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A world fit for children?

A UNICEF report published on Dec 10 gives the most comprehensive data to date on progress towards the Millennium Development Goals (MDGs). Although there has been much international attention focused on MDG-4—to reduce under-5 mortality by two-thirds between 1990 and 2015—the report also details child-focused statistical information on all of the eight MDGs, in addition to data on World Fit for Children targets. These targets cover important factors in child health and wellbeing which are not included in the MDGs, such as child labour, violence, and discrimination.

The report combines all appropriate and latest available information and relies on data from UNICEF global databases, Multiple Indicator Cluster Surveys, and Demographic and Health Surveys, which vary in the time period in which information is collected and collated. Therefore, although some statistics in the report are new, other figures are more familiar.

Although the number of children who die before their fifth birthday has fallen below 10 million, many countries, particularly in sub-Saharan Africa and south Asia, have made little progress. There is no information available on mortality rates from some countries, which is unsurprising given that a staggering 51 million children born in 2006 have not had their births registered. As highlighted in our recent Who Counts? Series, such data gaps are serious and hamper international efforts to devise sensible strategies to protect children.

Pneumonia remains the most common cause of death in children under 5 years, taking the lives of more children than AIDS, malaria, and measles combined. Yet according to 2006 data, the percentage of children under 5 years with suspected pneumonia who receive antibiotics is dismally low—in Haiti this proportion is only 3%. And, in sub-Saharan Africa, only 40% of children with suspected pneumonia are taken to an appropriate health provider. Lack of access to appropriate treatment is a recurring theme throughout the UNICEF report. In 2006, 380 000 children died of largely preventable AIDS-related causes and only 15% of children received antiretroviral therapy.

The non-MDG information is more difficult to quantify. For example, the number of children displaced because of conflict—around 8 million—is only an estimate. For discrimination due to disability, the results of a survey in 17 countries, presented for the first time in the report, are limited to only quantifying the number of 2–9 year-old children with at least one disability.

There are three important key messages from the UNICEF report. First, there have been advances in certain indicators in child health—vitamin A provision, insecticide-treated bednet coverage, and exclusive breastfeeding. Second, indicators depending on a functional health system—for example, the treatment of malaria—have largely stalled. Finally, countries mired in violent conflict or afflicted by HIV are finding it especially hard to respond to children’s needs.

One frustration with this welcome wealth of statistical information is that there is little attempt to put any of the data into context with recent global initiatives for child health, such as the Global Business Plan—an initiative led by the Prime Minister of Norway to intensify efforts to accelerate progress towards MDG-4.

Statistics can be a useful tool for advocacy. But information can only be truly effective when used as a springboard for further action. For instance, the international community has known for years about the appalling figures on access to essential medicines for children. Every year the deaths of about 6 million children could be prevented if only they had access to available, safe, effective, and affordable medicines. Yet, although most welcome, it was only last week that WHO officially launched an initiative—Make Medicines Child Size—which aims to target a range of medicines that still require paediatric formulations. The initiative also includes the first international list of 206 essential medicines for children. This initiative deserves to be widely supported since it promises to be one of the most effective international levers to improve child health.

Mahatma Gandhi famously said, “the greatness of a nation and its moral progress can be judged by the way its animals are treated”. Surely the way in which nations treat children is a better indicator of status and decency? The UNICEF report is a stark reminder that a world fit for children is still a distant aspiration. Although there have been some advances made so far, the international community should not become complacent and must further increase its efforts to do more to improve the health of one of the world’s most vulnerable groups. ■ The Lancet

For Progress for Children: A world fit for children statistical review see http://www.unicef.org/publications/index_42117.html
For the Lancet Who Counts? Series see http://www.thelancet.com/online/focus/who-counts/collection
FDA off-track on off-label drug promotion

The US Food and Drug Administration (FDA) has been considering changes in its guidelines that would allow pharmaceutical and medical device manufacturers to supply physicians with journal articles on the unapproved uses of their products. A draft of the controversial new guidelines was released on Nov 30 by US Congressman Henry Waxman, a California Democrat. In a letter to FDA Commissioner Andrew C von Eschenbach, Waxman rightly denounced the proposed changes.

Under US law, once a drug is approved for one indication, physicians may prescribe it for other indications. Such “off-label” use is common; indeed, for some conditions use of off-label drugs is the recognised standard of care. However, in the past, manufacturers in the USA have been forbidden to promote off-label use of drugs and devices. A primary reason for the ban is the concern that once a company had obtained approval for one use, it would have little incentive to seek FDA approval for new indications, and, instead, would rely on off-label use to boost sales.

Under the proposed changes, company representatives would be able to distribute to physicians articles on the off-label use from peer-reviewed journals and textbooks. The information must not be false or misleading, and supplements and books sponsored by the manufacturer cannot be used. Additionally, when off-label use is controversial, the company must summarise opposing views and provide at least one article representing those views. Supporters of the proposed changes contend that information presented within the guidelines’ constraints will help physicians make more informed decisions.

Unfortunately, the industry’s record on supplying unbiased information to physicians about approved drugs is poor, and it is unlikely to do better when it comes to providing information about off-label use. Physicians wanting to know more about off-label use of drugs and devices would do far better to do their own literature search and to consult reviews by independent research groups (eg, the Cochrane Collaboration) that do not have the conflicts of interest that manufacturers do. Manufacturers should concentrate on proving that off-label uses of their products are indeed safe and effective by seeking official approval for such indications. ■

A step-change for UK biomedicine

UK Prime Minister Gordon Brown wants to make Britain the best place in the world for science. Last week, he made the first steps towards realising this vision by backing plans for a new £500 million biomedical research facility to be built in central London. The new centre, called the UK Centre for Medical Research and Innovation (UKCMRI), is a collaborative venture between the government-funded Medical Research Council, two of the UK’s largest research charities—the Wellcome Trust and Cancer Research UK—and University College London. The centre aims to boost partnerships and cross-disciplinary work between the organisations involved and nearby hospitals to improve human health. There will be a strong focus on translational research at the facility, where 1500 scientists and support staff are expected to work on health issues affecting developed and developing countries.

The opportunities for scientists at the centre, expected to open in 2013, should attract researchers from across the world and hopefully entice British talent back from abroad. Although the new centre is not on the same scale as some science parks (eg, Biopolis in Singapore), the quality of the research undertaken will at least be on a par—and probably superior.

The UK is already a world leader in many areas of biomedical research. The increasing scale and complexity of science, together with the interdisciplinary and international nature of the most successful science collaborations, mean that UKCMRI will have to offer a different way of doing research. For example, large genome-wide association studies are finding links between single nucleotide polymorphisms and common human diseases. Discovering how these genetic variants actually work and translating this basic research into the clinic will require a huge scientific effort.

Although the exact scientific strategy for the centre is yet to be decided, the potential of UKCMRI to bolster UK science, the economy, and most importantly, improve health globally, is substantial. The plans for this new endeavour will be welcomed by the public and the scientific community alike. ■

For the draft guidance document see http://oversight.house.gov/documents/20071130103225.pdf
Artificial kidneys: progress and promise

Two technical breakthroughs in the past century changed kidney failure from a fatal to a treatable disease: artificial kidneys (in the 1940s) and vascular access that allowed for repeated dialysis (the 1960s). What began then as exploratory efforts to sustain life and relieve uraemic symptoms in selected patients now provides life-saving renal-replacement therapy to millions worldwide. After the introduction of maintenance haemodialysis, physicians quickly became aware that the consequences of uraemia respond slowly and progress while patients are on haemodialysis, and that more dialysis was necessary to sustain life. In the 1970s, the initial response was to increase the size of the dialysis machine, the rate of flow of blood and dialysate, and the duration or frequency of dialysis, all of which yielded positive results.1

Two treatment-related factors then became the focus of attention: the dose of dialysis and the size of molecules removed by the dialysis membranes. Kinetic studies for urea led to the introduction of a surrogate measure of the dialysis dose calculated from the clearance of urea over the duration of dialysis expressed as a fraction of the urea distribution volume in the patient (Kt/V). Improvements in membrane biocompatibility and porosity allowed for the clearance of larger solutes. And, as the safety of treatment and the ability to deliver dialysis in a quantifiable manner improved, the therapy became more efficient and duration decreased to 3·5–4·0 h three times weekly, which emerged as the standard of care.1,2

Unfortunately, the morbidity and mortality of patients on maintenance haemodialysis remained unacceptably high and the incidence of kidney failure continued to rise, due in large part to the increased prevalence of the main causes—hypertension and diabetes—in an ageing population. As a result, the regimen of three-times weekly, high-efficiency haemodialysis was questioned. The idea that more is better reappeared after reports that high-intensity dialysis—achieved by increasing the frequency of dialysis treatments to six times a week or the duration of dialysis to 6 h or longer—brought about improvements.3 Although the total dose of dialysis is greater in high-intensity dialysis than in high-efficiency dialysis, additional benefits arise from the increased clearance of large solutes and avoidance of major and sudden shifts in blood chemistries and extracellular fluid volume in high-efficiency dialysis. Most studies that show benefits of high-intensity dialysis used laboratory tests with surrogate markers of outcome in a small number of patients selected for motivation and favourable clinical characteristics; there are only a few retrospective and observational studies.4 The most compelling evidence is a recent report of a small and short randomised trial that showed reversal of left-ventricular mass with frequent nocturnal haemodialysis.5 A randomised trial, sponsored by the National Institutes of Health, is underway in the USA and should provide better evidence on the potential benefits of high-intensity haemodialysis.6

The technical achievements that made high-intensity dialysis possible are limited by dependence on a stationary artificial kidney, be it at home or at a centre, which immobilises the patient for the duration of therapy. From the outset, investigators have wanted to develop a portable dialysis machine. In fact, Wilhelm Kolff, who developed the first artificial kidney, experimented with a wearable machine and reported its successful use in the 1970s.7 In today’s Lancet, Andrew Davenport and colleagues report a pilot study that shows successful single use of a wearable artificial kidney for 4–8 h in eight patients who had been stable on maintenance haemodialysis for several years.8 This report is a major step forward in miniaturisation of the dialysis device and liberation of the patient from dependence on a fixed site for treatment. Three of the
patients had serious adverse effects involving coagulation and vascular access, the very problems that haunted initial attempts at dialysis in the 1920s and 1940s. These and other potential problems that might arise from the repeated use of the new device will have to be resolved in further studies as the investigators move forward from this proof-of-concept phase.

What has made the wearable artificial kidney possible is sophistication in dialysis research, well beyond that of its early empirical approach. Nanotechnology and molecularly engineered membranes with selective permeability characteristics have given hope of a continuously functioning and implantable nephron system. By the same token, genetic engineering has allowed the development and use of membranes implanted with renal tubular cells that mimic kidney functions other than mere filtration. The wearable artificial kidney reported today is a small first step in the long road to wearable blood-cleansing devices. Lessons learned from further study should pave the way for realising the future promise of dialysis with artificial kidneys.

Garabed Eknoyan

Cardiac toxicity of sunitinib

Sunitinib malate is a novel tyrosine-kinase inhibitor that is effective for the treatment of some cancers for which few active systemic therapies are available. Sunitinib inhibits many kinase receptors, including vascular endothelial growth factor (VEGFR) receptors, stem-cell-factor receptor (KIT), platelet-derived growth-factor receptors, colony-stimulating-factor 1 receptor, FLT3, and RET. In a randomised study, patients with previously untreated metastatic renal-cell carcinoma had longer median progression-free survival on sunitinib (11 months) than did those on interferon alfa (5 months), and sunitinib was also associated with a higher objective response rate (31% vs 6%). Similarly, in patients with advanced gastrointestinal stromal tumour who had failed previous treatment with imatinib, the median time to progression in patients receiving sunitinib was 27 weeks but only 6 weeks in those on placebo. Sunitinib has been approved for treatment of advanced renal-cell cancer and advanced gastrointestinal stromal tumour after resistance or intolerance to imatinib.

Sunitinib is often associated with adverse effects, such as fatigue, diarrhoea, nausea, hand-foot syndrome, mucositis, rash and skin discolouration, and laboratory-test abnormalities. Although thyroid-function abnormalities commonly arise during sunitinib treatment, hypothyroidism was detected only rarely in large studies. Yet, in one series, abnormal serum concentrations of thyroid-stimulating hormone were recorded in 62% of patients treated with sunitinib for imatinib-resistant gastrointestinal stromal tumour, and 36% developed persistent primary hypothyroidism with a mean time to hypothyroidism of 50 weeks. In another series in which patients received sunitinib for metastatic renal-cell carcinoma, 85% had one or more abnormality in their thyroid-function tests that was consistent with hypothyroidism. Hypothyroidism might partly explain sunitinib-associated fatigue, but is probably not the only cause.

In today’s Lancet, Tammy Chu and colleagues have studied another previously under-reported
sunitinib-related adverse effect, cardiac toxicity. In their retrospective study, two of 75 participants with imatinib-resistant gastrointestinal stromal tumour had a cardiac infarction and six (8%) developed congestive heart failure. For patients treated at the dose approved by the US Food and Drug Administration, left-ventricular ejection fraction declined progressively during sunitinib treatment from a baseline of 64·5% to 59·4% after the fourth cycle, and 19% of patients had a reduction in ejection fraction of 15 percentage points or more during treatment. A large proportion (47%) of patients developed hypertension (>150/100 mm Hg). 12 (18% ) of 68 patients with data had modest increases in serum troponin concentration above the normal reference range. In a mouse model, Chu and colleagues found that sunitinib exposure caused mitochondrial damage and apoptosis in cardiomyocytes.

Is sunitinib indeed notably cardiotoxic, and do the latest findings have clinical relevance? Sunitinib has been assessed in clinical trials and in a large expanded-access programme.1,6 Although some signs of cardiotoxicity were seen,17 cardiotoxicity has not been a major concern in published reports. Yet, I believe Chu and colleagues are probably correct, and can be congratulated for vigilance and for careful documentation of their cases.

Recent findings by Schmidinger and colleagues4 thus far published only as an abstract, also suggest that sunitinib has clinically relevant cardiotoxicity. In that study, 73 consecutive patients with normal serum creatine kinase and cardiac troponin-T concentrations at baseline were treated with sunitinib or sorafenib. Creatine kinase (myocardial-band isoenzyme) rose in 23% of patients, accompanied by clinical symptoms in 10%. Six of 17 evaluated patients had abnormal echocardiographical findings, such as reduced left-ventricular function. These results seem to accord with those now reported by Chu and colleagues. Of note, cardiac adverse effects associated with sorafenib seem similar to those related to sunitinib (Schmidinger M, University of Vienna, Vienna, Austria; personal communication).

Patients treated with sunitinib need careful monitoring not only for hand-foot syndrome and other well-established adverse effects, but also for thyroid and cardiac function. Although data are limited and more research is needed, sunitinib might be at least as cardiotoxic as trastuzumab.9 Longitudinal monitoring of left-ventricular ejection fraction is standard practice in breast cancer patients treated with trastuzumab. Such monitoring and an electrocardiogram10 also seem indicated in patients treated with sunitinib. Patients with coronary artery disease, severe heart disease, or previous treatment with anthracycline may be at particularly high risk of cardiac failure and possibly cardiac infarction during sunitinib therapy, and will need close follow-up. Sunitinib-related hypertension should be treated promptly. The putative molecular mechanisms of sunitinib-associated cardiac failure warrant further study (table).11 Prospective studies that evaluate cardiac effects of other multiple kinase inhibitors are needed.

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I have received honoraria for speaking and for advisory board meetings from Novartis and Bayer Schering Pharma, and have received payment for one testimony from Pfizer.

Adjuvant chemotherapy of colorectal cancer

Adjuvant chemotherapy with fluorouracil and levamisole for 1 year after the surgical resection of node-positive (stage III) colon cancer was established in 1990.1 Subsequent trials supported the benefit of adjuvant fluorouracil but not levamisole. The biochemical modulation of fluorouracil by folinic acid enhanced cytotoxicity, and 6 months’ treatment was as effective as 12 months.2 The risk of death for stage III tumours was reduced by 30%, translating to a 10–13% absolute improvement in survival.3,4 Irinotecan and oxaliplatin improved outcome in advanced disease and were therefore evaluated in the adjuvant setting. Only oxaliplatin with fluorouracil and folinic acid improved disease-free survival (by an additional 7%),3,4 and this regimen became a widely accepted standard for patients deemed fit enough to receive two cytotoxic drugs after surgery. The oral fluoropyrimidines capecitabine and tegafur also have similar efficacy to fluorouracil.5,6

However, for node-negative (stage II) carcinoma of the colon, debate remained about adjuvant chemotherapy. Trials that included such tumours had insufficient events within this subgroup to reach conventional statistical significance, although the hazard ratios suggested a similar reduction in the risk of death as with stage III tumours. A pragmatic policy evolved, in which the 25% of patients with stage II tumours considered at accentuated risk of recurrence because of penetration of the serosa (T4), extramural venous invasion, poorly differentiated histology, presentation with obstruction, or a yield of less than 10–12 lymph nodes were offered adjuvant treatment.

Adjuvant treatment of rectal cancer had taken a divergent course because, by contrast with colon cancer, local recurrence in the pelvis is a dominant feature. This risk can be reduced by radiation given after or preferably before surgery. However, removal of the mesorectum in its entirety, with the primary tumour, reduces local recurrence and obviates the need for radiotherapy in early tumours (which do not reach the surgical margin);7 such tumours are best identified by preoperative MRI of the pelvis.8 This approach is a valid alternative to offering all patients radiotherapy, so there is an increasing number of patients with rectal cancer who have had surgery without radiotherapy and are candidates for adjuvant chemotherapy.

In today’s Lancet, the QUASAR Collaborative Group report the results of one of the largest adjuvant trials, to date, of chemotherapy versus surgery alone in colorectal cancer (mostly stage II).9 The investigators confirm that chemotherapy produces a small (3–6%) increase in survival at 5 years. This benefit might have been underestimated in view of the large proportion of patients who received the weekly fluorouracil schedule, which may not be as effective as the 4-weekly schedule. A pragmatic study design was used to facilitate high recruitment of a heterogeneous group of patients with curatively resected colorectal cancer in whom the use of adjuvant chemotherapy was uncertain, thereby ensuring representation of patients with stage II disease (less than 10% of patients had stage III disease), rectal cancer, and those aged over 70 years. In subgroup analysis, patients with rectal cancer benefited as much as those with colon cancer. However, patients aged over 70 years did not benefit, which might reflect insufficient statistical power to detect small survival gains in this subgroup. In pooled

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analyses of fluorouracil-based and combination therapy, there was a survival benefit in patients aged over 70 years. This population is often under-represented in trials but carries a substantial proportion of the disease burden.

