Emission consists of contraction of the epididymis, vas deferens, seminal vesicles, and prostate, and closure of the bladder neck. Rhythmic contraction of the perineal muscles propels the ejaculate forward. Some medical disorders preclude ejaculation, orgasm, or both, as shown in table 4. About 20% of men with lower urinary tract symptoms (in the absence of infection) report painful ejaculation.150</td>
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</table>
bowel syndrome. This disorder is characterised by burning pain localised at the entrance (vestibule) of the vagina from sexual and non-sexual contact. Both the primary form of vulvar vestibulitis syndrome (from the first intercourse attempt) and the secondary form are of uncertain aetiology. Genetic factors could act to reduce the production of interferon or mannose-binding lectin, which are of importance for innate resistance against microorganisms. Vulvar vestibulitis arises most commonly in the presence of specific alleles of the interleukin-1 receptor antagonist and melanocortin-1 receptor, which are associated with pale skin and increased risk of infections.

Most women with vulvar vestibulitis syndrome also have spontaneous dysaesthesiae in the form of vulval burning (vulvodynia), consistent with neuropathic pain. Vulvodynia can happen premenstrually, or intermittently or constantly throughout the monthly menstrual cycle. Increased numbers of intraepithelial nerve-endings, possibly as a consequence of mast-cell activity in repeated inflammation, could contribute to the hyperalgesia.

Women with vulvar vestibulitis syndrome show generally increased sensitivity to pain stimuli. Augmentation of genital sensory processing, similar to that recorded in fibromyalgia, idiopathic back pain, irritable bowel syndrome, and neuropathic pain at non-genital sites, can be seen on functional MRI of the brain. Therefore, vulvar vestibulitis syndrome might include mechanisms that are genital-specific in addition to those that are generalised, and possibly centrally mediated.

A subgroup of patients with vulvar vestibulitis syndrome have a history of recurrent candidiasis. Candida can induce an immunological response that results in pathological changes in cutaneous T-lymphocyte cells and chronic inflammatory skin disease in genetically susceptible women. Compared with women with other skin disorders, women with vulvar vestibulitis syndrome were significantly more likely to react to Candida albicans (but not other standard allergens or vulval organisms) on patch testing.

Whether as a cause or a consequence, pelvic floor hypertonia is typically present in vulvar vestibulitis syndrome in common with irritable bowel syndrome, constipation, haemorrhoids, interstitial cystitis, and instances of chronic abdominal pain. The pelvic floor musculature is indirectly innervated by the limbic system and therefore, is highly reactive to emotional stimuli and states. Moreover, coitus entails an anatomical match or mismatch between penis and the degree to which the woman can relax. Penile diameter does appear to be relevant when the woman has vulvar vestibulitis syndrome.

Initiation of hormonal contraceptives that contain low-dose oestrogen before the age of 16 could predispose women to vulvar vestibulitis syndrome. A significantly lower pain threshold, especially in the posterior vestibulum, has also been associated with the use of hormonal contraceptives in women without vulvar vestibulitis syndrome.

Despite earlier contradictory data, recent studies confirm that women with vulvar vestibulitis syndrome have high levels of psychological distress, depression, pain catastrophisation (irrational escalation of negative thoughts on pain), anxiety-disorders, perfectionism, somatisation (physical symptoms from psychological distress), and harm avoidance. These women also report hyper-vigilance for coital pain and exhibit a selective attention bias towards pain stimuli. Mechanisms of the mind can initiate processes such as neurogenic inflammation. However, women with vulvar vestibulitis syndrome are more sensitive than other women to noxious stimuli, irrespective of their personality traits.

The treatments for dyspareunia outlined in table 5 are not evidence-based; they include chronic-pain medications along with sexual and psychological counselling. Non-penetrative sex is advocated. Partial or complete vestibulectomy can bring short-term relief of dyspareunia, but conservative treatment can be equally efficient for management of pain, and fear of pain, during intercourse. Research has shown that patients’ acceptance of the rationale for their treatment correlates with better outcome and reduction of pain.

Although the aetiology of dyspareunia must be investigated with careful clinical examination, this might be impossible initially in some women with histories of chronic introital dyspareunia who are unable to tolerate any entry by a penis, dildo, or tampon, and show muscle tightening or fear that is characteristic of vaginismus. In such patients, examination is deferred until after treatment, such as education about vaginismus, cognitive behavioural therapy, and sex therapy, allows a detailed examination and the subsequent use of graded vaginal inserts. Physicians treating women with vaginismus commonly note exaggerated disgust and aversion to contact with sexual fluids, religious orthodoxy, negative messages about sex from childhood, a history of poorly executed attempts at pelvic examination, and unassertiveness of a male partner. As with vulvar vestibulitis syndrome, outcome for treatment of vaginismus is not scientifically validated. Although many clinicians define vaginal penetration as the goal of treatment, future outcome measures should be broadened to include attainment of sexual pleasure.