In QUASAR, the survival benefit in stage II disease was less than that for recurrence-free survival. Disease-free survival at 3 years is an accepted surrogate for 5-year overall survival, although the association is greater in stage III than in stage II disease. Factors such as death from non-cancer-related events, fewer events, a smaller absolute benefit, heterogeneity of disease, and later recurrence confound the association of 3-year disease-free survival and overall survival in stage II disease. Additionally, current potentially curative interventions for recurrent disease, including aggressive metastasectomy with more effective systemic therapies, might weaken the correlation between disease-free and overall survival. Nevertheless, in stage III disease, validation of 1-year and 2-year disease-free survival as surrogates for overall survival might be possible, which would facilitate earlier reporting of adjuvant studies.

For example, a lack of difference in 1-year disease-free survival predicts the same result for overall survival at 5 years, an observation which could prove to be a useful futility indicator in future studies. However, we should be cautious when extrapolating these statistical assumptions to current trials of biological agents, such as cetuximab and bevacizumab, because these agents could delay rather than prevent recurrences.

Current options for management of stage II disease are no treatment, fluoropyrimidine alone, or oxaliplatin/fluorouracil for high-risk stage II disease. However, the decision to treat stage II colorectal cancer should be taken with the patient after consideration of the size of the benefit versus potential toxic effects. Although online tools assist the physician in assessing risk/benefit, they do not take account of all the risk factors for recurrence nor the nuances of comorbidity best appreciated in the clinic. In elderly patients, cognitive status, polydrug use, and psychosocial factors are also important in decision making.

However, most patients with resected stage II colorectal cancer have a good prognosis and identification of patients most likely to benefit from therapy remains important. Histopathological variables, such as high-risk features in stage II disease, and recognition that stage II and III disease are heterogeneous entities are still directive when stratifying therapy. Additionally, the prognostic potential of several molecular markers has been evaluated. The continued development of genomic platforms might assist in identifying new prognostic/predictive molecular markers and signatures which, with ongoing randomised trials of novel adjuvant therapies and assessment of shorter duration of therapy, will help to refine the treatment of stage II and III colorectal cancer.

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DC has received research funding or honoraria, or sat on advisory boards for, Roche, Sanofi, and Merck. NS has received honoraria from Sanofi and Merck.

Prevention of hepatitis C in Japan: a lesson for us all

In today’s *Lancet*, Hideo Yasunaga reports the devastating effect that the use of fibrinogen products had in the transmission of hepatitis C virus in Japan. Most disturbing is that this transmission could have been prevented with knowledge of the available evidence. The review presents the systematic failings that took place at all levels of the health-care system when fibrinogen was routinely used to prevent bleeding in patients with disseminated intravascular coagulation from 1964 until at least 1989.

The results of acquisition of hepatitis C are dire; at present 2–4% of the world population is infected. 85% of those infected will develop life-long disease which is characterised by persistent liver dysfunction and possible liver failure. Hepatitis B and C viral infections account for almost all cirrhosis and primary liver cancer throughout most of the world.

So what went wrong? Having approved unheated fibrinogen concentrate in 1947, the US Food and Drug Administration revoked its licence in 1977 because of hepatitis cases from transmission of fibrinogen. However, obstetricians in Japan still recommended its use well beyond this date, and the Japanese Ministry of Health and Welfare continued to endorse fibrinogen after the revoking of its licence. At its peak, 76 500 products were administered yearly in Japan, which was a third of the worldwide use of plasma-derived products. Diagnostic criteria for fibrinogen use were arbitrary, leading to inconsistency and overuse. Furthermore, purchase of the products at less than the official reference price led to increased profits for medical institutions.

The transmission of hepatitis C virus through contaminated blood products is not a problem restricted only to Japan; it is a worldwide issue. The commonest cause of transmission before 1992 was through blood transfusions. The use of pooled blood (blood from groups of people was used to manufacture single products) meant that one contaminated unit would have been enough to infect thousands of patients. Patients with haemophilia in Canada were infected with hepatitis C virus from contaminated blood from prisoners in the 1980s. Thousands of people in Europe contracted HIV and hepatitis through delivery of infected products. For instance, many patients with haemophilia in Scotland were infected with hepatitis C after contaminated blood from US prisoners was imported into the UK. Studies since the 1960s had shown that blood donors with raised concentrations of alanine aminotransferase were three to five times more likely to transmit hepatitis than were those with normal concentrations. Screening for alanine aminotransferase could have prevented up to 40% of cases of hepatitis C virus after transfusion; the net loss in units of donated blood would have been about 3%. Transmission from blood products and organ transplants was virtually eliminated by the introduction of a more sensitive test for antibody to hepatitis C virus in mid-1992. Individuals at risk before 1992—who received a blood transfusion or transplant—should be tested for hepatitis C infection.

Policymakers should recognise the difficulties individuals encounter in their claims for compensation. In Japan, the Osaka court has ruled that the makers of fibrinogen and the state were responsible for the transmission of the virus and awarded damages to nine people. All except one were women who were given the product when they gave birth. The presiding judge ruled that the manufacturer (Mitsubishi Pharma Corporation, Osaka, Japan, formally known as Green Cross Corp) was responsible for nine infected cases after August, 1985, but before this date—because of little knowledge about the risk of transmission—the manufacturer and state were not deemed responsible. Plaintiffs have been plagued by discrimination and prejudice; most are waging lawsuits without revealing their real names. There are also many others who cannot claim compensation even if they wanted to, because their medical records have been lost and their link to infected blood products cannot be proved.

The cause of harm is a recurring theme in medicine—there have been serious incidents involving anti-arrhythmic drugs, thalidomide, and cyclo-oxygenase 2 inhibitors. Too much medical decision making is done on the basis of poor-quality evidence: neither basic theory nor professional opinion by itself is a reliable guide for safe and effective treatment. For a long time, clinicians in Japan perceived that the benefits of fibrinogen would outweigh the actual outcomes that were not seen until much later. Perversely, there are no benefits to fibrinogen in obstetric practice. Previously, the dissemination of information remained patchy; now drug regulation has tightened up substantially and dissemination of information has improved. Can this problem arise again? Unquestionably
the answer is yes; only after licensing in the USA and after marketing surveillance was troglitazone found to cause liver failure and withdrawn.14

Why do we still use ineffective treatments? One reason is that our expectations for the benefits of treatment are too high.15 We have to recognise that treatments can sometimes do more harm than good, occasionally on a devastating scale.15 The duty of doctors is to do good for patients; however, that sometimes means doing nothing—watching and careful observation should not be replaced by blind optimism. It is in everyone’s interest that the findings of this review, and others, are in the public domain.

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We declare that we have no conflict of interest.

html (accessed May 11, 2007).
html#13 (accessed May 18, 2007).

Global health and Japan’s foreign policy

In 2008, Japan will host two major conferences, the Fourth Tokyo International Conference on African Development (TICAD IV) and the G8 Hokkaido Toyako Summit. At this important diplomatic juncture, Japan will take up and call for a stronger engagement of the international community in global health.

In 2000, during the G8 Kyushu Okinawa Summit, Japan launched the Okinawa Infectious Diseases Initiative1 and appealed for international collaboration. This led to the establishment of the Global Fund to Fight AIDS, Tuberculosis and Malaria. The UN Millennium Summit, in 2000, laid the foundation for the Millennium Development Goals (MDGs), including health goals to be achieved by 2015. Also in 2000, a historical statement announced the eradication of poliomyelitis in WHO’s Western Pacific region.2

Since then, international awareness about the need to tackle infectious diseases has increased. The Global Fund now saves 3000 lives each day; it has saved 1.5 million so far. And yet, 6 million people still die every year from AIDS, tuberculosis, or malaria. We still face serious challenges in maternal, newborn, and child health. In sub-Saharan Africa, 166 in 1000 children die before their fifth birthday, which is 20 times higher than the number in developed countries. The risk of death related to pregnancy and childbirth is one in 16, which is 200 times higher for women in sub-Saharan Africa than for those in developed countries. At this rate, we are likely to miss the health-related MDGs.

One vital aspect of health is water and sanitation. In a developed country such as Japan, nearly everyone has access to safe drinking water. In sub-Saharan Africa, the proportion is only 56%. For adequate sanitation facilities, including toilets, nearly all the developed world has access, compared with only 37% in sub-Saharan Africa.

Next year we reach the midpoint for the achievement of the MDGs by 2015. At TICAD IV, Japan intends to take up the issue of health in Africa, and at the G8 Summit,
the wider issue of global health. The objective will be to develop a common framework for action shared by the international community. Where should the international community go from here? Human security is a concept that is very relevant to cooperation in the 21st century. That is to say, it is vitally important that we not only focus on the health of individuals and protect them, but also strive to empower individuals and communities through health-system strengthening.

To date, international efforts in the health sector have largely centred on measures against infectious diseases. From now on, it is essential to promote a comprehensive approach to strike at the root of the problem, especially through the promotion of research and development and strengthening of health systems, including human-resource development and retention. Disturbingly, sub-Saharan Africa contains 11% of the world’s population and 25% of the disease-related burden, but the region has only 3% of the world’s health workers. The importance of human-resource development and retention on a considerable scale is self-evident. The disease-specific and comprehensive approaches complement each other. Striking a good balance between them will be at the core of the international framework that we aim to develop at Toyako.

The effectiveness of integrating two intersecting approaches has been empirically proven by Japan’s experiences. Postwar Japan focused on the promotion of maternal and child health and tackled infectious diseases, such as tuberculosis. A holistic approach included the spread of vaccinations and regular health check-ups at health centres and schools, provision of nutritional education, and school lunches, which together led to overall improvements in the population’s health.

Japan has shared its experience with developing countries by, for example, dissemination of the Maternal and Child Health Handbook in Indonesia. It began when one Indonesian doctor came across this handbook during training organised by the Japan International Cooperation Agency. This empowerment tool for mothers has reached several other countries in Asia and the rest of the world, for example, in Palestine.

The development and retention of human resources is important for the running of health systems. Basic education and gender equality are essential, because they underpin health systems. The development of road networks is also relevant. We may have to transport patients, doctors, nurses, and medical supplies quickly. We also need means of communication that are readily available.

The proposed framework for action cannot be promoted by the Japanese government alone. Diverse stakeholders will have to collaborate. Developing countries, including those in Africa, must have ownership of the health agenda. The Hideyo Noguchi Africa Prize will be supporting various health efforts in Africa, and will be presented for the first time at the TICAD IV. Major developed countries, including the G8 and international organisations, need to show clear political will to support the efforts of developing countries as their partners. New emerging donor countries, NGOs, the business sector, and private foundations also have roles to play. No less important, any proposed framework for action cannot be formulated by health experts alone. We need experts from various fields to be involved in this process.

The TICAD IV and G8 Summit next year will be excellent opportunities for the international community to strengthen their collaboration and build a framework based on a participatory approach suited to the 21st century. Japan, as G8 chair and host to TICAD, will aim to achieve this.

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I declare that I have no conflict of interest.
Sebastiaan Mastenbroek and colleagues have reported that the use of preimplantation aneuploidy screening to select chromosomally normal embryos for in-vitro fertilisation (IVF) does not improve rates of pregnancy at 12 weeks. Their randomised trial in more than 400 women aged 35–41 years compared outcomes of up to three IVF cycles with or without screening. The pregnancy rate was significantly decreased in the aneuploidy screening arm (25% vs 37%; rate ratio 0·69, 95% CI 0·51–0·93).

A clear distinction should be made between pre-implantation aneuploidy screening and preimplantation genetic diagnosis, in which IVF is done in couples with a known genetic disease, solely to obtain embryos for diagnosis. In principle, only non-affected embryos are implanted. This method is preferred by some women over prenatal diagnosis during pregnancy, because it avoids the need for termination if an affected fetus is diagnosed.

Aneuploidy screening (counting abnormal chromosome numbers) was developed to improve embryo selection in infertile couples, by implanting only euploid embryos. Promising data that suggest higher pregnancy rates and reduced miscarriage rates after such screening have been reported over the past decade. This technique is currently advocated widely for patients with advanced maternal age (more than 37 years), for patients who present with repeated implantation failure (ie, unsuccessful previous IVF), in women who have had repeated miscarriages, and for the IVF technique of single-embryo transfer. Unfortunately, all previous studies were observational, uncontrolled, and often in selected populations of patients.

Two large randomised trials have shown no benefit of preimplantation aneuploidy screening for pregnancy and delivery rates. Several possible reasons for this lack of benefit are proposed: technical reasons include both damage to the remaining embryo during blastomere biopsy, reducing its developmental potential; and limitations of current fluorescence in-situ hybridisation technology (90% accuracy) that allows only a few chromosomes to be seen. The testing of all chromosomes would probably even increase observed aneuploidy rates. Mosaicism (ie, differences in the chromosomal constitution of some cells during early development of the embryo) is another possible reason for confusion. A single blastomere might thus be classified as abnormal, whereas the remaining (not examined by biopsy) blastomeres in the embryo are normal. The opposite can also occur, contributing greatly to false-positive or false-negative results.

Of course, if only one blastomere is examined, mosaicism cannot be detected. Test results could theoretically improve with the study of two blastomeres. The removal of two blastomeres has been argued as being detrimental for embryonic implantation potential. But two arguments against this idea are convincing. Reported rates of embryo implantation after the removal of one blastomere (17·6%) were similar to those after two were removed (17·1%). Moreover, in a randomised trial in women aged 37 years or younger, implantation rates of day-5 blastocysts were similar with or without preimplantation aneuploidy screening after the removal of one blastomere (47·4% vs 42·8%). A final reason for confusion is lack of knowledge about the natural course of mosaicism; mosaic preimplantation embryos might be self-correcting.

Theoretically, preimplantation aneuploidy screening seems a solid technique with the potential to improve embryo selection and clinical outcomes in IVF. Unfortunately, its clinical usefulness has not been confirmed by existing data from well-designed trials. However, more randomised studies are underway. The disappointing results of studies of aneuploidy screening suggest that at present science has to overcome the mysteries of embryo biology. Detailed fundamental research about the biology of a cleaving embryo is mandatory. The conclusion seems justified that, on the basis of current evidence, aneuploidy screening should be considered as a research tool and not be advocated for routine care of patients.
Managing risk: identifying environmental causes of disease

In most areas of science, non-experimental evidence does not command a great deal of public attention. In health, it frequently becomes a matter of urgent public concern. From the safety of vaccination to the risks of passive smoking, the validity of non-experimental research has often been a flashpoint of political as well as scientific debate. Yet observational research underpins a vast amount of clinical and public-health knowledge that is fundamental to daily medical practice and to policymaking. High-profile reversals of a few flawed or over-interpreted research studies should not be allowed to damage the overall credibility of non-experimental methods in medicine.

In 2006, and with these concerns in mind, the UK’s Academy of Medical Sciences launched an inquiry—with Prof Sir Michael Rutter in the chair—into the environmental causes of disease. The inquiry team’s mandate was to investigate five key points: the strengths, limitations, and potential of non-experimental methods for the identification of environmental causes of disease; the lessons from successful and less successful examples of non-experimental research; how non-experimental studies should deal with complex multifactorial causes; how experimental and non-experimental approaches should be coordinated to identify causal mechanisms of disease; and how non-experimental research is communicated. The final report by the Academy is published today. Its recommendations are shown in the panel.

The modern understanding of causal inference in medicine and public health was (and remains) best summarised by Bradford Hill. His nine principles have guided investigators for over 40 years. Yet the rapid developments in statistical methods—eg, statistical modelling, propensity scores, and sensitivity analyses—can sometimes obscure the need for careful, rigorous, and sometimes sceptical reasoning in drawing inferences about cause and effect. There are many good examples of how non-experimental research studies have produced reliable causal inferences—smoking and lung cancer; lipids and coronary artery disease; perinatal defects; and thalidomide and teratogenicity. But there have also been some notable errors and failures—over the measles, mumps, and rubella vaccine; hormone replacement therapy and coronary artery disease; the safety of calcium-channel blockers; caffeine in pregnancy; and vitamin supplements and mortality. The common lesson from the misleading claims that arose from these examples is that small pilot studies with no or inadequate controls, perhaps driven by individuals who are seeking to advance one particular and contentious point-of-view, should be viewed with great caution.

Even with high-quality non-experimental research, the question remains: what should one do with the findings? Despite the fact that observational research can never prove cause and effect with absolute certainty, action can sometimes be justified. The vital point that is so often forgotten is that all results of scientific research—experimental or non-experimental—are provisional. No single study should be relied on to change behaviour or policy alone. Any individual finding should be replicated across several contrasting populations before it can

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We declare that we have no conflict of interest.

7 Cohen J, Wells D, Munne S. Removal of two cells from cleavage stage embryos is likely to reduce the efficacy of chromosomal tests that are used to enhance implantation rates. Fertil Steril 2007; 81: 496–503.
be considered reliable. The safest course of action for the policymaker is always to be guided by the totality of available evidence. Sometimes the risk or hazard associated with not acting may be greater than the risk of acting. Before the results of randomised clinical trials became available, many experts argued that this was the case with male circumcision in the prevention of HIV transmission. It is certainly the case for child abuse.

One particular concern that the Academy’s working group drew attention to was the ambiguous attitude of government to research. There is evidence of a decline in the scientific expertise of the UK’s civil service. All senior government officials should have at least a basic understanding of scientific methods and peer review. Even when non-experimental research follows best scientific practice, mistakes can still be made at the final hurdle—the communication of those findings to colleagues and to the public. The main responsibility lies with researchers to report their results accurately, clearly, and fairly. Although in the past much attention has focused on the responsibilities of science and health journalists, editors of medical journals have been a relatively neglected group. Yet journals have a central part to play in securing and maintaining public trust in science. Editors of medical journals have dual and sometimes conflicting responsibilities: to ensure that the integrity of the research literature is preserved and strengthened, and to promote the dissemination of new ideas and discoveries that may challenge established beliefs. Editors manage risk: they must balance newness with trueness. They must be vigilant when considering potentially controversial findings based on non-experimental methods. A recent investigation by Science after the South Korean cloning fraud concluded that research papers should be risk-assessed by editors and that, in special cases, primary data should be made available to reviewers and readers to enable the verification of conclusions. Risk assessment aims to identify particular features of a piece of work that should trigger more intensive peer review. A high-risk paper might be one that would provoke a sharp scientific, clinical, public-health, or policy controversy if published.

The Academy’s report offers guidance for researchers (eg, whenever possible, build in replications across different samples), clinicians (eg, use continuing professional development to keep up with clinically relevant research advances), policymakers (eg, make sure scientific advisers give a balanced assessment of evidence), and funders (eg, be willing to support systematic reviews). These proposals are supplementing and strengthening existing recommendations about the reporting and interpretation of non-experimental research.1

An overarching goal for everyone who generates and uses research should be to embrace the value of scientific evidence at all levels of public policymaking. Each of us has a role to play in building a strong and sustainable evaluative culture in society. We need to think more carefully and creatively about how we discharge that role.

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I sat on the Academy of Medical Sciences working group with: Michael Rutter (chair), Philip Dawid, Arnon Hingorani, Peter Jones, Kay-Tee Khaw, Bill Kirkup, Geoff Mulgan, Catherine Peckham, Andrew Pickles, Robert Souhami, and Geoff Watts.

Panel: Recommendations by the Academy of Medical Sciences on the environmental causes of disease2

1 Government should build on their recent efforts to integrate science into policymaking by increasing capacity-building further by:
   - embedding researchers into policy teams
   - providing senior civil servants with scientific training
   - seconding scientists to government
   - establishing a cadre of evidence brokers within government who are trained in both science and policy

2 Research Base Funders’ Forum should lead an initiative to reaffirm funders’ support, where appropriate, for high-quality non-experimental research into the environmental causes of disease, encourage studies to test previous findings in different circumstances, and undertake systematic reviews

3 Department of Health (and other relevant government departments) should ensure that there is a greater emphasis on both pilot studies and systematic rigorous evaluations of the effects of interventions in developing and implementing health policy

4 Research Base Funders’ Forum should lead an initiative to foster responsibility for the accurate communication of non-experimental research, including consideration of whether it would be feasible to make accurate communication of results a requisite of funding

5 Department of Health, Research Councils, and charities funding research into environmental causes of disease and interventions to prevent or treat disease should continue to involve the public and patients’ organisations by inviting them to participate in their expert scientific advisory committees

1 Academy of Medical Sciences. Identifying the environmental causes of disease: a report by the Academy of Medical Sciences. London: Academy of Medical Sciences, 2007.


Clinical update: bariatric surgery

Because of the worldwide epidemic of obesity, the number of operations for bariatric surgery has increased more than five-fold within 5 years in most developed countries. In parallel, evidence is accumulating that surgically induced weight loss provides a survival benefit for morbidly obese patients. In two recent cohort studies, Lars Sjöström and Ted Adams, and their respective colleagues, showed that bariatric surgery compared with conservative management reduced long-term mortality in morbidly obese patients. After adjustment for population characteristics, the decrease in mortality rates in the two studies amounted to 29% (95% CI 8–46%) and 40% (33–55%), respectively.

Obesity surgery is appropriate for adult patients with a body-mass index (BMI) of 40 kg/m² or more, or with a BMI between 35 and 40 kg/m² with obesity-related comorbidities such as type 2 diabetes mellitus, hypertension, cardiomyopathy, sleep apnoea, asthma, pseudotumour cerebri, osteoarthritis, and hyperlipidaemia. These criteria have remained unchanged since 1991, but last year Paul O’Brien and colleagues, in a well-designed randomised study (albeit a small one), showed that the BMI threshold should possibly be lowered to 30 kg/m². Various contraindications must be taken into account, although most have not been derived from firm clinical evidence. Severe mental or cognitive retardation are therefore generally considered absolute contraindications. Psychiatric disorders (psychotic, personality, or affective disorders, alcoholism, or drug abuse) and lack of compliance with follow-up requirements are considered as potential negative predictors for obesity surgery, but they should not generally be seen as contraindications to bariatric surgery. However, preoperative evaluation sometimes requires consultation by a psychiatrist and nutritionist.

Bariatric procedures (panel) can be divided into those that reduce food intake (ie, gastric restriction) and those that reduce food uptake from the digestive tract (ie, malabsorption). The two most common procedures worldwide are laparoscopic adjustable gastric banding and Roux-en-Y gastric bypass, which is done through an open approach or laparoscopically. Both approaches have strong support among bariatric surgeons. One of the reasons for the rapid spread of obesity surgery around the world was the reduction of perioperative risks by the use of laparoscopic access, which today can be used for all bariatric procedures.

The modern technique of laparoscopic adjustable gastric banding is simple and well standardised. Since the introduction of the adjustable gastric band, two bands have mainly been available: the Lapband (Bioenterics) and the SAGB (Swedish Adjustable Gastric Band; Obtech Medical). There is no statistically significant difference in postoperative weight loss and complications between the Lapband and the SAGB. Both bands are adjusted on the hydraulic principle of injecting isotonic liquid into the port. Port-related complications, such as problems with port puncture, are a drawback of the hydraulic bands. To avoid port-related complications, a telemetrically adjustable band was developed. This band has been successfully implanted in patients but outcome data in the long term were disappointing.

The gastric bypass procedure allows different modifications. Standard Roux-en-Y gastric bypass includes a pouch volume of about 20–30 mL, an alimentary limb of at least 75 cm, and a biliary limb of at least 50 cm. Long-limb gastric bypass seems to be preferable in superobese patients. Special forms of gastric bypass are banded gastric bypass (Fobi and Campella technique) as well as the mini-gastric (or one-loop) bypass, but the spread of these techniques is limited. The performance of laparoscopic gastric bypass has some specific technical aspects. Gastrojejunostomy can be done with a circular or linear stapler or hand-sewn. With a circular stapler, the

Panel: Currently used bariatric procedures

Gastric restrictive operations
• Laparoscopic adjustable gastric banding
• Sleeve gastrectomy
• Vertical banded gastroplasty

Malabsorptive operations
• Biliopancreatic diversion
• BPD with duodenal switch

Malabsorptive/restrictive operations
• Roux-en-Y gastric bypass
• Mini-gastric bypass

Gastric stimulation
• Gastric pacemaker
• Intragastric electrical stimulation
anvil can be introduced transorally or transgastrically. Because of the risk for oesophageal injury by transoral introduction, transgastric anvil placement is safer. The Roux limb can be placed antecolic or retrocolic as well as retrogastric or antegastric. Antecolic and antegastric Roux-limb placement is the easiest way and can be recommended for less experienced bariatric surgeons. The closing of defects in the Roux-limb mesentery (Petersen’s hernia) and jejun-jejunostomy mesentery is needed to avoid bowel obstruction.

Other bariatric procedures are less frequent compared with gastric banding and gastric bypass. Vertical banded gastroplasty is a non-adjustable restrictive procedure and is nowadays almost abandoned from the surgical repertoire.

In its classic form, biliopancreatic diversion consists of partial gastrectomy with a Roux-en-Y gastroenterostomy. In its duodenal-switch form, a vertical sleeve gastrectomy is combined with a duodenoenterostomy. A few data have been published about limb length, but it is generally recommended that the common limb should measure more than 50 cm but less than 100 cm. Of note, no randomised trial has compared biliopancreatic diversion with other procedures. The biliopancreatic technique, however, can lead to massive weight loss: as much as 70% of the patient’s initial excess weight. The technique, especially with a duodenal switch, is more difficult than gastric bypass to do laparoscopically. These procedures can be recommended only for bariatric surgeons who are well trained in laparoscopic approaches.

Laparoscopic sleeve gastrectomy can be done as an initial weight-loss procedure followed by second-stage duodenal switch for high-risk patients with morbid obesity or in addition to gastric banding when weight loss is insufficient. The biggest drawback of this procedure is the potential for sleeve dilatation, resulting in a stop in weight loss or even a gain. However, the operation can be used as a stand-alone bariatric procedure for some special groups of high-risk patients.

Gastric stimulation is still widely considered to be an experimental procedure because of a lack of long-term results. Controversy exists about the best surgical procedure, because little evidence is available about the comparative effectiveness of the different procedures. In accordance with current opinion, laparoscopic adjustable gastric banding is generally considered to be safe and quick, but the long-term outcome and quality of life, especially for eating patterns, have been questioned. On the other hand, the long-term efficacy of adjustable gastric banding could be improved by the development of new band devices. Band-related complications include band slippage, leak, intolerance, infection, and migration, as well as insufficient weight loss. The management of these complications includes: band replacement for slippage, leak, and migration; band removal for infection; band removal plus Roux-en-Y gastric bypass for intolerance; band in situ plus sleeve gastrectomy for insufficient weight loss; and the addition of biliopancreatic diversion or band removal plus the Roux-en-Y technique for insufficient weight loss.

More complex bariatric procedures, such as Roux-en-Y bypass or especially biliopancreatic diversion, have a greater potential for serious perioperative complications, including lethality and malnutrition, but are possibly associated with better long-term outcome in terms of weight loss. They also require less dietary restriction. Last year, a systematic review of medium-term weight loss after bariatric operations revealed that biliopancreatic diversion and banded Roux-en-Y gastric bypass appear to be more effective than both standard Roux-en-Y method and laparoscopic adjustable gastric banding. Complications of Roux-en-Y bypass or biliopancreatic diversion include anastomotic leakage, stomal stenosis, gastric distension, gastrointestinal haemorrhage, small-bowel obstruction, gastrojejunal ulcers, and nutritional deficiencies, as well as inadequate weight loss.

Currently, the choice of surgical procedure partly depends on the repertoire of the surgeon, because most surgical centres cannot offer the full range of possible operations. Some centres prefer Roux-en-Y gastric bypass or biliopancreatic diversion, while others have nominated laparoscopic adjustable gastric banding or laparoscopic sleeve gastrectomy as their first-choice procedure and do the Roux-en-Y technique or biliopancreatic diversion only when the laparoscopic procedure has failed. Furthermore, the use of the different procedures varies between Europe (where laparoscopic adjustable gastric banding is common), North America (where Roux-en-Y bypass is common), and other parts of the world. Most probably, tailored criteria for selection of patients might better select those who are likely to benefit from one rather than the other procedure. On the balance...
between risks and benefits, patients with more severe obesity (eg, BMI>50 kg/m²) are generally considered good candidates for Roux-en-Y bypass or biliopancreatic diversion, whereas adjustable gastric banding or sleeve gastrectomy may be more appropriate in milder degrees of obesity. Of course, candidates for obesity surgery should receive full information about the different procedures.

The effectiveness of obesity surgery has been traditionally measured only in terms of excess weight loss, for which data clearly indicate the effectiveness of all procedures. Today, research emphasis is more on the effect of surgery on obesity-related comorbidities, which can affect metabolic, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and urological organ systems. Additionally, the psychological benefits of weight loss are being investigated. New data indicate that at least some bariatric procedures exert their beneficial metabolic effects not only by weight loss but also through a change in hormone release (ghrelin, peptide YY, and glucagon-like peptide 1) from the gut. This finding corresponds to clinical observations that obesity in patients with diabetes is especially amenable to bariatric surgery.

As can be expected from other surgical disciplines, the results of surgery critically depend on the expertise of the surgeon and the multidisciplinary team. Now that the gold-rush mentality and the mushrooming of centres for bariatric surgery have started to fade, it is more important that knowledge and skills are concentrated in bariatric surgery centres. Mortality in high-volume centres is lower than in lower-volume centres. Additionally, the formation of centres of excellence, quality assurance methodology needs to be, and will be, applied to bariatric surgery.

In summary, there is good evidence to show that bariatric surgery is more effective than non-surgical approaches in the therapy of morbid obesity. However, no single operation is ideal for every morbidly obese patient, and all operations also entail some disadvantages.

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We declare that we have no conflict of interest.

A small wooden monument stands in the tiny village of Geregere, in the Pader district of northern Uganda. A reminder of a violent past, it commemorates the massacre of 27 local people 5 years earlier by the rebel Lords Resistance Army (LRA). All the victims’ names are listed, three of them in red. When a member of our group questions the names in red, the answer seems hardly credible. The bodies of the three individuals, once cut to pieces, were roasted in a giant cooking pot by members of the rebel army.

The LRA, who want to run the country by rules similar to the biblical Ten Commandments, have been at war with the government of President Yoweri Meseveni for two decades. But now there are signs of peace. With no skirmishes for over a year, the government has given the LRA an ultimatum to formally end the brutalisation of thousands of northern Ugandans. The conflict has left behind a bloody trail of indiscriminate murder and abuse—a horrific tale of abducted children, young boys brainwashed and trained as child soldiers, and girls as young as 8 years kidnapped and forced to become the wives of the foot soldiers and commanders of the rebel army.

The unofficial peace of the past year has not translated into much positive change for the local communities. Disbelieving that the peace can be sustained, many northern Ugandans remain too frightened to move away from the internally displaced people (IDP) camps, homes for most of the population during the civil conflict. Around 16 000 people occupy a camp in Lira Palwo. It is one of the newer decongestant camps located closer to rural communities than the larger, more centralised camps used in the height of the conflict. Once permanent peace in the region is achieved, people are expected to move from the communal homes in the decongestant camps to their nearby villages.

A typical dwelling in the camp is a room with dry mud walls, 3 metres square. Sanitation is almost non-existent; an appalling stench from the pit latrines permeates the camp. Unlike the larger settlements where villagers became night commuters for safety during the worst parts of the conflict, here there is space to cultivate the land for cassava (a fibrous root common in the local diet), ground nuts, and beans. Despite grim living conditions, the IDP camps remain a safe haven for more than a million people in the north of the country.

Another place of safety is the newly created centre for orphaned children in Patongo, a project funded by the Humanitarian Aid Relief Trust, a non-governmental organisation (NGO) based in the UK. The centre, which officially opened in October, houses 35 orphans aged 5 years or younger, whose parents were killed by LRA attacks or HIV/AIDS. Most of the children arrived at the centre from the villages with varied health problems. With skin infections on the body and scalp, most of the children will probably have a combination of one or more of HIV, malaria, schistosomiasis, respiratory infections, and general water-borne diarrhoeal disease. Despite the clean dormitories with new bednets, sanitation remains the same desperate problem inside the children’s centre as at the IDP camp, with unclean water sourced from a bore hole over a mile away. The nurse at the centre has limited supplies, mainly adult preparations of ineffective chloroquine for treating malaria.

At the opening of the centre, older children perform a vibrant piece of musical theatre. Darting around, grabbing one another, forcing another child away, it soon becomes clear what is taking place. “They are re-enacting the kidnapping and abduction of the LRA soldiers”, explains Christine, the centre manager. “But they are happy, they are looking for peace.” We meet some of the older children who calmly tell us their own personal accounts of
abduction, forced violence and murder, and sexual abuse (see Web Focus).

Sharp contrasts define the provision of health care in the region. A government-run primary health-care clinic is situated near the children's centre. The premises are dusty and used ampules and swabs lie abandoned on the floor. A nurse practitioner lists the services offered there: first aid, malaria treatment, tuberculosis screening, and basic obstetric care. The clinic is also in its second year of providing HIV counselling and testing and antiretroviral therapy. Although treatment is free, there is no medical doctor to run the clinic; the nurse talks enthusiastically and expects the clinic to be upgraded from level three to four, once a doctor and enhanced maternity service and basic operating theatre are introduced. By contrast, 50 km north in Calonga, a shiny district hospital with graceful nurses in starched blue and white uniforms offers a range of medical services, though inpatients pay 500 Ugandan shillings (US$0·30) for their first visit. The hospital, although receiving some government funding, largely benefits from many years of investment from an Italian philanthropic organisation. Philanthropy, unsurprisingly, is central to the infrastructure of communities living in poverty with limited government resources, and especially in post-conflict locations such as northern Uganda. Gulu is a bustling town in the north, with a strong NGO presence. Caritas is typical of a larger NGO providing a range of services in the Gulu area, often in partnership with local government. Their main aim is to reach out to the most vulnerable people in local communities by providing health and medical assistance, and a range of social-support services to help people overcome alcoholism—a major problem in the adult male population. Many of the men have been emasculated by seeing their wives and children abducted and raped in front of their eyes. With a myriad of NGOs in Gulu alone, coordination and avoiding duplication of effort is key. Caritas’ work, in line with government policy, aims to complement the work of other agencies in the region.

Although many of the local people extend hands of warm friendship, and are trying to be positive about their future, it becomes clear that the north is a neglected region, with poor awareness internationally and insufficient support from its own people. Reports of ineffective plastic hoes and poor seed supplies from the south reinforce the belief that northern Uganda remains largely ignored. Meanwhile, back in Kampala, millions of dollars of public money are being spent on roads, buildings, and the international airport at Entebbe, ahead of the meeting of Commonwealth leaders.

In addition to the obvious physical challenges confronting northern Uganda—grinding poverty and its close association with poor nutrition, inadequate sanitation, the constant battle against malaria and HIV—there is another kind of public-health concern that is emerging among northern communities trying to rehabilitate after the civil war: mental health.

Sister Margaret Achin is unique in northern Uganda, being a qualified psychotherapist and counsellor. On a 3-year grant from Caritas, she coordinates a counselling service in Gulu for people highly traumatised by the war. As we walk into her office she points to a drawing of a mournful young woman hanging on the wall. “That is Mary”, she says. Sister Margaret says that Mary is not a real person but that “some of the young women who come here for counselling have been sexually abused by the LRA over the past few years. They need Mary. Unable to discuss their own trauma, we talk about Mary and how terribly she has suffered. Gradually, the young women transfer their anguished feelings to Mary, and begin to exorcise their trauma”. Other visitors to the counselling service have other kinds of trauma to overcome, alcoholism, or are trying to cope with the loss of a loved one from abduction or murder, or in adjusting to disability inflicted by the civil conflict.

Like so many NGO activities, this rare mental-health service can barely scratch the surface. Margaret’s counselling can only reach people within 25 km of Gulu, and uncertainty remains about future funding for the project. As I leave Sister Margaret’s office, her parting words highlight one of the health priorities for the Ugandan population post-conflict: “The war of guns may be over…now we need to deal with the war of trauma”, she says.

Richard Lane
The battle to reform health-care coverage in California

In trying to reform the health-care system in California, Republican governor Arnold Schwarzenegger is taking on a monster worthy of the Terminator. His main demon is one that bedevils health-care coverage throughout the USA: affordability. Norra MacReady reports.

About 47 million people in the USA, or more than 15% of the population, lack health insurance. Nearly 7 million of those individuals reside in California, so the rest of the nation is watching closely as governor Arnold Schwarzenegger, a Republican, and State Assembly Speaker Fabian Nuñez, a Democrat, try to cobble together a plan that will ensure coverage for virtually everyone in the state. For their part, state policymakers are looking for lessons from Massachusetts, which passed its own health-care reform legislation in 2006. The lawmakers must devise something that satisfies a diverse array of interests representing the entire spectrum of political philosophies while melding with current state and federal regulations governing health-care delivery to the very young, the very old, and the very poor, all without bankrupting the state.