For the treatment of dyspareunia in general, a multidimensional, multidisciplinary approach is recommended, with attention to the patient’s experience of pain; their emotional and psychological profile; any past genital mutilation or sexual abuse; the genital mucous membrane; the pelvic floor; and the sexual relationship.

**Integrating medical and psychosocial effects of disease on sexual function**

In middle-aged and elderly men and women, attitudes about sexual intercourse, and about the disease in
question, can have a more significant effect on sexual function than do biomedical factors.129,137 Also, especially in women, feelings of intimacy are often more important than feelings of sexual arousal.129 Whereas sexual function is affected by physical sensations, mobility, and physiological changes in the genital region, the appreciation of intimacy is far less dependent on physical capacities. Sexual dissatisfaction in chronic disease is therefore highly variable, and is strongly modulated by personal, societal, and relationship factors, and by past experiences, all of which need to be taken into account when sexual dysfunction is addressed (panel).

Future directions
Both an increased understanding of sexual physiology and a wider acceptance that sexuality is often an important part of life might encourage physicians to routinely consider risk factors for sexual dysfunctions, to assess and manage those dysfunctions, and to avoid iatrogenesis. Improved assessment, which includes validated questionnaires revised to take account of contemporary views of sexual response, could increase our understanding of the prevalence of sexual dysfunction in different patient cohorts. Inclusion of men and women who are no longer sexually active into relevant studies is a desirable goal.

We need to investigate whether pharmacological or non-pharmacological treatments of vascular risk factors can improve deficient genital congestion and whether antagonists of the renin angiotensin system are more able to decrease oxidative stress injury than other treatments. Erectile dysfunction might be an appropriate outcome measure for clinical trials of lipid-lowering drugs; one prospective study139 has suggested that an improvement to risk factors for coronary heart disease in midlife will lessen the frequency of both erectile dysfunction and coronary artery disease.

Acknowledgments
We thank Dr Peter Rees for his helpful review of the manuscript and Maureen Piper for her excellent secretarial support.

Conflict of interest statement
R Basson was a temporary consultant to Pfizer (about the relation between female sexual dysfunction and a molecule under investigation) and on one occasion to Solvay. Her clinical practice occasionally necessitates provision of medicolegal reports without prejudice. W Weijmar Schultz is participating in an international study to assess the effects of Livial on sexual functioning over and above its ability to relieve climacteric symptoms in postmenopausal women with sexual dysfunction. This study is financed by Organon. He has no personal financial relations with this company.

Contributors
R Basson wrote the first ten sections and the future outlook. She also edited other sections. W Weijmar Shultz wrote the three sections on dyspareunia in men and women and on the integration of medical and psychosocial effects of disease on sexual function. Both authors have read and approved the final version.

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The eye in hypertension

Tien Wong, Paul Mitchell

Hypertension has a range of effects on the eye. Hypertensive retinopathy refers to retinal microvascular signs that develop in response to raised blood pressure. Signs of hypertensive retinopathy are frequently seen in adults 40 years and older, and are predictive of incident stroke, congestive heart failure, and cardiovascular mortality—indeed, independently of traditional risk factors. Hypertension is also a major risk factor for the development of other retinal vascular diseases, such as retinal vein and artery occlusion, and ischaemic optic neuropathy. High blood pressure increases the risk of both development of diabetic retinopathy and its progression. Adequate control of blood pressure has been proven in randomised clinical trials to reduce vision loss associated with diabetic retinopathy. Finally, hypertension has been implicated in the pathogenesis of glaucoma and age-related macular degeneration. Recognition of the ocular effects of blood pressure could allow physicians to better manage patients with hypertension, and to monitor its end-organ effects.

Hypertension has profound effects on the structure and function of the eye. First, the retinal, choroidal, and optic nerve circulations undergo a series of pathophysiological changes in response to raised blood pressure, resulting in a range of clinical signs referred to as hypertensive retinopathy, hypertensive choroidopathy, and hypertensive optic neuropathy. Second, hypertension is an important risk factor for the development of potentially blinding vascular diseases of the eye, including retinal vein and artery occlusion, retinal–arteriolar emboli, and diabetic retinopathy. Finally, hypertension might be a pathogenic factor for non-vascular ocular diseases, including two of the leading causes of blindness—glaucoma and age-related macular degeneration. We summarise the links between hypertension and these disorders.

Direct ocular effects of hypertension

Hypertensive retinopathy refers to retinal microvascular signs that are related to raised blood pressure. The underlying pathophysiology of these signs can be divided into stages. The initial response of the retinal circulation to a rise in blood pressure is vasospasm and an increase in vasomotor tone, which is seen clinically as generalised retinal–arteriolar narrowing. Subsequently, chronic arteriosclerotic changes, such as intimal thickening, media-wall hyperplasia, and hyaline degeneration, develop. These changes manifest as diffuse and focal areas of arteriolar narrowing, opacification of arteriolar walls (described as silver or copper wiring), and compression of the venules by arterioles at their common adventitial locations (termed arteriovenous nipping or nicking). With more pronounced high blood pressure, the blood–retinal barrier breaks down, resulting in exudation of blood (haemorrhages), lipids (hard exudates), and subsequent ischaemia of nerve-fibre layers (known as cotton-wool spots). In the setting of severely high blood pressure, raised intracranial pressure and concomitant optic nerve ischaemia can lead to disc swelling (papilloedema), which is sometimes referred to as severe or malignant hypertension or hypertensive optic neuropathy. Other mechanisms linking high blood pressure with signs of hypertensive retinopathy could include inflammation, endothelial dysfunction, and angiogenesis.

Clinically, signs of hypertensive retinopathy are classified into four grades of increasing severity. Although this system is widely used, early retinopathy grades are difficult to distinguish. Further, the prognostic implications of early hypertensive retinopathy grades are unclear. Thus, a three-grade classification system has been proposed. In this system, mild retinopathy would be identified by retinal–arteriolar signs, such as generalised and focal arteriolar narrowing, arteriolar wall opacification, and arteriovenous nipping (figure 1A). In addition to these signs, moderate retinopathy would be recognised by flame-shaped or blot-shaped haemorrhages, cotton-wool spots, hard exudates, microaneurysms, or a combination of all of these factors. Severe retinopathy would display some or all of these retinopathy signs, as well as swelling of the optic disc (figure 1B).

Population-based studies that used retinal photographs and standardised assessment methods to define signs of retinopathy detected signs of hypertensive retinopathy in 2–14% of the non-diabetic population aged 40 years and older. The investigators reported that these signs were strongly associated with high blood pressure. One population-based study related both the prevalence, and incidence, of hypertensive retinopathy signs to raised blood pressure. Computer-imaging techniques have been used to show that high blood pressure is associated with narrower retinal–arteriolar diameters, but does not affect venular diameters.

Search strategy and selection criteria

We searched MEDLINE using PubMed with the search terms “systemic hypertension” and “blood pressure”, in combination with “eye”, “retinopathy”, “retinal arterial disease”, “arterio-venous nipping”, “retinal vein occlusion”, “retinal artery occlusion”, “retinal embolus”, “retinal macroaneurysm”, “ischaemic optic neuropathy”, “diabetes”, “glaucoma”, and “age-related macular degeneration”. We largely selected publications in the past 5 years, but did not exclude older publications that are commonly referenced or highly regarded. We also searched the reference lists of articles identified by this search strategy and selected those we judged relevant. Review articles are also cited to provide readers with more details and references.
Generalised retinal–arteriolar narrowing and arteriovenous nipping are related not only to a patient’s current blood pressure levels, but also to levels measured in the past, suggesting that these signs are persistent markers of chronic hypertensive damage. By contrast, focal arteriolar narrowing, retinal haemorrhages, microaneurysms, and cotton-wool spots have been associated only with concurrently measured blood pressure, and so might represent transient blood pressure changes.

Retinal–arteriolar narrowing might also be used to predict subsequent development of hypertension in individuals initially classified as normotensive. Thus, retinal–arteriolar narrowing, possibly indicating more widespread peripheral vasoconstriction, could be an early marker of overt hypertension.

Hypertensive retinopathy has long been regarded as a marker of systemic vascular disease elsewhere in the body. The hypothesis of a link between hypertensive retinopathy and stroke has been the most consistent, and has been supported by anatomical, physiological, and pathological studies. In a 3-year population-based cohort study of atherosclerosis risk, incident stroke events were more common in participants with signs of hypertensive retinopathy than in participants without retinopathy (figure 2). In an analysis that controlled for blood pressure, diabetes, lipids, and other risk factors, moderate signs of hypertensive retinopathy (cotton-wool spots, retinal haemorrhages, and microaneurysms) were associated with a two-fold to four-fold higher risk of incident stroke. Weaker associations between signs of mild hypertensive retinopathy and risk of stroke were also seen.

Although studies of the association between hypertensive retinopathy signs and heart disease have produced inconsistent results, various symptoms of hypertensive retinopathy have been linked with coronary-artery stenosis on angiography, and with incident coronary heart-disease events in both men and women. Some investigators suggest that moderate hypertensive retinopathy could be used to predict incident congestive heart failure, even in individuals without a previous history of myocardial infarction. Retinopathy signs have also been associated with other indicators of hypertensive target-organ damage, such as microalbuminuria and renal impairment and left ventricular hypertrophy.
Various national guidelines for management of hypertension recommend assessment of retinopathy to enable risk stratification.38,39 Patients with mild retinopathy will probably only need routine care, whereas patients with moderate signs might benefit from further assessment of blood-pressure control (eg, home or 24-hour blood-pressure monitoring), assessment of other vascular risk (eg, cholesterol levels) and, if clinically indicated, appropriate risk-reduction therapy (eg, cholesterol-lowering agents). In patients with borderline or so-called white coat hypertension, physicians could interpret mild or moderate signs of retinopathy as evidence for end-organ damage, and as an indication that antihypertensive therapy could aid in treatment. Additionally, in patients with established hypertension, signs of retinopathy could suggest a need for close observation of blood pressure, supplementary antihypertensive therapy, or both. Patients with severe retinopathy need urgent antihypertensive management.