The effort offers a glimpse of the problems unique to the US health-care system, and helps to explain at least in part why universal health care has been such a hard sell in the USA. Americans have "a cultural ambivalence toward a centralised system", said Jonathan Oberlander, associate professor of social medicine and Health Policy and Administration at the University of North Carolina in Chapel Hill. Such proposals, he explained, tap into deep-rooted questions about what the role of government should be.

What is more, said Oberlander, surveys have shown that despite their complaints, about 85% of Americans who have health insurance are satisfied with it, and fear that efforts to tinker with the system might diminish their level of coverage. In other words, "Do I want Congress telling me what my benefits should be?" said Jonathan Gruber, professor of economics at the Massachusetts Institute of Technology, who was a consultant for the Schwarzenegger plan. On the other hand, he warned, "it is foolish to have a system in which 47 million people do not have health insurance".

In California, the governor and the Democrats each presented a proposal earlier this year. The Democratic-controlled state legislature defeated Schwarzenegger’s bill, whereas the governor vetoed the Democrats’ proposal. Speaker Nuñez was originally hoping to present his Assembly colleagues with a revised Democratic bill to vote on by early December, but has now postponed it in favour of ongoing negotiations with the governor. The two sides are trying to hammer out a single compromise measure that can be presented as a ballot initiative in 2008 so voters can have their say. The major sticking point is the problem that bedevils health-care coverage throughout the USA: affordability.

The governor’s plan includes a universal mandate, in which adults would be required to obtain insurance, either at work, or with an individual plan purchased directly through an insurance company. Minimum coverage will include an annual deductible of US$5000, and a total out-of-pocket maximum of $7500, although the specific benefits such policies will have to provide have not yet been finalised. The premiums for these plans are projected to cost about $100 per month for people without employer-subsidised coverage.

Relief would be available for families or individuals at certain income levels. The governor’s proposal would cap premium payments at 5% of income for anyone with an income up to 250% of the federal poverty level (FPL), and they would be able to obtain low-cost insurance through a state purchasing pool. People with incomes of 250–350% of the FPL would be eligible for tax credits to offset the cost of their insurance. Children’s care would be fully subsidised for families with incomes up to 300% of the FPL.

Still, under Schwarzenegger’s plan, people whose incomes make them ineligible for any government subsidies could find themselves spending as much as $8700 yearly for the most minimum level of coverage. This category would include individuals earning $40 000–60 000 per year, a very modest income by Californian standards.

The Democrats are reluctant to require an individual mandate. Labour unions are a traditional Democratic
The printed journal includes an image merely for illustration

constituency, and the leadership of the California chapter of the Service Employees International Union has expressed concern that the mandate would be too expensive for many low-income people, a view shared by many Democrats. The Assembly proposal would have employees either participate in an employer-sponsored programme, or obtain insurance through a specially created purchasing pool, unless those costs exceeded 5% of their income. In California, the Democrats’ plan would ensure full subsidisation for adults up to 150% of the FPL, and cap all out-of-pocket spending, not only on premiums but also on other health-related items as well, such as copayments and prescription drugs, at 5% of income for people with incomes at 150–300% of the FPL. What is more, they would like to make some form of premium assistance available to families earning up to 400% of the FPL, which works out to $82 000 for a family of four.

Both plans allow anyone who is satisfied with their employer-provided coverage to keep it. However, if businesses with at least ten employees choose not to provide insurance for their workers, the Democrats would have them contribute 7.5% of their payroll to the state purchasing pool, whereas the more business friendly governor asks for only 4%.

Neither side has yet to find an entirely satisfactory way of funding this endeavour. In addition to employer contributions, individual premiums will provide some of the money, and hospitals will be taxed on a percentage of their annual patient revenues. Schwarzenegger’s most controversial suggestion is to license the state lottery to a private firm, and use those revenues to help fund his health-care proposals. He had also suggested levying a tax on physicians’ incomes, but quickly backed down in response to protest from the California Medical Association. The Assembly proposal similarly asks citizens to pay premiums and would have the additional income come from the higher tax imposed on employers, an increase in cigarette taxes, and hospital fees.

Still, some observers worry that too many people will find these requirements too expensive. As Speaker Nuñez said at a special hearing on Oct 31, "Is it realistic to require people to buy insurance they cannot afford?” Others have pointed out that neither proposal places any restraint on the extent to which insurers can raise prices. So a policy that costs $100 per month today may be $125 or $150 next year. “The subsidies are key”, said Oberlander. “If they cannot keep the premiums down, they will have to increase the subsidies, or the burden for individuals will increase.” Essentially, insurers now “get to charge what they can get away with”, said Donna Gerber, director of government relations for the California Nurses Association. In her opinion, it is a mistake to keep the insurance companies in the picture at all. She said the governor’s lottery proposal shows “how desperate one gets in trying to keep the insurance companies involved”.

Nuñez has stated that the Democrats support a single-payer system, at least in theory. But installing such a plan would require an overhaul of the US health-care system so massive as to make it politically and economically unfeasible, said Gruber. The current proposals “build on the existing system [of employer-provided health insurance], instead of shredding it and starting anew”. Besides, he noted, a multiple-payer system has several advantages, including competition, innovation, and choice.

Schwarzenegger’s proposal “may not be perfect, but it is a very good plan”, said Hector Flores, a family physician who practises in east Los Angeles, a low-income neighbourhood. Flores is one of the very few physicians who supported a tax on doctors’ incomes, as it meant that “everybody must ante up something: it is part of a shared responsibility”. Flores also pointed out that both parties’ proposals offer incentives for preventive care, such as immunisations, mammograms, colonoscopies, and prenatal care. In that way, they do represent a true reform of the current “illness-oriented” health-care system, which, he said, “is like closing the barn door after the horse is out”.

But the dream of a single-payer system for California is not completely dead. State Senator Sheila Kuehl, a Democrat, has been promoting a bill for just such a system since 2003. Her proposal is modelled on Medicare, the federal health-care programme for senior citizens. As with Medicare, her bill would be funded through a combination of payroll and income taxes, but there would be no premiums, deductibles, or copayments to worry about. People would still be able to choose their own doctors and hospitals, and their prescription drugs, vision, and dental care also would be covered. Last spring, Kuehl’s bill made it through the state Senate and the Assembly Appropriations Committee only to be vetoed by governor Schwarzenegger. It will be presented to him again next year.

Passage of any of these measures would at least be a start towards improving health-care coverage in the state. Until then, many Californians, like their fellow Americans, will remain just one serious illness away from financial ruin.

Norra MacReady
Book

**An ethnographic study of HIV/AIDS in China**

Sandra Teresa Hyde’s *Eating Spring Rice* is the first major ethnographic study in the English language of the HIV/AIDS epidemic in the People’s Republic of China. Bridging medical anthropology with public health, as well as Chinese cultural politics of race, ethnicity, and sexuality, this is a timely and enjoyable book that should be recommended to those who are interested in understanding the interconnections of HIV/AIDS with ideology, discourses, practices, and cultural imaginations.

Hyde has been an observer of the epidemic’s unfolding in China since the mid-1980s. As a college student, she was involved as early as 1985 in a survey of attitude and knowledge about AIDS among ordinary Chinese. She has since continued research on AIDS, focusing on China’s Yunnan province that borders Laos, Burma, Thailand, and Vietnam.

Yunnan province has a population of more than 44 million, including 25 of China’s 55 officially recognised ethnic minority groups. Within the Chinese borders, Yunnan province is also ground zero of China’s AIDS epidemic, and 80,000 individuals in Yunnan are estimated to have contracted HIV, mostly from sharing needles in injection drug use. The total number of individuals currently living with HIV/AIDS in China is about 650,000, according to the Chinese Ministry of Health. Within Yunnan province, Hyde’s field research concentrated on the city of Jinghong, capital of Xishuangbanna Dai Minority Autonomous Prefecture. Throughout her fieldwork, she interviewed Chinese government officials, migrant workers, health workers, as well as a small group of sex workers and travelling businessmen who were attracted to Jinghong partly because of its thriving sex industry.

Instead of merely examining government documents and research papers sponsored by the government, Hyde explores what she calls “state narratives” by analysing first-hand material collected through interviews with agents of the Chinese state machinery, including a senior health official at the provincial level, a middle-ranking anti-epidemic station official, and a health worker. This analysis is used to support one of Hyde’s key contentions: that Chinese government officials, health workers, and social scientists view and implement HIV/AIDS prevention with a heavy cultural bias against people from ethnic minority groups, imagining them as the main vectors of the disease. And such an imagination, Hyde suggests, is based on a Han Chinese belief that minority women are more prone to promiscuity and that the border regions of China where many ethnic minority groups live are fraught with various kinds of dangers, including uncommon infectious diseases.

Hyde also argues that the prefecture of Xishuangbanna became an AIDS control belt that was tightly watched by Chinese epidemiologists, although it was, in fact, extremely hard to find AIDS patients there. Hyde challenges the widely held view among Chinese health workers and social scientists that the victims of the first wave of the HIV/AIDS epidemic in China were people from ethnic minorities in the country’s southwestern border regions. What Hyde tells us here is that these health workers and social scientists projected a Han-Chinese-centred fear of AIDS upon those from ethnic minority groups, and so found an easy target for blame and a self-gratifying incentive to take action. I do not, however, find Hyde’s proposition entirely convincing. There is no doubt that many Han Chinese citizens have a biased view about ethnic minorities and this prejudice penetrates into the thinking of some government officials, health workers, and social scientists. But it does not mean that the attention being paid to people from ethnic minorities for HIV/AIDS prevention is misplaced. To my knowledge, in 1990 most AIDS victims in Yunnan were among ethnic minority groups. By 1995, the confirmed cases in Yunnan were predominantly among Chinese citizens. What I think this means is that HIV/AIDS finds different victims over time and that China’s ethnic minorities were, indeed, the main victims of the first wave of the epidemic.

Hyde’s analysis of the role of ethnicity in the sex trade in Jinghong is very specific, but is therefore a somewhat unrepresentative view of this issue. Hyde believes that the city’s thriving sex trade had a lot to do with the Han Chinese male fantasy about ethnic minority women’s sexuality, particularly that of Dai women. Hyde offers not a single case of Dai prostitution in Jinghong, and suggests that sex workers in Jinghong were actually Han Chinese who habitually wore Dai women’s dress when they received clients, therefore giving Han men the impression that they were having sex with exotic Dai women. This might well be the situation in Jinghong at the time of Hyde’s fieldwork, but one would be wrong to conclude that the sex trade in Yunnan in particular, and in China in general, does not involve women from ethnic minorities. The sex trade that has developed with the growth...
of a market economy in China cuts across the boundaries of ethnicity, and there are sex workers from all kinds of ethnic backgrounds in China.

Apart from these two issues, Eating Spring Rice is a truly remarkable book in the sense that it reveals the strength of ethnography in teasing out the nuances of problems that are often presented and discussed in black-and-white terms. Hyde does not accept easy answers and is determined to look for sensitive interpretations of the cultural politics of HIV/AIDS in China.

Hyde finished her final field research trip to Yunnan in 2002. A year later, the Chinese government tripled the amount of money targeted at HIV/AIDS and began to allow international and domestic non-government organisations to work in HIV/AIDS prevention and care. In September, 2003, the Chinese government announced a new policy for comprehensive HIV/AIDS prevention and treatment. The “Four Free and One Care Policy” has the following aims: free antiretroviral drugs to AIDS patients who are rural residents or people with financial difficulties living in urban areas; free voluntary counselling and testing; free medicine to HIV-infected pregnant women to prevent mother-to-child transmission and HIV testing of newborn babies; free schooling for children orphaned by AIDS; and economic assistance to the households of people living with HIV/AIDS. All of these marked a dramatic policy change. From a time when official denial and blame ruled high-level discourses on AIDS, China has entered a phase of greater openness and seriousness in confronting HIV/AIDS. With an HIV prevalence rate below 1%, Chinese health officials are cautiously confident that their country will not become a high prevalence country so long as the nationwide effort to control the epidemic does not lose its momentum.

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**In brief**

**Book** Longing to sleep

Imagine spending 15 months without sleep. Then imagine spending those same 15 sleepless months feeling feverish, being so neurologically disabled that you cannot walk, and knowing that your impending death will be your first and last opportunity to rest. The Family that Couldn’t Sleep is the haunting tale of a Venetian family afflicted by fatal familial insomnia (FFI): an autosomal dominant inherited prion disease that strikes in middle age with this unusual clinical picture of insomnia and neurological degeneration.

This poignant and intriguing medical mystery follows the Italian family’s story from their first remembered relative with FFI, who was a Venetian doctor in the 18th century, to the present generation, as they seek to understand the disease and its cause. D T Max details the trials and tribulations as the family finally discover that the likely cause is a prion disease. The book touches upon the stigma that this previously unknown, misdiagnosed, and misunderstood disease brought to the Venetian family—in the past, some members of the family were viewed with suspicion and thought to be “possessed” or suffering from alcoholism.

Unravelling the pathogenic mystery of FFI is just one part of this highly instructive, meticulous, and frank scientific narrative. Max also explores prion biology, discussing the first cases of scrapie in the UK in the 18th century, the Kuru outbreak in Papua New Guinea in the 1950s, the UK controversy of bovine spongiform encephalopathy (BSE) and variant Creutzfeldt-Jacob Disease (vCJD) in the early 1990s, and findings in the USA of chronic wasting disease and the first US cases of BSE and vCJD.

From diverse sources that include interviews and letters, Max outlines not only the causes of these outbreaks, but the scientific dispute that ensued. The research into prion diseases, which are caused by infectious proteins, has been an area riddled with controversy ever since the new theories underlying their transmission and progression were first proposed.

Max cajoles the reader into reflecting on whether the emergence of prion diseases was self-inflicted by human nature—perhaps through cannibalism, or by misdirected efforts to improve meat and milk production by in-breeding, or through the practice of feeding previously herbivorous livestock unnatural animal-protein supplements. He also questions whether the BSE epidemic and transmission to human beings as vCJD could have been prevented or perhaps better handled.

This book is an extraordinary accomplishment. It would be a challenge to read it without becoming fascinated by the underlying science, experimental controversy, and personal stories of the emotional challenges faced by the sufferers of FFI. And, be warned, this book may well keep you up at night while you wait for the mystery to be revealed.

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**The Family That Couldn’t Sleep: Unravelling a Venetian Medical Mystery**


Py 336. £17·99.


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Ten most wanted
October, 2007

1. Thiazolidinediones (Articles, Sept 29)

2. HPV and cervical cancer (Seminar, Sept 8)

3. H5N1 infection (Articles, Sept 29)

4. Drug safety and thiazolidinediones (Editorial, Sept 29)

5. The ADVANCE trial (Articles, Sept 8)

6. Thiazolidinediones (Comment, Sept 29)

7. Women: more than mothers (Editorial, Oct 13)

8. Ambulatory blood pressure (Articles, Oct 6)

9. Headache after 60 pints of beer (Case Report, Sept 29)

10. Intergroupe Francophone du Myelome (Articles, Oct 6)

Lifeline

Alan Bernstein is the inaugural Executive Director of the Global HIV Vaccine Enterprise. As the founding president of the Canadian Institutes of Health Research, he built the organisation into a leading research agency. Throughout his career he has made extensive contributions to the study of embryonic development, haemopoiesis, and cancer.

What has been the greatest achievement of career?
Working with my graduate students and postdoctoral fellows and watching them embark upon their own journeys in science. They are the future.

Who inspired you?
I had a music teacher in high school who convinced each of us that we were capable of great things.

If you had not entered your current profession, what would you have liked to do?
I would have been an orchestra conductor.

Who was your most influential teacher and why?
My PhD adviser, Jim Till, who had a key role in discovering stem cells. Jim’s enthusiasm for science, his integrity, and his concern for people have been major influences in my career.

What would be your advice for a newly qualified doctor?
Treat the person, not the disease. Individualised care and concern is as important as pills.

What is the best piece of advice you have ever received, and from whom?
Lou Siminovitch, the Canadian geneticist, taught me that other aspects of one’s life are as important as science.

What is your favourite play?
Rosencrantz and Guildenstern Are Dead by Tom Stoppard. I love everything by Stoppard. His constant theme is about questioning reality and the importance of perspective to what we think, see, and feel.

What are you currently reading?
Stars and Bars by William Boyd.

What is your worst habit?
I don’t suffer fools gladly.

What one invention would most improve your life?
A pill that you took at bedtime that would allow you to wake up and speak another language.

Which would you choose, money or power?
Money, because it gives you choices.

What is your greatest fear?
Failure.

If you can have dinner tonight with a famous person of your choice (dead or alive), who would it be?
Dmitri Shostakovich, the greatest composer of the 20th century. I’d ask him about his political views and his music.
Obituary

Arthur Kornberg


Robert Baldwin met Arthur Kornberg in 1958 at a conference on biophysics in Boulder, CO, USA. Kornberg, who was about to move from Washington University to Stanford University to create a department of biochemistry, was just one of the eminent scientists at the month-long conference on the subject now known as molecular biology. “I had a very clear picture, by the end of the conference, that molecular biology was going to be a very important field of work, and I could also see that Arthur Kornberg’s department was going to be a centre of this work”, Baldwin said.

Baldwin joined Kornberg’s department in 1959, along with Kornberg’s former postdoctoral students Paul Berg, who later won the 1980 Nobel Prize in Chemistry for his work on nucleic acids, and Robert Lehman. Kornberg was working on the synthesis of DNA at the time, and had recently discovered DNA polymerase. “What he did was that he discovered, rather soon, that DNA synthesis was a multi-enzyme problem”, Baldwin said. He began with bacteriophages, but modern molecular biology techniques were not available so the work was difficult. “It was a very complicated business”, Baldwin recalls. “Arthur was a master at doing this, and he succeeded and eventually did this not only for these small bacteriophages but for E coli itself.”

In October, 1959, Kornberg and Severo Ochoa shared the Nobel Prize in Physiology or Medicine. Kornberg won for the discovery of DNA polymerase, while Ochoa won for his work on RNA synthesis. Together, their work has made possible much of biotechnology. It was working with Ochoa for a year in the 1940s that inspired Kornberg’s life-long love of enzymes. “It has been my conviction...that you have to know the actors in order to understand the plot”, Kornberg said in 1997. “And the actors are the enzymes.”