Evidence suggests treatment of hypertension could reverse the changes seen with retinopathy. Laboratory studies in animals40 and clinical case series41 have shown regression of retinopathy signs with control of blood pressure. However, whether regression of hypertensive retinopathy is accompanied by a reduction in cardiovascular risk remains uncertain. We also need to know whether specific medications, such as those thought to improve microvascular structure and function (eg, angiotension-converting enzyme [ACE] inhibitors and statins), would reduce retinopathy damage beyond the effects of lowered blood pressure and lowered cholesterol alone. If so, use of such medications in patients with hypertensive retinopathy could also have additional therapeutic value in prevention and treatment of cardiovascular diseases.

**Hypertension as a risk factor in ocular disease**

**Retinal vein occlusion**

Hypertension predisposes patients to development of retinal vein occlusion, a common, sight-threatening retinal–vascular disorder.42–45 Retinal vein occlusion is characterised clinically by dilated and tortuous retinal veins and the presence of retinal haemorrhages, cotton-wool spots, and oedema of the macula and optic disc. These features are seen either in all four quadrants (central retinal vein occlusion; figure 3A), or in only one (branch retinal vein occlusion; figure 3B). Central retinal vein occlusion occurs in both ischaemic and non-ischaemic forms. Patients with an ischaemic central retinal vein occlusion typically present with poor visual acuity and a relative afferent papillary defect. Fluoroscein angiography of the fundus can show capillary non-perfusion. These patients have a poorer visual prognosis and are at risk of secondary neovascular glaucoma.46

Epidemiological studies of retinal vein occlusion in the general population are rare.44–45 Population-based surveys44,45 generally indicate that central retinal vein occlusions arise in 0·1–0·4% and branch retinal vein occlusions in 0·6–1·1% of adults aged 40 years and older. The 10-year cumulative incidence was reported to be 0·4% for central retinal vein occlusions and 1·2% for branch retinal vein occlusions.47

Almost all relevant studies have recorded a strong and consistent link between hypertension and the risk of retinal vein occlusion.42–45 One investigation showed that participants with hypertension were five times more likely to have a branch retinal vein occlusion than those without hypertension.45 Moreover, mild hypertensive retinopathy was strongly correlated with branch retinal vein occlusion, with an odds ratio of 17 for focal arteriolar narrowing, and 23 for arteriovenous nipping (figure 3B).46 Retinal vein occlusions arise in 0·1–0·4% and branch retinal vein occlusions in 0·6–1·1% of adults aged 40 years and older. The 10-year cumulative incidence was reported to be 0·4% for central retinal vein occlusions and 1·2% for branch retinal vein occlusions.47

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occlusion is also associated with other cardiovascular risk factors, including diabetes,\textsuperscript{42–44} cigarette smoking,\textsuperscript{43–45} carotid artery disease,\textsuperscript{45} and various haematological abnormalities (eg, hyperhomocysteinaemia, anticardiolipin antibodies, protein S and C deficiencies, activated protein C resistance, and factor V Leiden mutation).\textsuperscript{48–50} Retinal vein occlusion has also been linked with stroke,\textsuperscript{51} coronary heart disease,\textsuperscript{44} and cardiovascular mortality.\textsuperscript{52} Management of patients with a retinal vein occlusion should include assessment of blood pressure control, standard cardiovascular risk factors, and haematological function. Ophthalmic follow-up is needed to diagnose and prevent the two main complications of retinal vein occlusion: neovascularisation and macular oedema.\textsuperscript{53,54} Randomised clinical trials have shown that prophylactic panretinal laser treatment does not necessarily prevent neovascularisation in ischaemic vein occlusions, and that laser treatment can be withheld unless the patient develops frank ocular neovascularisation.\textsuperscript{55–58} Focal laser treatment can assist, however, in prevention of visual loss in some patients with macular oedema from branch retinal vein occlusion.\textsuperscript{55} Several treatment strategies for macular oedema (eg, injection of steroids or antivascular endothelial growth factor agents into the vitreous)\textsuperscript{37} have been proposed, but their effectiveness and safety will need to be confirmed by randomised clinical trials. Although treatment of hypertension has not been proven to reduce the risk of complications associated with retinal vein occlusion, or prevent the development of this disorder in the unaffected eye, physicians should more closely monitor blood pressure and consider initiation or modification of therapy in patients with this eye disorder.

Retinal emboli

Retinal–arteriolar emboli are discrete plaque-like lesions, lodged in the lumen of retinal arterioles.\textsuperscript{59} These emboli are heterogeneous, and can be composed of cholesterol crystals (reflective emboli) or fibrin, platelets, calcium, or other materials (non-reflective emboli).\textsuperscript{59} Retinal emboli can be single or multiple, and can be seen in one or both eyes.\textsuperscript{60}

Epidemiological studies report that asymptomatic retinal emboli are fairly common in adults aged 40 years and older. Two large population-based studies have reported prevalence rates of 1·3% and 1·4%,\textsuperscript{61,62} and the 10-year incidence of retinal emboli has been recorded as 2·9%.\textsuperscript{63} Asymptomatic retinal emboli are often transient; in one study 90% of retinal emboli detected in baseline photographs were not present 5 years later.\textsuperscript{64} The main risk factors for retinal emboli are hypertension, diabetes, and cigarette smoking.\textsuperscript{46,47} In Australia, investigators showed that individuals with hypertension had a two-fold higher risk of prevalent and incident retinal emboli than those without hypertension,\textsuperscript{61,63} but that this risk was increased to six-fold higher in hypertensive people who also smoked cigarettes.\textsuperscript{46}

Retinal emboli have two important clinical implications. First, the distal portions of occluded arterioles could be ischaemic, and thus, could result in frank retinal artery occlusion (figure 4). Second, people with retinal emboli have a higher risk of thromboembolic stroke and cardiovascular disease.\textsuperscript{62–64,66} In one study, participants with retinal emboli were twice as likely to have prevalent coronary heart disease and four times as likely to have carotid artery plaque as those without emboli.\textsuperscript{45} Another study associated the presence of retinal emboli with a two-fold higher risk of stroke mortality, independent of blood pressure and other risk factors.\textsuperscript{67}

Because of their increased risk of cardiovascular disease, patients with retinal emboli will need thorough systemic assessment, concentrating on hypertension control and other modifiable vascular risk factors. Although the source of the emboli (eg, carotid or cardiac) should be identified, the value of carotid ultrasonography or transthoracic echocardiography for detection of this source in asymptomatic patients remains controversial. Some studies suggest that up to 80% of people with asymptomatic retinal emboli do not have substantial carotid stenosis.\textsuperscript{68} The usefulness of carotid endarterectomy in asymptomatic retinal emboli in patients with major carotid artery stenosis is also uncertain.\textsuperscript{69} Patients with retinal emboli and atrial fibrillation will need systemic anticoagulation treatment.

Retinal artery occlusion

Retinal artery occlusion occurs commonly in patients with hypertension.\textsuperscript{60,61} Central retinal artery occlusion
presents with a sudden, painless, unilateral loss of vision and typically appears as a cherry red spot (figure 5). Occlusion of a branch retinal artery, by contrast, could present with a visual-field defect, and loss of central vision can be slight (figure 4). In up to 70% of cases of branch retinal artery occlusion retinal emboli is visible in the vessels at the optic disc, or downstream in branch retinal arterioles; these signs are present in about 20% of cases when the occlusion arises centrally.68,69

On the basis of clinic outpatient data, the yearly incidence of central retinal artery occlusion has been estimated at about one in 10 000, occurring typically in people aged 60–65 years.68 However, a population-based study showed a significantly lower incidence of only 0·07 per 10 000 people per year.70 Retinal artery occlusion is associated with hypertension and other cardiovascular risk factors, with haematological abnormalities, and with both subclinical and clinical stroke.68,71,72 Nearly half the patients with retinal artery occlusion in one study were reported to have echocardiographic abnormalities, and 10% needed systemic treatment.73 The disorder has been associated with an increased risk of cardiovascular disease and mortality.74 In a prospective study of 9 patients with retinal artery occlusions followed-up for a mean duration of 4·2 years, the absolute risk of death was estimated at 8% per year; coronary events caused 60% of the deaths, and stroke only 3%.75 Mortality rates might also vary due to the presence of retinal emboli; a study of 86 patients with retinal artery occlusions showed that mortality rates for those without visible retinal emboli were similar to age–sex controls, whereas patients with visible emboli had substantially higher mortality than controls.75

Thorough cardiovascular and cerebrovascular assessments, including analysis of carotid and cardiac images, are necessary for patients who present with retinal artery occlusions. The presence of retinal emboli has low predictive power for detection of significant carotid-artery stenosis, and thus should not affect decisions to do carotid ultrasonography.76 Central retinal artery occlusion is usually regarded as an ocular emergency. Attempts to restore ocular circulation and preserve vision include rapid dislodgement of the embolus by digital massage of the eyeball; paracentesis to remove anterior chamber fluid and lower intraocular pressure; and breathing into a paper bag to induce carbon-dioxide-related vasodilation.77,78 More aggressive treatment strategies such as selective ophthalmic artery fibrinolysis via the femoral artery have been suggested, but their effectiveness has yet to be proved.79–81

Retinal macroaneurysm
Retinal arterial macroaneurysm, a fusiform or sacular dilatation of the retinal arterioles, is an uncommon disorder almost always seen in patients with hypertension.82–84 In one hypothesis for the cause of retinal macroaneurysm, the retinal–arterial walls become less elastic with ageing, as both the medial muscle fibres and intima are gradually replaced by collagen. This decrease in elasticity renders the arterioles susceptible to dilatation caused by raised blood pressure. Hypertensive patients, with impaired autoregulation, are at particular risk. Subsequently, loss of the muscular coat, with thinning and fibrosis of arterial walls could lead to dilatation, hyperpermeability, and finally rupture of the macroaneurysm.