Kornberg earned his bachelor’s from City College in New York, and then his medical degree from the University of Rochester in 1941. He joined the Coast Guard, but ended up in research after the director of the National Institutes of Health (NIH), Rolla Dyer, saw a small study he published on jaundice in 1942. He would remain at the NIH until 1953, when he became chair of the Washington University microbiology department in St Louis.

In 1959, he left for Stanford, where he would remain until his death. Of the six original members of the department Kornberg founded, Melvin Kohn was the only person to ever leave the department. “It is very unusual, and the reason why everyone stuck together was that Arthur set about to design a department that would be an ideal workplace”. Kornberg introduced a number of innovations, including shared lab spaces that mixed research groups. Baldwin said that Kornberg was “an excellent colleague. I think everyone agrees with that”. He was demanding, particularly in the early days of the department. “He wanted very high quality work and he wanted a lot of it”, Berg said. “It was a very hard-working department.”

Kornberg wrote a number of books, including major textbooks on DNA synthesis. In the 1970s, he turned some of his attention to studying bacterial spores and sporulation as a model development system. Getting enzymes out of spores proved frustrating, however, and after a few years he turned all of his efforts back on DNA synthesis research. In about 1990, he returned to a project that he and his first wife, Sylvy, who died in 1986, had begun working on together. In 1956, the couple had discovered polyphosphate in Escherichia coli. Kornberg hadn’t done anything with the work since then, but he was convinced that the polyphosphates were critical energy stores for bacteria that could lead to other findings. Kornberg was still working on the problem until a week before his death, Baldwin said.

Kornberg is survived by his third wife, Carolyn Frey Dixon, and three sons, Roger, Thomas, and Kenneth. Roger won the Nobel in Chemistry for his work on eukaryotic transcription, and Thomas is a biophysicist who helped isolate an important enzyme from the Cairns mutant in 1969. Kornberg was predeceased by his first two wives, the former Sylvy Ruth Levy and the former Charlene Walsh Levering.

Ivan Oransky
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Ethical treatment of military detainees

As physicians, we solemnly commit ourselves to respect human life and the dignity of every individual; to treat the sick and injured with competence and compassion and without prejudice; to refrain from supporting or committing crimes against humanity; and to condemn all such acts. These professional obligations that all physicians strive to uphold are just as important today as they were more than 30 years ago during the life and death of Steve Biko (Sept 8, p 823).

Since the issue of detainee abuse under US custody first surfaced, leaders of the American Medical Association (AMA) have met on several occasions with high-ranking officials at the United States Department of Defense (DoD) to advocate for the treatment of detainees that is consistent with the AMA ethics policy that prohibits torture. At its 2006 Annual Meeting, the AMA House of Delegates adopted a new ethics policy on the topic of physicians’ participation in interrogation. This new policy clearly prohibits physicians’ involvement in “behavioural science consultation teams”, The AMA also reaffirmed existing policy by releasing a public statement that condemned forced feeding of hunger strikers.

In addition to making our position known to the DoD, representatives from the AMA were invited to visit the detention facilities at Guantanamo. These visits provided an opportunity for challenging the legality of the war against Iraq. Justice was, however, done to a serving German army officer who was cleared by the supreme court in Germany when he obeyed his conscience and refused to obey orders pertaining to the Iraq war.

We request to have assurance from the UK military, backed up with documentation, that the doctors they employ are given clear instruction on what to do about torture—eg, the definition of torture, when and to whom to report instances of torture, and action to be taken against those guilty. To fail to give clear guidance is a failure of duty to peculiarly vulnerable employees.

We declare that we have no conflict of interest.

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“If...the machine of government... is of such a nature that it requires you to be the agent of injustice to another, then, I say, break the law.”

Henry David Thoreau (1849)

Involvement in torture is not limited to US and apartheid-era South African doctors. Currently Canadian doctors face allegations of torture in Afghanistan, and, according to Amnesty International, Physicians for Human Rights Israel, and others, assisting in torture is a regular part of the job of many Israeli doctors. There are also unconfirmed reports of UK military doctors assisting in torture and deliberately giving incorrect causes of death on certificates.

The UN convention against torture (2005), ratified by the UK government, obliges governments to investigate and prosecute where there is suspicion of assisting in or turning a blind eye to torture. If it will not follow up and prosecute, it is bound to extradite to a country that will.

When there is an authoritarian government, illegal or legal war, or occupation, doctors are at great risk of going along with evil practices. The brave ones who refuse deserve our respect and help, for their paths will be lonely. We remember what injustice was meted out to the British air force medical officer Malcolm Kendall-Smith, who faced criminal charges for challenging the legality of the war against Iraq. Justice was, however, done to a serving German army officer who was cleared by the supreme court in Germany when he obeyed his conscience and refused to obey orders pertaining to the Iraq war.

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Correspondence
Treating clinically isolated syndromes suggestive of MS

Regarding Ludwig Kappos and colleagues’ article on the long-term benefits of β-1 interferon in multiple sclerosis (Aug 4, p 389),1 I have always been sceptical about starting treatment with any of the immunomodulatory drugs after a clinically isolated symptom suggestive of multiple sclerosis because, in a substantial number of instances, the patient can have disseminated encephalomyelitis2 rather than multiple sclerosis. Without impugning the diagnostic ability of the neurologists involved in the study, I wonder whether even a mandatory second event did not mean that the patient had recurrent disseminated encephalomyelitis?1

The now complete reliance on the MRI (or perhaps more commonly, the radiologist’s report) as the basis for the diagnosis of multiple sclerosis, is a major source of such error;2 as is the practice by some clinicians of regarding a relapse, or a second event, as being confirmation of multiple sclerosis, irrespective of the clinical features or the MRI characteristics of the initial presentation.4,5

The use of the expanded disability status scale (EDSS) as a measurement of progression also raises problems. Since this assessment is subjective, the fact that many physicians in different countries recorded values on this scale raises questions about uniformity and reliability. The EDSS varies during the day depending on fatigue, ambient temperature, and other factors; there is no mention that it was recorded at the same time of day or under the same conditions in all the study centres.

Finally, perhaps it was unavoidable, but it is disturbing to see that employees of the pharmaceutical company that makes the drug were active participants in the study.

I declare that I have no conflict of interest.

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Authors’ reply

We are confident that Charles Poser’s concerns as to the diagnostic process applied in BENEFIT are not substantiated. The McDonald diagnostic criteria,4 which, in clinical practice and research, have replaced those developed by the committee under Poser’s chairmanship, clearly state that diagnosis of multiple sclerosis depends on a careful interpretation of both clinical and MRI findings. In the study protocol, the diagnostic process for inclusion into our study and for confirmation of the second clinical event was carefully defined and included a thorough review of each individual case by two separate central adjudication committees.2,3 MRI—if interpreted as defined in the McDonald criteria—not only allows for an earlier diagnosis of multiple sclerosis but can also protect from a false-positive diagnosis in certain situations.4

The debate about the existence of relapsing disseminated encephalomyelitis as a separate disease entity in adults is ongoing. Acute disseminated encephalomyelitis typically occurs in children, and its distinguishing features from multiple sclerosis have been described in a consensus paper.5 At inclusion, no patients in BENEFIT fulfilled the major criteria for this diagnosis, which include encephalopathy, and none of the confirmed relapses during the 3-year observation period had features suggestive of disseminated encephalomyelitis.

Accurate and reproducible assessment of neurological deficits remains a problem for a complex disease like multiple sclerosis. In the BENEFIT study, assessments of the expanded disability status scale (EDSS) were based on a standardised neurological examination by specially and uniformly trained physicians. Because these EDSS physicians were not involved in daily care and therefore efficiently blinded as to the assigned treatments, any increased variability in assessments—since they were not systematically biased—would rather have reduced the power of the study to detect the effect on disability shown.

Most clinical trials of the size required to provide reliable results in multiple sclerosis are done with the active support of corporate sponsors. On the basis of a previously agreed charter, we academic members of the study’s steering committee shared full responsibility for the way in which the study was conducted as well as the assessment and publication of the data generated. Furthermore, we were impressed by the dedication and professional quality standards of the employees of the sponsor who were actively involved in the conduct of the study.

We declare that we have no conflict of interest other than that stated in the original paper.

Ludwig Kappos, Xavier Montalban, Hans-Peter Hartung, Marc Freedman, Chris Polman, for the BENEFIT Steering Committee

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Correspondence

For details of the training method used by EDSS physicians, see http://www.neurostatus.net/training/index.php

Remote ischaemic preconditioning

The work by Derek Hausenloy’s group on remote ischaemic preconditioning (Aug 18, p 575) is important because of the simplicity of the intervention used, and the potentially large effect it can have on day-to-day practice. We wish to add a few caveats to the interpretation of the results.

The primary outcome measure was the difference in troponin-T concentrations between the two groups 72 h after surgery. This difference did not reach significance. Technically, therefore, this was a negative trial. However, Hausenloy and colleagues choose not to highlight this lack of difference and instead to emphasise the differences seen at 6, 12, 24, and 48 h. Although the troponin-T concentrations were “significantly” different at these time points (no confidence intervals are given), this cannot be taken as definitive evidence of the effect of remote ischaemic preconditioning.

The drawbacks of such an analysis include the high false-positive rates that arise out of comparing repeated measurements, and the likelihood that successive observations on a given individual are correlated. Hausenloy and colleagues also present a post-hoc summary measure (area under the curve) incorporating these troponin values. But the method adopted to calculate this area is not stated and the results are presented in µg/L instead of the expected h.µg/L. Finally, short-lived increases in the concentrations of troponin T might not represent true myocyte death or injury.

It is important to consider the results of this trial in the light of these observations, particularly because of the small number of patients involved and of previous negative studies.

We declare that we have no conflict of interest.

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Authors’ reply

In our small, proof-of-concept randomised controlled trial, we showed that remote ischaemic preconditioning (RIPC) using short, intermittent episodes of ischaemia and reperfusion of the forearm was able to reduce myocardial injury in adult patients undergoing elective coronary artery bypass graft (CABG) surgery. The total area under the curve (AUC) troponin-T concentration over the whole 72-h postoperative period was the primary outcome measure and not the 72-h serum troponin-T concentration as suggested by Niveditha Devasenapathy and Ganesan Karthikeyan. The trial was therefore not a “negative study” because the AUC troponin-T concentration was significantly reduced by the RIPC intervention.

The confidence intervals for the serum troponin-T concentrations at the different time-points after CABG surgery were originally included in a table, but for the sake of clarity this had been replaced by a figure in the final published manuscript. This table is now included below and details of the confidence intervals at the different time-points are displayed (table)

In reference to the potential drawbacks of using repeated measurements of serum troponin-T concentration, it was important for us to show that there was a significant difference in the total AUC troponin T between RIPC and control, which is a more robust measure of myocardial injury.

A standard method was used to determine the AUC troponin-T concentration over the 72-h post-CABG period. Essentially, the total AUC = AUC (0–6 h) + AUC (6–12 h) + AUC (12–24 h) + AUC (24–48 h) + AUC (48–72 h). The AUC for each time period = [(troponin-T concentration at y h– troponin-T concentration at y h–1)/2] × total number of hours. However, we do agree that the units for AUC should have been presented as “h.µg/L” and not “µg/L”.

Devasenapathy and Karthikeyan state that our results should be interpreted with caution given a previously published negative clinical study. In that study, however, RIPC was examined in the completely unrelated clinical setting of elective coronary artery bypass graft surgery

Table: Mean (SD) serum troponin-T concentrations (µg/L) over the 72 h after coronary artery bypass graft surgery

<table>
<thead>
<tr>
<th></th>
<th>RIPC</th>
<th>Control</th>
<th>Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 h</td>
<td>0.31 (0.29)</td>
<td>0.59 (0.45)</td>
<td>-0.28 (0.01 to 0.42)</td>
<td>0.039</td>
</tr>
<tr>
<td>12 h</td>
<td>0.37 (0.19)</td>
<td>0.69 (0.48)</td>
<td>-0.32 (0.11 to 0.53)</td>
<td>0.002</td>
</tr>
<tr>
<td>24 h</td>
<td>0.30 (0.14)</td>
<td>0.52 (0.43)</td>
<td>-0.22 (0.08 to 0.36)</td>
<td>0.003</td>
</tr>
<tr>
<td>48 h</td>
<td>0.30 (0.17)</td>
<td>0.52 (0.49)</td>
<td>-0.22 (0.01 to 0.42)</td>
<td>0.036</td>
</tr>
<tr>
<td>72 h</td>
<td>0.25 (0.16)</td>
<td>0.48 (0.64)</td>
<td>-0.23 (-0.05 to 0.50)</td>
<td>0.111</td>
</tr>
</tbody>
</table>

RIPC: remote ischaemic preconditioning.

* Correspondence
percutaneous coronary intervention, which is hardly comparable to the setting of CABG surgery.

Devasenapathy and Karthikeyan remark that short-lived elevations in serum troponin T might not represent true myocardial death or injury. The serum concentrations of troponin T we saw in our clinical study were indicative of significant myocardial necrosis, the cause of which could be attributed to several causes including myocardial ischaemia–reperfusion injury, direct manipulation of the heart, and coronary microembolisation. Crucially, increased concentrations of troponin T in serum after CABG surgery have been associated with worse clinical outcomes in previously published clinical studies. Whether the reduction in serum troponin-T concentrations we saw in patients treated with RIPC translates into an improvement in clinical outcomes will need to be determined by future clinical studies.

We declare that we have no conflict of interest.

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Dabigatran versus enoxaparin after total hip replacement

Bengt Eriksson and co-workers (Sept 15, p 949) indicate two potential confounders without reporting their effects on outcomes. The design of the RE-NOVATE trial allowed low-dose aspirin and compression stockings, which both reduce rates of postoperative thromboembolism;2,3 aspirin can increase bleeding rates. Were aspirin and compression stockings used in comparable proportions in the three randomised study groups? Did the rates of thromboembolism and bleeding differ? These data should be reported.

Among the challenges of thromboembolism prevention trials,4 blinding merits mention. Not a single one of the major thromboembolism trials, including RE-NOVATE,1 has reported blinding efficacy. Subcutaneous heparins can induce haematomas at injection sites much more commonly than subcutaneous placebo. Haematomas at injection sites could therefore unblind treatment allocation. We still lack data on whether unblinding by this mechanism occurs at all, or how frequently it happens. Future trials should fill this gap by assessing and reporting the success of blinding,5 in particular when testing subcutaneous anticoagulants.

We declare that we have no conflict of interest.

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Bengt Eriksson and colleagues1 published an excellent study that allowed us to draw several conclusions, albeit different ones from theirs.

First, Eriksson and colleagues state that, on hospital discharge after orthopaedic surgery, deep-vein thrombosis (DVT) prophylaxis is obligatory. However, a more recent meta-analysis showed that, within this context, extended thromboprophylaxis did not significantly affect any important outcome.2 Additionally, Skedgel and colleagues3 did a cost-effectiveness analysis and concluded that there is insufficient economic evidence to support extended thromboprophylaxis with low-molecular-weight heparin (LMWH) after total hip arthroplasty.

Second, Eriksson and colleagues excluded 31·6% of the patients in the dabigatran 220 mg group, 24·4% in the dabigatran 150 mg group, and 21·3% in the enoxaparin group from the final analysis of data. As well as being large exclusions in themselves, the difference among the groups was significant, which was not mentioned by Eriksson and colleagues, and compromises the study outcome.

Third, why was dabigatran etexilate compared with enoxaparin and not fondaparinux? Was this comparison ever considered? Was there any interference from the pharmaceutical industry sponsoring the study? Turpie and colleagues4 concluded that fondaparinux was consistently more effective than enoxaparin in preventing venous thromboembolism in patients undergoing major orthopaedic surgery. And a cost-effectiveness analysis of fondaparinux compared with enoxaparin as prophylaxis against venous thromboembolism in patients undergoing major orthopaedic surgery suggested that fondaparinux improves outcomes and is cost-saving.

Finally, we believe that phase II and small phase III clinical trials should continue to use sensitive imaging
modalities for the detection of largely asymptomatic DVT as a means of testing the biological efficacy of a new intervention. However, these studies should be followed by large clinical trials that use a clinically important DVT outcome. Positive venography in asymptomatic patients in the late postoperative period is not an acceptable outcome in isolation.

We declare that we have no conflict of interest.

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Authors’ reply

Christoph Pechlaner and Peter Marschang highlight the use of aspirin and graduated compression stockings in our trial. The efficacy benefit of aspirin in patients undergoing hip replacement surgery has not been shown. Specifically, in the Pulmonary Embolism Prevention trial, patients who underwent hip replacement and received aspirin showed no significant efficacy benefit over placebo. In our trial, the use of aspirin and compression stockings was similar in the three treatment groups (table), with no significant difference in any efficacy or safety outcome among patients using either therapy alone or in combination.

We agree that small injection-site haematomas can appear more frequently in patients receiving active treatment than in those receiving placebo injections. However, in individual cases it will probably be difficult for patients and nurses to differentiate between treatments owing to a wide variation in patients’ responses. Rates of discontinuation were not different between the treatment groups and all assessments of efficacy and safety endpoints were done by blinded central adjudication committees.

Herlon Martins and colleagues question the evidence for the use of extended prophylaxis on reduction in clinically relevant outcomes. In the quoted systematic review by O’Donnell and colleagues, a lower absolute risk, but similar relative risk reduction in symptomatic events to that reported by Eikelboom and colleagues was noted. However, both analyses noted that the use of extended prophylaxis reduced the frequency of symptomatic venous thromboembolism by about two thirds.

We agree that the cost-effectiveness of anticoagulant therapies for extended prophylaxis requires careful consideration. In particular, low-molecular-weight heparins, which require subcutaneous administration, have only been shown to be cost effective if home-based self-administration is adopted. The cost-effectiveness of oral anticoagulants such as dabigatran etexilate, which are given once daily without the need for coagulation monitoring, can therefore be regarded as an attractive and cost-effective alternative to existing regimens. An economic evaluation of data from RE-NOVATE is currently being developed.

23·9%, 25·6%, and 22·8% of randomised patients were excluded from the primary efficacy analysis, with no significant difference between the treatment groups. In studies that use venography to detect venous thromboembolism, a loss rate of this order is regarded as acceptable and is consistent with that reported in other studies. Furthermore, our sensitivity analyses, as well as those done in the accompanying Comment by John Norrie, confirm that missing data did not compromise the efficacy findings.