Data from large case series suggest that about a fifth of macroaneurysms are bilateral, and one in ten are multiple.82 Macroaneurysm is usually an incidental finding in asymptomatic patients, but can also present acutely, with visual loss secondary to haemorrhage or exudation. Hypertension has been reported in up to 75% of patients with macroaneurysms.82 Patients with uncontrolled hypertension might initially present with visual loss caused by macroaneurysm.84 Visual recovery typically occurs spontaneously with thrombosis of the macroaneurysm and resolution of the haemorrhage and exudate.85 However, residual retinal damage from chronic macular oedema and hard exudate deposition might lead to persistent poor vision. Anecdotal data suggest that laser treatment could be useful in some cases, especially when exudation affects the macula.

Ischaemic optic neuropathy
Like the retinal circulation, optic nerve circulation is prone to the effects of hypertension and other vascular risk factors.86–90 Ischaemic optic neuropathy is the most frequent acute optic neuropathy in patients aged over 50 years.90 Either the anterior or the posterior segment of optic nerve can be affected. Anterior ischaemic optic neuropathy accounts for 90% of cases, and typically presents with sudden visual loss and optic-disc oedema.
Figure 6: Ischaemic optic neuropathy
DS=disc swelling.

Diabetic retinopathy
Diabetic retinopathy is the most specific microvascular complication of diabetes and one of the main causes of visual impairment, especially in people of working-age. A population-based study in the USA suggested that 33% of diabetic people aged 40 years and older have retinopathy, and 8% have vision-threatening retinopathy. Diabetic retinopathy has an early, non-proliferative stage and a more advanced proliferative stage. Raised blood pressure is an independent risk factor for both the initial development of retinopathy and its subsequent progression. Impaired retinal–vascular autoregulation in response to high blood pressure plays a part in this association, since diabetic patients with hypertension seem to be less able to regulate retinal blood flow than non-diabetic patients. In diabetes, hypertension can also result in endothelial damage in the retinal vasculature and increased expression of vascular–endothelial growth factors.

Epidemiological studies in individuals with diabetes provided initial evidence that hypertension might be important in development and progression of retinopathy. However, a relation between high blood pressure and retinopathy was seen in some, but not all studies. In a population-based study, high blood pressure was associated with an increased 14-year rate of diabetic retinopathy in participants with type 1 diabetes, independent of baseline retinopathy status, glycosylated haemoglobin, duration of diabetes, and other risk factors. However, in participants with type 2 diabetes, neither systolic nor diastolic blood pressure was related to the incidence and progression of retinopathy. Other studies recorded associations between the severity of diabetic retinopathy severity and systolic (but not diastolic) blood pressure, and showed that such associations tended to weaken with increased age. The variability of these results could indicate differences in study design, effects of selection bias in clinic-based studies, selective mortality in older patients with type 2 diabetes, or measurement errors in the assessment and definition of hypertension.

Clinical trial data subsequently provided clear and consistent evidence of the role of hypertension in the development and progression of diabetic retinopathy. In a prospective study in the UK, 1048 patients with hypertension were randomly assigned to a regimen of tight control (aiming for blood-pressure levels below 150/85 mm Hg with atenolol or captopril) or less tight control (blood pressure below 180/105 mm Hg). Investigators noted that participants under tight blood-pressure control, had reductions of 37% in risk of microvascular disease, 34% in rate of progression of retinopathy, and 47% in deterioration of visual acuity. Atenolol and captopril proved equally effective for decreasing the risk of microvascular complications, which suggests that reduction of blood pressure per se was more important than the type of medication used. Importantly, the effects of blood pressure control were independent of glycaemia. After 6 years of follow-up, participants in
this study with baseline blood pressure in the highest third of the population (systolic blood pressures >140 mm Hg) were three times as likely to develop retinopathy as those in the lowest third (systolic blood pressures <125 mm Hg). No threshold systolic blood pressure was identified for this association, but the data suggested that for each 10 mm Hg reduction in systolic blood pressure, the risk of retinopathy might fall by 10%. Longer term follow-up of patients in this study have lent support to the early results.

In general, data from epidemiological studies and clinical trials lend support to clinical recommendations that control of hypertension and blood pressure in patients with type 2 diabetes should help to prevent retinopathy and other microvascular complications. A randomised controlled clinical trial showed that intensive blood pressure control was more beneficial than conventional control for normotensive patients with type 2 diabetes but not for hypertensive patients. Another study showed that in patients with type 2 diabetes and microalbuminuria, an intensive, multifactorial approach that targeted hyperglycaemia, hypertension, and dyslipidaemia, reduced the risk of retinopathy by 60%, compared with conventional treatment alone.

Reduction of blood pressure, even in the normotensive range, could potentially lessen the risk of diabetic retinopathy. The results of one study showed that in patients with type 1 diabetes who were normotensive, and who had no evidence of microalbuminuria, treatment with an ACE inhibitor, reduced the progression of retinopathy by 50% over a 2-year period, after adjustment for glycaemic control. Progression to proliferative retinopathy was also reduced by 80% in the group given ACE inhibitor compared with controls. However, these results have been criticised because the placebo group had significantly higher levels of mean glycosylated haemoglobin than the treatment group, even though this difference was adjusted in statistical analyses. This study suggested that ACE inhibitors might have an additional beneficial effect in prevention of retinopathy—indeed, reduction of blood pressure. This additional benefit was postulated to be mediated via a more favourable retinal–haemodynamic profile, enhancement of nitric oxide production, reduction of endothelial dysfunction, blockage of vascular endothelial growth factors, and reduction of activity by matrix metalloproteinases.

Some have suggested that hypertension could increase the potential risk factor for age-related macular degeneration, on the basis of its purported effects on the choroidal circulation. An association between hypertension and risk of age-related macular degeneration has been noted in both cross-sectional and prospective data, but has not been shown consistently in all studies. One study, the Beaver Dam Eye Study, reported that raised systolic blood pressure at baseline was not related to prevalent age-related macular degeneration, but did increase the 10-year risk of the disorder. Another study, the Blue Mountains study in Australia, has shown that focal arteriolar narrowing, a marker of hypertensive retinopathy damage, was associated with the incidence of some signs of age-related macular degeneration. Many of the risk factors for cardiovascular disease (such as cigarette smoking, carotid artery disease, and systemic markers of inflammation) also predispose patients to this disorder. Furthermore, the disorder has been linked with a high risk of stroke and cardiovascular mortality.

A wide range of treatment options for age-related macular degeneration, including vascular endothelial growth-factor inhibitors, have been developed in the past decade. However, specific antihypertensive medication or treatments to lower blood pressure have not proven beneficial for prevention of the development or progression of disorder. Observational studies suggest that antihypertensive medications do not affect the risk of this disorder.

Glaucoma
Glaucoma is a group of disorders characterised by progressive damage to the optic nerve and loss of visual field. This disorder is the second leading cause of irreversible blindness worldwide, and affects more than 50 million people. The main risk factor for glaucoma is high intraocular pressure. Systemic hypertension is suspected to increase the risk of the development and progression of glaucoma. Several pathophysiological mechanisms have been proposed to explain this putative association. First, direct microvascular damage from systemic hypertension could impair blood flow to the anterior optic nerve. This notion is supported by studies linking glaucoma to abnormal ocular blood flow and narrowing of the retinal vasculature. Second, hypertension could interfere with autoregulation of the posterior ciliary circulation, which is already impaired in glaucoma. Third, antihypertensive treatment could induce hypotensive episodes, especially at night, which could reduce blood flow to the optic-nerve head, resulting in additional damage to the optic nerve. Fourth, other cardiovascular risk factors linked with hypertension (eg, diabetes and cardiovascular disease) could affect vascular perfusion of the optic-nerve head. Finally, systemic blood pressure is closely related to intraocular pressure, the main risk factor for glaucomatous optic-nerve damage.
Epidemiological studies have not, however, shown a consistent association between hypertension and glaucoma. Three population-based studies reported a cross-sectional association. In one, people with hypertension were 50% more likely to have glaucoma, after adjustment for glaucoma risk factors such as intraocular pressure, than those without. Hypertension also accounted for the greatest population-attributable risk for glaucoma compared with other risk factors, suggesting that from a public-health perspective, hypertension might be more important than less common risk factors carrying a two-fold to three-fold higher risk of glaucoma. Nonetheless, prospective studies have not proven an association between either systolic or diastolic blood pressure and incidence of glaucoma.

Part of the difficulty in understanding the link between blood pressure and glaucoma is the distinction between the independent effects of blood pressure with intraocular pressure, and the difference between the two (perfusion pressure). One study noted that low perfusion pressure (low systemic blood pressure combined with high intraocular pressure) was a stronger risk factor for glaucoma than was systemic hypertension per se. Further, hypertension was a risk factor for glaucoma in older participants, but not in those who were younger. This finding could indicate that the damaging effects of hypertension vary with age—ie, in younger people, raised blood pressure could protect against glaucoma, since in this age group, retinal vessels have not yet undergone chronic microvascular damage.

In terms of clinical management, physicians should be aware of the association between blood pressure and intraocular pressure. Whether treatment with antihypertensive medications can prevent progression of glaucoma is unclear. Improved blood pressure control in individuals susceptible to intraocular pressure could possibly help to stabilise glaucoma.