Fondaparinux was not used as the comparator therapy because it is not licensed for extended prophylaxis after hip-replacement surgery. Enoxaparin, on the other hand, is the most widely used prophylactic therapy for this indication, with a well established efficacy and safety profile.

Finally, the use of venography to detect deep-vein thrombosis and its clinical relevance are still debated. With clinical event rates in our trial in the region of 1%, a similar trial using this outcome as the primary endpoint would require enrolment of more than 25 000 patients, depending on the non-inferiority margin used, thereby creating logistical difficulties. The close correlation between venographic and clinical outcomes supports the continued use of venography as an appropriate surrogate in these trials.

BIE has received honoraria from Boehringer-Ingelheim for consultancy. SH is an employee of Boehringer-Ingelheim.

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Folic acid fortification and cancer risk

After long deliberation, the UK Food Standards Agency (FSA) has recommended the fortification of flour with folic acid to reduce the numbers of pregnancies affected by neural tube defects. However, on Oct 17, 2007, the FSA indicated that a decision on fortification is to be delayed until the Chief Medical Officer considers recent publications on the issue of folate acid and colorectal cancer. Two papers are likely to be considered: Cole and colleagues and Mason and colleagues.1,2

The Cole paper reports the results of a randomised trial of folic acid in prevention of colorectal adenoma recurrence in a group of patients who had had adenomas removed. The conclusions have been misinterpreted. The paper does not show that folic acid supplementation poses a hazard. It relates to colorectal adenomas (benign tumours), not carcinomas. The incidence of adenomas in those who were and were not allocated folic acid supplements was almost identical over the two 3–4 year consecutive periods of follow-up (relative risks of 1.04 [p=0.58] and 1.13 [p=0.23]). Cole and colleagues correctly conclude that 1 mg/day folic acid did not reduce colorectal adenoma risk, but neither did it increase it. The results (table 3 of the paper) are negative. The only hint of increased adenoma risk is in a subset analysis related to the incidence of three or more adenomas. Secondary analyses, when based on such small numbers (13 placebo, 30 folic acid), are prone to the effects of chance producing formally significant results, particularly when there was no excess risk (relative risk 0.97) in people with one or two adenomas. A similar trial showed no excess of adenomas with folic acid.3

The paper by Mason and colleagues reports on a temporal association between folic acid fortification and an increase in colorectal cancer in the USA and Canada. Mason and colleagues suggest the possibility of a causal link, but the data do not support this. The incidence of colorectal cancer declined until 1995 in the USA and 1996 in Canada, then increased. Mandatory folic acid fortification was in place by Jan 1, 1998, in the USA and about a year later in Canada. The rise in colorectal cancer incidence therefore started before the introduction of fortification on any large scale and so could not have been caused by fortification. Figure 3 in the paper shows that endoscopy rates for colorectal cancer among people aged 50 years and older increased after 1996. Cancer screening is always associated with an increase in incidence because of the effect of early detection. Colorectal cancer mortality rates in the USA show no upward trend. The rates decline by about 2% per year between 1990 and 2000.4 Canada also had a continuing decline in colorectal cancer mortality rates until 1995. The paper by Mason and colleagues therefore provides no grounds for concern. It is misleading to link the rise in incidence between 1996 and 2000 to folic acid fortification. The FSA and the Chief Medical Officer can be confident in recommending that the UK Government introduce the mandatory fortification of flour, which could prevent about 400 pregnancies affected by neural tube defects each year, reducing both the number of terminations of pregnancy and of children born with these defects. We declare that we have no conflict of interest.

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2004

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A wearable haemodialysis device for patients with end-stage renal failure: a pilot study

Andrew Davenport, Victor Gura, Claudio Ronco, Masoud Beizai, Carlos Ezon, Edmond Rambod

Summary

Background More frequent haemodialysis can improve both survival and quality of life of patients with chronic kidney disease. However, there is little capacity in the UK to allow patients to have more frequent haemodialysis treatments in hospital and satellite haemodialysis units. New means of delivering haemodialysis are therefore required. Our aim was to assess the safety and efficiency of a wearable haemodialysis device.

Methods Eight patients with end-stage kidney failure (five men, three women, mean age 51.7 [SD 13.8] years) who were established on regular haemodialysis were fitted with a wearable haemodialysis device for 4–8 h. Patients were given unfractionated heparin for anticoagulation, as they would be for standard haemodialysis.

Findings There were no important cardiovascular changes and no adverse changes in serum electrolytes or acid-base balance. There was no evidence of clinically significant haemolysis in any patient. Mean blood flow was 58.6 (SD 11.7) mL/min, with a dialysate flow of 47.1 (7.8) mL/min. The mean plasma urea clearance rate was 22.7 (5.2) mL/min and the mean plasma creatinine clearance rate was 20.7 (4.8) mL/min. Clotting of the vascular access occurred in two patients when the dose of heparin was decreased and the partial thromboplastin time returned towards the normal reference range in both of these patients. The fistula needle became dislodged in one patient, but safety mechanisms prevented blood loss, the needle was replaced, and treatment continued.

Interpretation This wearable haemodialysis device shows promising safety and efficacy results, although further studies will be necessary to confirm these results.

Introduction Nearly 130,000 patients worldwide have chronic kidney failure that requires treatment with either dialysis or renal transplantation. Despite haemodialysis being an established treatment for chronic kidney failure, the survival of haemodialysis patients remains poor because of increased cardiovascular risk, and is similar to that of patients with solid organ malignancies.1 The quality of life and survival of haemodialysis patients could be improved by increasing the dose of dialysis (in terms of urea clearance) at each treatment and by increasing the frequency of such treatment from the traditional three times a week to five or more treatments per week.2–5 Indeed, daily dialysis would be closer to physiological norms.1

Hospital haemodialysis and satellite units generally do not have the capacity to offer patients more frequent haemodialysis treatments.3–9 Other forms of renal replacement therapies must be developed to allow more patients with chronic kidney failure access to more frequent dialysis. One potential advance would be to develop a dialysis system that was wearable, so that patients could do dialysis at home. This idea is not new, with a wearable artificial kidney being reported in the 1970s.5 However, a miniaturised version has been developed over the past few years, which has been tested extensively in the laboratory and in animal models.6,7 A simpler version of this device—a wearable haemofilter—has been piloted successfully in patients who need chronic dialysis.8 Here, we report a pilot trial of a wearable artificial haemodialysis device in human beings.

Methods Patients Eight patients with established chronic kidney disease treated by regular haemodialysis three times a week volunteered for the trial and gave written informed consent. Five of the patients were men, the average age of the group was 51.7 (SD 13.8) years (range 26–67 years), and all patients had been established on haemodialysis for an average of 17.9 years (range 4–29 years). The original cause of kidney failure was glomerulonephritis in four patients and polycystic kidney disease in three others; one patient had obstructive uropathy.

This prospective pilot study was approved by the UK Medicines Health Regulation Authority (MHRA) and ethics committee alpha of University College Hospital, London, UK.

Procedures Patients were connected to the wearable haemodialysis device (Xcorporate Inc, Los Angeles, CA, USA; figure 1) via their usual vascular access for haemodialysis, and were given unfractionated heparin for anticoagulation, as they would be for standard haemodialysis. The heparin dose was adjusted to maintain an activated partial thromboplastin ratio of 1.5–2.0. Patients were encouraged to eat and drink as normal during treatment. Because the efficacy of the artificial device had not been established, the MHRA requested that the treatment would not replace a standard intermittent haemodialysis...
treatment. As a result, fluid removal to achieve target postdialysis (dry) weights was not an objective of this study.

The wearable haemodialysis device used a commercially available 0·6 m² high flux dialyser (Gambro Dialysatoren, Hechingen, Germany), made of polysulfone. A specially designed pulsatile blood pump, powered by a standard 9-V battery, pumped the blood and dialysate in a countercurrent direction. The dialysate was regenerated with series of sorbent canisters containing urease, activated charcoal, hydroxyl zirconium oxide, and zirconium phosphate. There were four micropumps (Sorenson, West Jordan, UT, USA), to infuse heparin into the blood circuit, and to infuse sodium bicarbonate,
magnesium, and calcium acetate into the dialysate circuit, and one pump to regulate ultrafiltration. The total weight of the device was about 5 kg.

Safety features included a servomechanism with a sensor that detected bubbles placed after the blood pump, designed to stop blood flow if air bubbles were detected in the blood circuit, and a second servomechanism to halt the ultrafiltration pump if the blood flow stopped for any reason. The pulsatile blood pump also had a self-limited capacity to generate negative pressure from the arterial side of the vascular access, such that significant negative pressures could not be applied to the vascular access. Thus, any disconnection on the arterial side would result in cessation of the blood pump. Special wetness sensors (Economical Liquid Sensor, Cole-Palmer, USA) were applied to both the arterial and venous access connections to detect any leak. Similarly, in the event of clotting within the circuit, any increased venous resistance would lead to changes in pressure that would cause the blood pump to stop.

Blood oxygen saturation and the cardiac cycle of patients were monitored continuously with a finger probe and standard chest leads (Model SC1000, Huntleigh Healthcare, Cardiff, UK). The cardiac cycle was also monitored with standard ECGs. Patients were weighed before and after treatment by use of multifrequency bio-impedance (InBody 720, Bio-Space, Gateshead, UK).

Biochemical tests were done at both the bedside (iSTAT, Abbott Laboratories, Maidenhead, UK) and in the hospital’s main clinical chemistry laboratory. The pH of the dialysate was regularly measured. To determine whether haemolysis occurred during treatment, haematocrit, serum haptoglobin, and lactate dehydrogenase were measured every 2 h. All patients were asked to complete a questionnaire after treatment to assess any adverse events and their satisfaction with the treatment.

### Statistical analysis

Clearance rates were calculated with the following equations:

\[
\text{Amount removed} = Q_b \cdot t (1 - Hct)(C_{in} - C_{out})
\]

\[
\text{Clearance (K)} = \frac{Q_b (1 - Hct) \times (C_{in} - C_{out})}{C_{out}}
\]

\[
\text{Standard urea clearance} = \frac{K \cdot t}{V}
\]

where \(Q_b\) is the blood flow rate (mL/min), \(t\) is time, \(Hct\) is haematocrit, \(C_{in}\) is the concentration of solute entering the dialyser, \(C_{out}\) is the concentration of solute exiting the dialyser, and \(V\) is the volume of body water.

Data were initially analysed as if normally distributed with Student’s \(t\) tests. However, to ensure that there were significant differences, or to ensure that variables had not changed during the study, we did additional non-parametric tests. For paired data, Student’s \(t\) tests or the Wilcoxon rank sum pair test was used. Statistical significance was taken as \(\alpha = 0.05\). All analyses were done with Prism version 3.02.

### Role of the funding source

The sponsors of the study had no role in the design of the study and interview questions, data collection, data analysis, data interpretation, writing, or revising of the report. The corresponding author had full access to all the data in the study, and had the final responsibility to submit the report for publication.

### Results

The MHRA specified that between two and four patients should be first treated for a maximum of 4 h. After successful and safe completion of this phase, treatment time could be extended up to a maximum of 8 h. Thus, the mean treatment time was 6.4 (SD 2.0) h (table 1). Before treatment, the mean serum urea concentration was 15.2 (SD 3.7) mmol/L, that of creatinine 622 (214) μmol/L, and that of glucose 3.8 (0.7) mmol/L. One patient with

![Table 1: Characteristics of patients](image-url)
diabetes had taken oral hypoglycaemic agents before treatment; no patients became hypoglycaemic during the study.

Mean bodyweight was lower after treatment than before treatment (p=0·01, paired t test), as was the ratio of extracellular to total body fluid (p=0·0019, paired t test; table 1). Although fluid removal to achieve target postdialysis weights was not an objective of this study, fluid was successfully removed without any adverse effect on cardiovascular measurements (data not shown).

During treatment, the mean blood flow was 58·6 (11·7) mL/min, with a dialysate flow of 47·1 (7·8) mL/min. Plasma clearance rates of urea and creatinine, as well as hourly standard urea clearance (Kt/V), are shown in table 1. Concentrations of serum electrolytes remained essentially stable during treatment (table 2), and there was no change in pH, and only a slight fall in bicarbonate levels after 4 h. Ammonia was not detected in the dialysate circuit at any time.

Blood pressure and heart rate remained stable during the study (table 2). Similarly, no patient was seen to desaturate or have any cardiac dysrhythmia during cardiac and pulse oximetry monitoring (data not shown). No changes were seen in the cardiac cycle when ECGs were done (data not shown). No significant changes in indicators of haemolysis were seen (table 2).

Bubbles of carbon dioxide, known to be released as a result of the decomposition of urea by urease in the sorbents cartridge, accumulated in the dialysate circuit from time to time during the study, creating technical difficulties with the dialysate flow. However, in no case did this lead to treatment discontinuation. One patient had clotting of her central venous access catheter, when the activated partial thromboplastin time fell to 45 s (normal 26–36 s); this patient discontinued treatment after 7 h. Another patient had clotting of the circuit at 4 h, when he was scheduled to discontinue the study, presumably because the activated partial thromboplastin time had been allowed to fall to ensure that there was no bleeding when the dialysis needles were removed. One patient suffered a temporary disconnection when one of his fistula needles became dislodged. Safety mechanisms within the artificial kidney ensured that the blood pump stopped when the needle was dislodged. The needle was reinserted quickly and treatment continued with no sequelae.

All patients were pleased with the treatment, and had no complaints (figure 2). They stated unanimously that they would recommend this device to other patients. Five patients who attempted to sleep during the study were able to do so without difficulty. Patient feedback also indicated that the median time to recover after treatment was 0 (range 0–1) min.

### Discussion

One of the key functions of an artificial haemodialysis device is to remove fluid gained in the interval between dialysis treatments. Although our objective was not to return a patient to their postdialysis target weight, we were able to remove fluid successfully during treatment without any adverse changes in cardiovascular variables and despite patients being encouraged to eat and drink while being treated. The wearable haemodialysis device is designed to be worn for lengthy periods every day, or potentially at all times. As such, the hourly volume of fluid gain needs to be considered.

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**Table 2: Electrolyte, acid-base changes, and markers of haemolysis and cardiovascular stability**

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>2</th>
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<th>6</th>
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<tr>
<td><strong>Serum electrolytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na (mmol/L)</td>
<td>133 (±7)</td>
<td>134 (±5)</td>
<td>135 (±3)</td>
<td>135 (±2)</td>
<td>135 (±2)</td>
</tr>
<tr>
<td>K (mmol/L)</td>
<td>4·2 (±3)</td>
<td>4·4 (±0·5)</td>
<td>4·1 (±0·3)</td>
<td>4·1 (±0·5)</td>
<td>4·1 (±0·5)</td>
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<tr>
<td>iCa (mmol/L)</td>
<td>1·1 (0·9)</td>
<td>1·11 (0·1)</td>
<td>1·13 (0·1)</td>
<td>1·14 (0·1)</td>
<td>1·11 (0·1)</td>
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<td><strong>Acid-base balance</strong></td>
<td></td>
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</tr>
<tr>
<td>pH</td>
<td>7·35 (±0·1)</td>
<td>7·35 (±0·06)</td>
<td>7·35 (±0·07)</td>
<td>7·33 (±0·05)</td>
<td>7·36 (±0·05)</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>24·9 (±3·7)</td>
<td>23·3 (±3·2)</td>
<td>22·2 (±2·8)</td>
<td>22·1 (±2·4)</td>
<td>22·0 (±3·3)</td>
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<td><strong>Markers of haemolysis</strong></td>
<td></td>
<td></td>
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<tr>
<td>Haematocrit (%)</td>
<td>0·358 (±0·03)</td>
<td>0·34 (±0·04)</td>
<td>0·358 (±0·03)</td>
<td>0·345 (±0·04)</td>
<td>0·35 (±0·04)</td>
</tr>
<tr>
<td>Serum haptoglobin (g/L)</td>
<td>1·29 (±0·8)</td>
<td>1·39 (±0·7)</td>
<td>1·20 (±0·8)</td>
<td>0·80 (±0·5)</td>
<td>0·85 (±0·5)</td>
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<tr>
<td>LDH (U/L)</td>
<td>307 (±145)</td>
<td>345 (±146)</td>
<td>381 (±93)</td>
<td>240 (±149)</td>
<td>353 (±39)</td>
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<td><strong>Cardiovascular measurements</strong></td>
<td></td>
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</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>139 (±28)</td>
<td>138 (±29)</td>
<td>137 (±35)</td>
<td>142 (±30)</td>
<td>153 (±12·5)*</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>86 (±20)</td>
<td>85 (±17)</td>
<td>85 (±18)</td>
<td>85 (±19)</td>
<td>96 (±13)*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>66 (±12)</td>
<td>64 (±9)</td>
<td>67 (±10)</td>
<td>66 (±6)</td>
<td>70 (±10)</td>
</tr>
</tbody>
</table>

Data are mean (SD). DBP=diastolic blood pressure, iCa=serum ionised calcium, K=serum potassium, LDH=lactate dehydrogenase, Na=serum sodium, SBP=systolic blood pressure. *One patient, with an SBP of about 80 mm Hg, did not contribute to 8 h blood pressure measurements because of circuit clotting.

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**Figure 2: A patient wearing the haemodialysis device**
fluid removed during a treatment should be much less than that during standard intermittent haemodialysis, which takes place three times a week. Since the risk of hypotenosis during dialysis treatments is mainly caused by the rate of ultrafiltration, we anticipate that a wearable haemodialysis device could provide greater cardiovascular stability than does standard haemodialysis.11

Blood and dialysate flow rates were much lower than were those achieved in conventional haemodialysis, as were the clearance rates for urea and creatinine. However, if we assume that the hourly clearance rate of urea reported here is adequate for treatment,16 and assume that there is a linear relation between this hourly clearance rate and time, extrapolation of our results suggest that, if this treatment could be done every day, then it might prove to be more efficient than could conventional haemodialysis.15,16 Clearances could be increased by increasing blood or dialysate flows, or both.

There were no adverse changes in the concentrations of serum electrolytes or in serum pH. The concentration of bicarbonate in the serum was slightly lower after 4 h than at baseline, but stayed constant thereafter. Further trials will be required to determine the optimum bicarbonate composition of the dialysate. Bicarbonate measurements can be affected by air contamination in the sample tube and by delays in laboratory analysis. There were no significant changes in haematocrit, serum haptoglobin, or lactate dehydrogenase concentrations, suggesting that there had been no clinically significant haemolysis during treatment.

Low-grade haemolysis often occurs during routine haemodialysis, due to flow through the vascular access and mechanical pressure generated by the standard roller pumps.7

Bubbles of carbon dioxide were noted in the dialysate compartment of the circuit during treatment, but not in the blood compartment. Carbon dioxide is known to form in the sorbents column, the result of the breakdown of urea by urease. This problem is not insurmountable, but will have to be resolved before larger scale trials of the device. This could be achieved either by disposing of or by dissolving the excess carbon dioxide, or by using new sorbent technology. Other workers are also trying to use nanotechnology to develop a wearable, or implantable haemodialysis device without requiring a dialysate.6

In two cases, clotting occurred in the patients’ vascular access; in both cases, the patients were not receiving adequate anticoagulants at the time. Thus for the wearable artificial kidney to be successful, patients require anticoagulation. We used unfractionated heparin as the anticoagulant, although other agents might be advantageous in the future. Anticoagulation requirements could be reduced by introducing heparin bonding, and some of the newer, longer acting synthetic heparinoids and direct thrombin inhibitors could prove better than standard heparin. However, in the cases when clotting occurred, the safety mechanisms engaged and stopped the blood pump. One patient had a temporary disconnection from the haemodialysis device when a needle became dislodged; again, the in-built safety mechanisms stopped the blood pump. From the patients’ perspective, there were no adverse effects, and all would recommend the treatment to other patients with end-stage renal failure. The reported time taken to recover after completion of the treatment—less than a minute—was considerably shorter than it was with standard haemodialysis, after which many patients feel unwell and take hours to recover.7

Larger trials of this device are needed to confirm the safety and efficacy of the treatment. In terms of future development, and to achieve greater efficacy, the wearable haemodialysis device needs to be worn continuously, or for extended periods every day to increase flows and therefore clearance rates. The device has the potential to become a practical means of delivering extended and more frequent dialysis to patients with end-stage kidney failure.

Contributors
The wearable artificial kidney was designed and developed by VG. The study project was designed by AD with advice from VG and CR. The study was done by AD, VG, MB, CE, and ER. First drafts were written by AD and VG, and were criticised by MB, CE, and CR. All authors saw and approved the final draft of the manuscript.

Conflict of interest statement
AD has no conflict of interest to declare. VG is a director of Xcorporeal Inc, and is their chief medical and scientific officer. MB and CE are employees of Xcorporeal and have been promised stock options. ER is a research scientist at BioQuantetics Inc, and has no other conflict of interest to declare. CR has no conflict of interest to declare.

Acknowledgments
We thank Sunita Hansraj and the nursing staff of the renal day ward at the Royal Free Hospital, and Michael Thomas and Chris Bunn at the Royal Free Hospital. Hans Pollaschegg provided expert advice during the study and reviewed parts of the manuscript. Funding for the study was provided by Xcorporeal and the special trustees of the Royal Free Hospital.

References


13 Twardowski ZJ. Treatment time and ultrafiltration rate are more important in dialysis prescription than small molecule clearance. Blood Purif 2007; 25: 90–98.


Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib

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Summary

Background Sunitinib, a multitargeted tyrosine-kinase inhibitor, which is approved by both US and European Commission regulatory agencies for clinical use, extends survival of patients with metastatic renal-cell carcinoma and gastrointestinal stromal tumours, but concerns have arisen about its cardiac safety. We therefore assessed the cardiovascular risk associated with sunitinib in patients with metastatic gastrointestinal stromal tumours.

Methods We retrospectively reviewed all cardiovascular events in 75 patients with imatinib-resistant, metastatic, gastrointestinal stromal tumours who had been enrolled in a phase I/II trial investigating the efficacy of sunitinib. The composite cardiovascular endpoint was cardiac death, myocardial infarction, and congestive heart failure. We also examined sunitinib’s effects on left ventricular ejection fraction (LVEF) and blood pressure. We investigated potential mechanisms of sunitinib-associated cardiac effects by studies in isolated rat cardiomyocytes and in mice.

Findings Eight of 75 (11%) patients given repeating cycles of sunitinib in the phase I/II trial had a cardiovascular event, with congestive heart failure recorded in six of 75 (8%). Ten of 36 (28%) patients treated at the approved sunitinib dose had absolute LVEF reductions in ejection fraction (EF) of at least 10%, and seven of 36 (19%) had LVEF reductions of 15 EF% or more. Sunitinib induced increases in mean systolic and diastolic blood pressure, and 35 of 75 (47%) individuals developed hypertension (>150/100 mm Hg). Congestive heart failure and left ventricular dysfunction generally responded to sunitinib being withheld and institution of medical management. Sunitinib caused mitochondrial injury and cardiomyocyte apoptosis in mice and in cultured rat cardiomyocytes.

Interpretation Left ventricular dysfunction might be due, in part, to direct cardiomyocyte toxicity, exacerbated by hypertension. Patients treated with sunitinib should be closely monitored for hypertension and LVEF reduction, especially those with a history of coronary artery disease or cardiac risk factors.

Introduction Small-molecule inhibitors, designed to inhibit tyrosine kinases that are mutated or are overexpressed in cancer cells, have improved the management of cancers such as chronic myeloid leukaemia, renal-cell carcinoma, and gastrointestinal stromal tumours.1 This targeted approach has resulted in improved antitumour activity with fewer toxic effects than traditional chemotherapies for many patients. However, tyrosine-kinase inhibitors also inhibit normal variants of tyrosine kinases in non-cancerous cells, which can lead to unexpected toxicities, including cardiotoxic effects.2–5 Tyrosine-kinase inhibitor-related cardiac dysfunction can be difficult to recognise in early clinical trials.6–* Furthermore, symptoms of congestive heart failure are often non-specific and can be wrongly attributed to malignant disease alone.

Sunitinib (Sutent, Pfizer, New York, NY, USA) is a US Food and Drug Administration-approved and European Union-approved, multitargeted tyrosine-kinase inhibitor that extends survival in patients with gastrointestinal stromal tumours or renal-cell carcinoma.6–12 Its targets include vascular endothelial-cell growth-factor receptors 1–3, platelet-derived growth-factor receptors α and β, FMS-like tyrosine kinase-3, KIT (stem-cell factor receptor), colony-stimulating factor-1 receptor, and the product of the human RET gene.13–17 Sunitinib is being assessed for activity in more than 25 different tumour types in more than 120 registered clinical trials, enrolling about 20 000 patients.18

Most of our knowledge of the cardiac effects of sunitinib comes from cancer efficacy trials that assessed overall safety.18–12,18–19 Although two cases of congestive heart failure were reported in a phase I study,19 Demetri and co-workers12 reported no systematic mean reduction in left ventricular ejection fraction (LVEF) in a phase III clinical trial in patients with gastrointestinal stromal tumours. Motzer and colleagues19 reported modest reductions in LVEF without clinical sequelae in renal-cell carcinoma patients. Although this study hinted at the potential for cardiotoxic effects, the absence of studies designed mainly to assess sunitinib-associated cardiovascular dysfunction leaves many questions about potential cardiotoxic effects unanswered. Our aims were therefore to review cardiac adverse events in patients with imatinib-resistant, metastatic, gastrointestinal stromal tumours on sunitinib. We also aimed to establish the mode of action of sunitinib in mouse models and cardiac myocyte cultures.
Methods

Patients

Between April, 2002 and June, 2004, 97 patients with imatinib-resistant, gastrointestinal stromal tumours were given repeating cycles of sunitinib as part of an open-label, single-arm, dose-escalation phase I/II trial at the Dana-Farber Cancer Institute, Massachusetts General Hospital, and Memorial Sloan-Kettering Cancer Center to assess drug efficacy and tolerability. A total of 75 patients (51 [68%] men, mean age 54.3 [SD 11–5] years) were enrolled at the Dana-Farber Cancer Institute and formed the cohort of our cardiovascular study. Patients had detailed baseline examinations and had follow-up visits every week with the Dana-Farber Cancer Institute oncology team during the trial. Longitudinal cardiac surveillance—including serial assessment of LVEF in each treatment cycle by radionuclide ventriculography—and blood pressure and troponin I measurements every week were instituted on Oct 22, 2002. Brain natriuretic peptide concentrations were not routinely monitored. The study was approved by the Dana-Farber Cancer Institute Institutional Review Board and done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

Cardiovascular review

Three cardiovascular specialists (MAR, TF, and MHC) developed endpoint definitions as guidelines to adjudicate cardiovascular events, using the standard cardiac criteria outlined below. On the basis of Fiedler and colleagues’ preliminary data, cardiovascular events of interest were defined as congestive heart failure and myocardial infarction. The electronic medical records—including serial assessment of LVEF in each treatment cycle by radionuclide ventriculography—and blood pressure and troponin I measurements every week were reviewed by TFC, MAR, and MHC. All deaths and potential non-fatal cardiovascular events were identified. Before the start of our study, oncologists at the Dana-Farber Cancer Institute adjudicated all deaths as either cardiovascular or non-cardiovascular. Because of the complex comorbidities of our patient population, we classified cause of death as cardiovascular only when there was concordance between oncology and cardiology reviewers.

Patients were classified as having congestive heart failure if they had: (1) documented symptoms or signs, or both, of congestive heart failure (ie, dyspnoea on exertion, orthopnoea, paroxysmal nocturnal dyspnoea, jugular venous distension, or pedal oedema); (2) reduction of LVEF to less than the lowest limits of normal (ejection fraction [EF] <50%); and (3) chest radiograph showing pulmonary oedema or symptomatic response in response to congestive heart failure therapy (ie, diuretics, angiotensin-converting enzyme inhibitors, or β blockers). Patients were classified as having myocardial infarction if their care providers diagnosed myocardial infarction on the basis of a typical increase in concentration of cardiac biomarkers (ie, troponin I >0·10 ng/mL) associated with clinical symptoms (ie, chest pain) and specific electrocardiographic changes. Asymptomatic increases in troponin I concentrations without electrocardiographic changes or without deterioration in LVEF were not regarded as myocardial infarction and were therefore tallied separately.

Patient studies

LVEF assessment was available for each cycle in all patients after institution of routine LVEF monitoring in October, 2002 (n=65). Ten patients went off study protocol before routine LVEF monitoring. All patients had their blood pressure measured at baseline and then every week during clinic visits. We analysed serial LVEF and blood pressure data for the subset of 36 patients (22 [61%] men, mean age 56.1 [SD 10·1] years) enrolled on the approved sunitinib dosing schedule. All 36 patients had baseline and serial LVEF assessment for each cycle of sunitinib.
administration. Patients received repeating cycles of sunitinib 50 mg per day for 4 weeks followed by 2 weeks of no treatment (50 mg per day, 4 weeks on and 2 weeks off). Data were obtained for cycles one to four (24 weeks), after which more than 50% of patients had been started on β blockers or angiotensin-converting enzyme inhibitors, or both, for hypertension control, which confounded our ability to quantify sunitinib-associated effects on LVEF and blood pressure. Baseline and serial LVEF assessments by radionuclide ventriculography were done at one centre (Dana-Farber Cancer Institute) on the last day of drug administration in every one of the first four cycles, and every other cycle thereafter. Interstudy variability of LVEF by radionuclide ventriculography at Dana-Farber Cancer Institute was 2–3 EF%. In accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3·0),21 hypertension was defined as systolic blood pressure greater than 150 mm Hg or as diastolic blood pressure greater than 100 mm Hg. We also assessed the effect of sunitinib at the cellular level by microscopy of endomyocardial biopsy samples from two index patients who developed congestive heart failure and left ventricular systolic dysfunction.

Mechanistic studies
Mechanisms of sunitinib-associated cardiotoxic effects were examined by: (1) functional and haemodynamic studies in mice given sunitinib; (2) transmission electronmicroscopy studies of mouse cardiac tissue; and (3) incubation of neonatal rat ventricular myocytes (cardiomyocytes) with sunitinib. Methods for these studies are presented in the webappendix.

Statistical analysis
Cardiovascular death, myocardial infarction, and congestive heart failure were used as the composite cardiovascular endpoint. Pretreatment variables assessed by univariate analysis included age, sex, history of anthracycline exposure, history of coronary artery disease, history of hypertension, β-blocker use, or angiotensin-converting enzyme inhibitor use.

Repeated-measures, mixed-model regression analysis was applied to assess LVEF at baseline and after every one of the first four cycles of sunitinib with 95% CIs for mean LVEF after each cycle. The covariance structure that best fitted the longitudinal data according to Akaike’s information criterion was compound symmetry, which fitted the longitudinal data according to Akaike’s information criterion was compound symmetry, which we used to model the data.22 Fisher’s exact test (binary variables), t test (continuous variables), and Mann-Whitney U test (non-Gaussian data) were used to compare baseline patient characteristics of the total cohort with the subgroup given the approved sunitinib dose.

Role of the funding source
The cardiovascular study was designed by MHC in collaboration with her academic colleagues. This investigation did not have a separate industry funding. The sponsors of the clinical trial had no role in the cardiovascular 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
Table 1 shows baseline characteristics for the entire cohort. All patients discontinued imatinib or other systemic anticancer agents at least 2 weeks before starting sunitinib. All had a baseline LVEF of 50 EF% or more and none had a history of congestive heart failure. Four patients had a history of coronary artery disease (mean baseline LVEF 56 [SD 4] EF%), but were without symptoms for at least 1 year before enrolment. Patients received sunitinib at or below the eventual approved dose of 50 mg per day, 4 weeks on and 2 weeks off, with the exception of four patients. These patients received 1–2 weeks of sunitinib 75 mg per day, before the dose was reduced to 50 mg per day, 2 weeks on and 2 weeks off. Median time in the study was 33–6 weeks (range 3–3–112·4 weeks). Of the 75 patients, 36 (48%) went

### Table 2: Rate of cardiovascular and fatal events

<table>
<thead>
<tr>
<th>Event</th>
<th>Total</th>
<th>Number of patients</th>
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</thead>
<tbody>
<tr>
<td>Death from any cause</td>
<td>10(13%)</td>
<td>10</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>1(1%)</td>
<td>1</td>
</tr>
<tr>
<td>Death from non-cardiovascular causes</td>
<td>9(12%)</td>
<td>9</td>
</tr>
<tr>
<td>Non-fatal cardiovascular events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1(1%)</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>6(8%)</td>
<td>6</td>
</tr>
</tbody>
</table>

### Table 3: Rate of left ventricular ejection fraction (LVEF) less than lower limits of normal, increased troponin concentration, and hypertension

<table>
<thead>
<tr>
<th>Event</th>
<th>Total</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (&lt;50%)</td>
<td>13(20%)</td>
<td>13</td>
</tr>
<tr>
<td>Increased troponin (&gt;0.10 μg/mL)</td>
<td>12(18%)</td>
<td>12</td>
</tr>
<tr>
<td>Hypertension (&gt;150/100 mm Hg)</td>
<td>35(47%)</td>
<td>35</td>
</tr>
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</table>

### Table 4: Predictors of cardiovascular events: univariate associations based on logistic regression analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>1.04</td>
<td>0.97–1.11</td>
<td>0.30</td>
<td>1.06</td>
<td>0.97–1.14</td>
<td>0.17</td>
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<tr>
<td>Sex</td>
<td>0.43</td>
<td>0.10–1.87</td>
<td>0.26</td>
<td>0.44</td>
<td>0.08–2.35</td>
<td>0.34</td>
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<tr>
<td>Anthracycline</td>
<td>1.38</td>
<td>0.25–7.66</td>
<td>0.72</td>
<td>0.79</td>
<td>0.09–7.18</td>
<td>0.83</td>
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<tr>
<td>Coronary artery disease</td>
<td>3.60</td>
<td>1.46–6.43</td>
<td>0.003*</td>
<td>1.75</td>
<td>1.05–2.92</td>
<td>0.03*</td>
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<tr>
<td>Hypertension</td>
<td>4.90</td>
<td>1.06–22.71</td>
<td>0.038*</td>
<td>2.63</td>
<td>0.49–14.19</td>
<td>0.27</td>
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<tr>
<td>β blocker</td>
<td>5.14</td>
<td>0.99–26.3</td>
<td>0.06</td>
<td>1.33</td>
<td>0.14–12.76</td>
<td>0.81</td>
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<tr>
<td>ACEI</td>
<td>0.01</td>
<td>0.00–0.04</td>
<td>0.23</td>
<td>0.00</td>
<td>0.00–0.00</td>
<td>0.93</td>
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</table>

Composite cardiac endpoint=cardiovascular death, myocardial infarction, and congestive heart failure. ND=upper limit of 95% CI is not determinable because none of the six patients taking angiotensin-converting enzyme inhibitors (ACEIs) at baseline had a cardiac event. *Statistically significant univariate predictor.
off study secondary to disease progression; 29 (39%) were transferred to the sunitinib continuation protocol; ten (13%) died within 30 days of their last sunitinib dose, generally as a result of progression of malignant disease, and were regarded as deaths during study.

Eight of 75 (11%) patients had a cardiovascular (fatal or non-fatal) event during the trial (table 2). Cardiac-associated death occurred 5 days after palliative debulking surgery. The patient needed substantial blood product support complicated by multiorgan failure, including myocardial infarction, pulmonary oedema, and cardiovascular changes. Another patient with a history of coronary artery disease had a non-fatal, non-ST-segment elevation myocardial infarction. All six patients with New York Heart Association class III–IV congestive heart failure were being given the approved or lower dose of sunitinib at the time of the event. One patient had received one cycle of 75 mg per day, 2 weeks on and 2 weeks off, followed by 81 weeks of 50 mg per day, 2 weeks on and 2 weeks off, before development of congestive heart failure. Clinical details of patients with congestive heart failure are provided in webtable 1. The median time to a cardiovascular event was 30·5 weeks (range 10·7–84·9 weeks).

Troponin I concentrations for every week were available in 68 patients (seven patients were enrolled before routine troponin I monitoring). In the 12 patients with abnormal increases in troponin I concentrations (table 3), most increases were modest (mean 0·74 [SD 0·98] ng/mL, normal limit <0·10 ng/mL). Whether these increases can serve as a biomarker of sunitinib-associated myocardial injury, as has been shown for anthracyclines, is still being assessed. Almost half the patients in the entire cohort developed hypertension (table 3).

The only significant univariate associations for the composite cardiovascular endpoint of cardiovascular death, myocardial infarction, and congestive heart failure were history of hypertension and history of coronary artery disease (table 4). Three of four (75%) patients with a history of coronary artery disease had a cardiovascular event versus five of 71 (7%) without coronary artery disease. Multivariable logistic regression analysis suggested that history of coronary artery disease was the only significant independent predictor (adjusted odds ratio 39·60, 95% CI 3·46–453·85, p=0·0004) of a cardiovascular event.