Future directions and conclusions
Hypertension affects a large proportion of the adult population worldwide, and has widespread effects on the eye. We argue that any patient with hypertension should have an ophthalmological assessment to detect hypertensive retinopathy or other retinal vascular complications. Individuals with moderate hypertensive retinopathy (eg, flame-shaped or blot-shaped haemorrhages, cotton wool spots, hard exudates, microaneurysms, or a combination of these) are at increased risk of cardiovascular disease, independently of standard risk factors. Nonetheless, several questions remain. First, no standardised hypertensive retinopathy classification system has been accepted for use in primary-care settings, has good reproducibility, and can show validity in predicting cardiovascular events. Furthermore, although studies have suggested that retinal photography might be more precise than clinical ophthalmoscopy for the detection of signs of mild retinopathy, no study has compared different methods of retinal assessment. In the absence of new data, physicians are encouraged to continue the practice of fundoscopy for hypertensive patients when indicated, and referral for an ophthalmological consultation when findings are equivocal. No evidence exists to back up a recommendation that all hypertensive patients should be routinely referred for an eye consultation. Second, in view of the substantial racial and ethnic variation in the prevalence and effect of hypertension, we need to understand the ocular effects of blood pressure in different racial and ethnic groups. Finally, we will need to find out if intensive blood-pressure control in patients with hypertensive eye diseases could reduce the risk of visual and systemic morbidity. Blood pressure control has been established as a treatment for diabetic retinopathy, but requires evaluation for other eye disorders linked with hypertension. Recognition of the ocular effects of hypertension could assist physicians in the overall management of hypertension and damage to target end-organs.

Contributors
T Y Wong did the literature review, and drafted the manuscript. P Mitchell made critical revisions to the manuscript, and provided additional figures. 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.

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

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References


Review


A bumpy ride to a discarded diagnosis

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In December, 2002, a 28-year-old woman presented at our outpatient clinic with colicky abdominal pain from right loin to groin accompanied by vomiting. She had had recurrent attacks of such pain and vomiting during the previous 10 years. Attacks lasted 2–3 h, and often started after an active day in the office, which included a lot of walking. Lying down provided some relief. She always felt discomfort (described as “bruising”) in the right loin when driving over speed-bumps. Attack frequency had increased in the previous 4 years, and many attacks occurred after activities involving walking. Her medical history revealed repeated admissions and visits to emergency and outpatient urology and internal medical departments in several hospitals since 1995. Renal stones were suspected, but extensive examination including several intravenous pyelograms (IVP), ultrasonography, and CT showed no stones. One IVP showed a twist in the right ureter; placement of a double-J catheter led to rapid pain relief but pain recurred after catheter removal. Diagnosis remained unclear over the years, and she was referred to psychiatrists and used many painkillers including morphine. She then started staying in bed as much as possible and eventually lost her job. Her marriage broke up, and she started receiving full disability benefits when she was just 30 years old. She was then referred to us.

On examination, the right side of her right abdomen was tender on palpation. The symptoms of renal colic, without signs of stones, occurring after long walks, with relief on lying down, together with the bruised feeling in the right loin when driving over speed-bumps, led us to a preliminary diagnosis of nephroptosis (floating kidney). In support of this diagnosis, our patient also mentioned that as a young girl she frequently had some discomfort in her right loin. In June, 2003, an IVP with standing excretory-urography at the end showed a descent and ventral rotation of the right kidney by two vertebral bodies (figure). A diuretic renogram showed a decrease in function of the right kidney (from 49% to 36%) on orthostasis. These findings supported a diagnosis of nephroptosis. However, a team of urologists who assessed her thereafter were not convinced that nephroptosis was the cause of her complaints. The patient arranged many second opinions and eventually, 29 months after the diagnosis, in 2005, a urologist in a peripheral hospital carried out nephropexy (fixation of the kidney) and the patient recovered completely. During the operation the right kidney could be easily moved from the upper abdomen to the pelvis. When last seen, in November, 2006, she was completely pain free, had just given birth to her first child, and was employed full-time. Ultrasoundography at this point showed no descent of the right kidney on orthostasis.

Nephroptosis is anatomically defined as renal descent of 5 cm or two vertebral bodies on orthostasis. Classic symptoms are episodes of acute abdominal pain and vomiting when upright with some relief on lying down (Dietl’s crisis). Pain can be caused by intermittent functional excretory obstruction, or forceful traction on the renal artery or perirenal nerves. Diagnosis is confirmed by IVP and/or renography demonstrating descent and decrease in renal blood flow, respectively, on orthostasis. However, nephroptosis is a common finding in slim young women and rarely causes symptoms. During the 20th century a wide range of symptoms were attributed to nephroptosis and nephropexy was done on unfounded grounds. As a result nephroptosis came to be known as a discarded diagnosis, and nephropexy as an ineffective treatment for an imaginary disease. Therefore, younger generations of doctors have little experience of this condition. Our patient, and several others, show that, after application of appropriate diagnostic criteria, nephroptosis should be considered as a real, not an imaginary, diagnosis.

References