The only significant univariate association for predictors of congestive heart failure was history of coronary artery disease (table 4). Two of four (50%) patients with coronary artery disease developed heart failure compared with four of 71 (6%) patients without coronary artery disease. Multivariate logistic regression analysis suggested that coronary artery disease was the only significant independent predictor (16·8, 1·9–152, 0·012) of congestive heart failure.

Baseline characteristics of 36 patients given sunitinib at the approved dose of 50 mg per day, 4 weeks on and 2 weeks off, is shown for all 36 patients. Three patients had no change in LVEF from baseline and are represented without bars.

Figure 1: Absolute maximum change in left ventricular ejection fraction (LVEF) from baseline in individual patients given the approved sunitinib dose

Individual data for absolute maximum change in LVEF from baseline to treatment with sunitinib 50 mg per day, 4 weeks on and 2 weeks off, is shown for all 36 patients. Three patients had no change in LVEF from baseline and are represented without bars.

Figure 2: Model of predicted change in mean left ventricular ejection fraction (LVEF) by treatment cycle

Repeated measures, mixed-model regression analysis of LVEF data derived from 36 patients during first four cycles of sunitinib treatment. An increase in number of sunitinib cycles was associated with a progressive reduction. The model predicted an initial 2% reduction from baseline, followed by 1·5% reduction per cycle for each subsequent cycle. Predicted LVEF at baseline was 64·5%; after cycle 1, 62·4%; after cycle 2, 62·3%; after cycle 3, 60·6%; and after cycle 4, 59·4%. *p=0·048 (cycle 1); †p=0·044 (cycle 2); ‡p=0·013 (cycle 3); and §p=0·007 (cycle 4). Vertical bars represent SE.

Table 1: Absolute ejection fraction change from baseline (EF%)

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<tr>
<td>Patients (n=36)</td>
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Figure 3: Absolute maximum change in left ventricular ejection fraction (LVEF) from baseline in individual patients given the approved sunitinib dose

Individual data for absolute maximum change in LVEF from baseline to treatment with sunitinib 50 mg per day, 4 weeks on and 2 weeks off, is shown for all 36 patients. Three patients had no change in LVEF from baseline and are represented without bars.

Figure 4: Model of predicted change in mean left ventricular ejection fraction (LVEF) by treatment cycle

Repeated measures, mixed-model regression analysis of LVEF data derived from 36 patients during first four cycles of sunitinib treatment. An increase in number of sunitinib cycles was associated with a progressive reduction. The model predicted an initial 2% reduction from baseline, followed by 1·5% reduction per cycle for each subsequent cycle. Predicted LVEF at baseline was 64·5%; after cycle 1, 62·4%; after cycle 2, 62·3%; after cycle 3, 60·6%; and after cycle 4, 59·4%. *p=0·048 (cycle 1); †p=0·044 (cycle 2); ‡p=0·013 (cycle 3); and §p=0·007 (cycle 4). Vertical bars represent SE.
York Heart Association class III–IV heart failure.22 Most had an LVEF reduction from baseline on sunitinib (figure 1). Two (6%) had reductions in LVEF of at least 20 EF% and seven (19%) at least 15 EF%. Four (11%) developed either congestive heart failure or LVEF reductions of at least 20 EF% to less than 50 EF%. Assessment of mean LVEF change by cycle for all patients and comparison with baseline showed a significant drop after every one of four cycles (figure 2). Mean reduction during the four cycles was 5 EF%.

Sunitinib induced significant increases in blood pressure in the total cohort within the first 4 weeks of cycle 1 (mean increase in systolic blood pressure 21 [SD 15] mm Hg and in diastolic blood pressure 14 [SD 10] mm Hg) (figure 3). During sunitinib treatment, the mean maximum increase in systolic blood pressure was 30 (SD 15) mm Hg and in diastolic blood pressure was 17 (SD 12) mm Hg. 17 of 36 (47%) patients given sunitinib at 50 mg per day, 4 weeks on and 2 weeks off, developed systolic blood pressure greater than 150 mm Hg or diastolic blood pressure greater than 100 mm Hg, or both, by cycle four. Grade-III hypertension (defined as a need for more than one drug or more intensive therapy than before) occurred in six of 36 (17%) patients (figure 4) by cycle three.23 Even with half the cohort being given angiotensin-converting enzyme inhibitors or β blockers for hypertension by the end of cycle four, mean systolic blood pressure and diastolic blood pressure for the group remained above baseline (figure 3). Furthermore, mean LVEF continued to decrease despite the initiation of angiotensin-converting enzyme inhibitors or β blockers.

Concentrations of serum electrolytes, including phosphorous and calcium, were monitored in all patients every 2 weeks and repeated as necessary. Hypocalcaemia and hypophosphataemia were not present in the patients with congestive heart failure or LVEF less than the lower limits of normal (<50 EF%), and thus were not believed to contribute to cardiac dysfunction. Thyroid-stimulating hormone concentrations were available for 67 of 75 patients. Routine monitoring of thyroid function at baseline and at the start of each treatment cycle was initiated in all patients enrolled after October, 2002 (n=53).24 Thyroid-stimulating hormone supplemen-
tation was initiated as needed. We compared the mean maximum increase in systolic blood pressure with congestive heart failure or LVEF less than the lower limits of normal (<50 EF%), and thus were not believed to contribute to cardiac dysfunction. Thyroid-stimulating hormone concentrations were available for 67 of 75 patients. Routine monitoring of thyroid function at baseline and at the start of each treatment cycle was initiated in all patients enrolled after October, 2002 (n=53).24 Thyroid-stimulating hormone supplementation was initiated as needed. We compared the mean maximum increase in systolic blood pressure with congestive heart failure or LVEF less than the lower limits of normal (<50 EF%), and thus were not believed to contribute to cardiac dysfunction.

Cardiomyocyte hypertrophy was present on light microscopy of endomyocardial biopsy samples obtained from two index patients who developed congestive heart failure and left ventricular systolic dysfunction on sunitinib (figure 5). Transmission electronmicroscopy showed aberrantly shaped, swollen mitochondria with effaced cristae and membrane whorls. No inflammation, oedema, or fibrosis was seen (figure 5).

Direct cardiotoxicity of sunitinib was examined in animals. Mice given sunitinib 40 mg/kg per day, a dose that produced blood concentrations comparable with

![Figure 3: Effect of sunitinib 50 mg, 4 weeks on and 2 weeks off, on blood pressure in 26 patients](https://www.thelancet.com/)

Changes in mean systolic and diastolic blood pressure during the first four cycles of sunitinib. Systolic blood pressure and diastolic blood pressure had increased from baseline by the first cycle, and remained increased through cycle four.

![Figure 4: Effect of sunitinib 50 mg, 4 weeks on and 2 weeks off, on hypertension](https://www.thelancet.com/)

Cumulative percentage of patients diagnosed with hypertension and on antihypertensive medication during first four cycles (24 weeks) of sunitinib (n=36). Hypertension was defined as >150 mm Hg systolic or >100 mm Hg diastolic blood pressure, or both. Grade-III hypertension denoted patients who needed more than one antihypertensive medication or who needed an increase in antihypertensive medication (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0), prescribed at the discretion of patient’s physician. By cycle 4, almost half the cohort developed hypertension, and 50% of patients were on antihypertensive medication.
those in patients, had striking abnormalities of cardiomyocytes (mitochondrial swelling and degenerative changes, including membrane whorls and effaced cristae [figure 6]) on transmission electronmicroscopy. Sunitinib also targeted mitochondria in cultured rat cardiomyocytes, leading to cytochrome-C release into the cytosol (figure 6). Cytochrome-C release can activate the mitochondrial pathway for cell death or apoptosis, and, consistent with this mechanism, sunitinib led to activation of caspase-9, an initiator caspase of the mitochondrial apoptotic pathway (figure 7). Sunitinib induced cardiomyocyte apoptosis, as assessed by terminal deoxynucleotidyl transferase-mediated deoxyuridine 5-triphosphate nick end labelling (figure 7).

Although mitochondrial damage in cardiomyocytes was induced by sunitinib in vivo and in vitro, apoptosis was not increased in hearts of sunitinib-treated mice (data not shown). By contrast with patients, however, sunitinib did not induce blood pressure increases in mice at doses given. Therefore, to study the effect of interaction of sunitinib treatment and hypertension on cardiac changes, we gave mice sunitinib for 2 weeks and added the α-adrenergic agent phenylephrine, during the second week, to mimic the blood pressure increases seen in sunitinib-treated patients. Systolic blood pressure increased from normal values of 90–100 mm Hg to 127 (SD 24) mm Hg in mice given sunitinib plus phenylephrine, and to 132 (SD 14) mm Hg in mice given

Figure 5: Endomyocardial biopsy samples from two index patients who developed congestive heart failure on sunitinib

Representative light photomicrographs from patients A and B (top panels) showed cardiomyocyte hypertrophy with mild degenerative changes and diffuse, moderate myocyte vacuolisation (arrows). There was no oedema, interstitial or replacement fibrosis, regional infarct or focal cell necrosis, or myocarditis, or inflammation. Transmission electronmicrograph from patient A (bottom left) showed swollen, abnormal mitochondrial configurations (arrow) with effaced cristae. Transmission electronmicrograph from patient B (bottom right) showed abundant cytoplasmic granular densities consistent with glycogen accumulation (G), membrane whorl (arrow), and lysosomal precipitates (arrowhead). Sarcomeres (S) appeared well organised and structurally normal in both patients. (Light microscopy, stained with haematoxylin and eosin, bar=25 µm; transmission electronmicroscopy, bar=1 µm.)

Figure 6: Effect of sunitinib on cardiac structure, mitochondrial function, and apoptosis

(A) Transmission electronmicroscopy of cardiac tissue from mice given control (left panel) or sunitinib (centre and right panels) at 40 mg/kg per day for 12 days. Images from mice given sunitinib were notable for swollen mitochondria with disrupted cristae (M). Increased magnification image (right panel) showed membrane whorls (arrow) within the mitochondria of myocytes from mice given sunitinib. (B) Cytochrome-C release from mitochondria induced by sunitinib in neonatal rat ventricular myocytes (NRVMs) in culture. NRVMs were incubated in media (control) or media containing sunitinib (1 µmol/L) for 30 h and 48 h. Cells were then stained for cytochrome C. The punctate staining in the control is consistent with mitochondrial-localised cytochrome C, whereas the diffuse staining in the sunitinib-treated cells represents release of cytochrome C from the mitochondria into the cytosol.
 Discussion

The principal finding of our study was that 11% of 75 patients with imatinib-resistant, metastatic, gastrointestinal stromal tumours given sunitinib for a median of 33.6 weeks developed cardiac adverse events. The most common event was New York Heart Association class III–IV congestive heart failure, which was reported in 8%. Analysis of patients given the approved sunitinib dose showed a steady reduction in LVEF during the first four cycles (24 weeks). Sunitinib also induced increases in blood pressure with almost half the patients developing hypertension. Additionally, sunitinib-associated cardiac dysfunction was associated in patients with abnormal histopathological changes, including myocyte hypertrophy and changes in mitochondrial structure without inflammatory or fibrotic changes.

By contrast with our findings, other multicentre phase III trials showed less cardiotoxicity with sunitinib. In a multicentre phase III, placebo-controlled, crossover trial, Demetri and colleagues did not report a reduction of mean LVEF in patients with imatinib-resistant, gastrointestinal stromal tumours who had been given the approved sunitinib dose. Our data showing sunitinib-associated LVEF reduction is supported, in part, by Motzer and colleagues, who reported a 10% rate of left ventricular systolic dysfunction in renal-cell carcinoma patients treated for a median of 6 months. However, only 2% of renal-cell carcinoma patients had grade-III reductions in LVEF (ie, to<40%) and none developed heart failure.

Differences in follow-up might partly explain the discrepancy between our findings and those of Demetri and colleagues. Their phase III trial was prematurely unblinded after a median of 10 weeks, when the first interim analysis showed improved survival with sunitinib. In our study, the median time to development of all cardiac adverse events was 30.5 weeks, with median time to onset of congestive heart failure at 33.4 weeks. Whether longer exposure to sunitinib might have allowed increased opportunity for patients to develop cardiovascular sequelae warrants investigation.

The divergent findings of Demetri and Motzer and their colleagues might be explained by differences in patient populations and in methods for obtaining data. Mortz and colleagues’ study excluded all patients who had received anticancer therapies. All our patients were previously given imatinib and 20% of 75 were also treated with an anthracycline, which might have contributed to the higher rate of sunitinib-associated congestive heart failure. Further investigation is warranted to assess the effects of previous anticancer drug therapy on cardiovascular susceptibility to sunitinib. However, our studies with mice and with cultured rat cardiomyocytes showed that sunitinib could be cardiotoxic in the absence of previous imatinib exposure, at least in these models. Finally, both phase III trials assessed LVEF by diverse non-invasive modalities (ie, echocardiography and radionuclide ventriculography) at different centres in several countries, which would result in larger measurement variability than with our study that used the same modality, imaging protocol, and interpretation team at a single centre.

Methodologies for assessment of cardiotoxicity differed between our study and these later phase III trials. Our retrospective cardiovascular-focused record review proved to be a sensitive approach for detection of cardiac adverse events in this population. Although forms for obtaining oncological trial data...
comprehensively capture patient symptoms, diagnoses such as congestive heart failure (that are made on the basis of symptom complexes within a clinical context) can be difficult to extract. The common triad of congestive heart failure symptoms—dyspnoea, fatigue, and peripheral oedema—are classified as respiratory, constitutional, and lymphatic/cardiovascular symptoms, respectively, making diagnosis of congestive heart failure difficult. A substantial proportion of patients with renal-cell carcinoma treated with sunitinib developed dyspnoea (15%), pitting peripheral oedema (11%), and fatigue (58%) (see prescribing information for sunitinib, 2007). Some of these symptoms could have been attributable to unrecognised heart failure.

The phase I/II study from which we derived our cardiovascular data included individuals with comorbidities (ie, coronary artery disease and hypertension), which might have predisposed our patient population to left ventricular dysfunction and congestive heart failure. Patients with uncontrolled hypertension were excluded from phase III trials. Now that sunitinib is approved, the treated patient population will probably include elderly adults with a history of coronary artery disease and other cardiac risk factors. Thus, we believe, our study, by contrast with phase III trials with more selective entry criteria than ours, might accurately represent the patient population that will receive sunitinib.

Our study was limited by the small patient cohort derived from a phase I/II clinical trial at one centre. The absence of a placebo group restricted our ability to measure the rate of congestive heart failure in patients with untreated gastrointestinal stromal tumours. The generalisability of findings from our protocol needs to be validated in larger, prospective, cardiovascular-focused studies in broader patient populations than that in our study. The sunitinib trials that are being done could provide an opportunity to define further the nature and rate of cardiac events with sunitinib.

Several angiogenesis inhibitors, including sunitinib, have proved to cause hypertension. The degree and rapid onset of hypertension associated with sunitinib in our study were unexpected, since phase III studies have shown a 15–24% rate of hypertension with sunitinib, compared with 47% (35 of 75 patients), that we recorded. The low rate of hypertension reported in phase III trials might have arisen because patients with uncontrolled hypertension were excluded at trial entry. Our patient population had their blood pressure monitored every week and, therefore, had an increased number of data points from which to assess the rate of hypertension. In view of our findings in the mouse suggesting that hypertension might play a part in myocardial injury and apoptosis, the contribution of hypertension to sunitinib-associated left ventricular dysfunction needs to be closely examined.

Left ventricular dysfunction and symptoms improved in five of six congestive heart failure patients after dose interruption, dose modification, or initiation of heart failure therapy, or both (webtable 1). Sunitinib was restarted in all five patients without recurrence of congestive heart failure. However, four patients had episodic LVEF reductions after restarting sunitinib. Whether restoration of normal left ventricular function represents true recovery at the cardiomyocyte level or it represents compensatory cardiac remodelling remains to be seen. Transmission electronmicrographs of patient endomyocardial biopsy samples and of mouse hearts, which showed mitochondrial injury with no apoptosis (at least in normotensive mice) and no replacement fibrosis, suggested potentially reversible injury. Indeed, some of the contractile dysfunction in patients might have resulted from impaired ATP generation secondary to mitochondrial dysfunction, and not from irreversible damage and myocyte loss. Identification of sunitinib-associated LVEF reduction would prompt medical intervention before the onset of symptomatic events (ie, congestive heart failure).

Our findings reveal evidence of sunitinib-associated heart failure, left ventricular systolic dysfunction, and hypertension in patients with imatinib-resistant, metastatic gastrointestinal stromal tumours. Cardiovascular adverse events were medically manageable in most patients. Close monitoring could be a prudent approach until large studies can clearly define the nature and rate of sunitinib-associated cardiovascular effects, especially in patients with cardiac risk factors, or history of coronary artery disease, or both. We need to define the most effective interventions for cardioprotection in these patients to avoid adverse cardiovascular events and enable uninterrupted, long-term sunitinib administration. Such understanding might guide clinical practice with other tyrosine-kinase inhibitors for which the range of cardiac effects are not yet fully known.

**Contributors**

TFC participated in clinical study design, clinical data collection and assembly, data analysis, and report writing. MAR participated in study design, data collection and analysis, supervision of mouse and cardiomyocyte studies designed and done by SMD with help from FC, EP, and NSI, and report writing. RK participated in study design, did mouse and cardiomyocyte studies done by RK, KW, and DMH, and participated in clinical data analysis and report writing. DZ participated in study design, statistical analysis, and report writing. LN participated in clinical data collection, assembly, review, and analysis. JD and SG participated in the initial conception of the study design, provision of study material and patients, and data collection and analysis. JAM participated in provision of study material and patients, and collection of clinical data. JHC assisted in pathology analysis under the supervision of FJS. AVD participated in clinical data collection and analysis. GDD was the principal investigator of the phase I/II trial and participated in study conception and design, provision of study material and patients, financial support, and report writing. MHC originally conceived and designed the cardiovascular study, collected and analysed the clinical data, assembled the clinical and basic teams, wrote the paper, and had oversight of the project.
Conflict of interest statement
JD has received speaker’s honoraria from Pfizer and has served as a consultant for Pfizer. SG has served as a consultant to Pfizer. GD has served as a consultant to Pfizer, Novartis, Bristol-Myers Squibb, Ariad, Johnson and Johnson, Genentech, Infinity Pharmaceuticals, ZymoGenetics, Alnylam, Idera, Bayer, and Serafino, is a member of the Scientific Advisory Board for Plexxikon and ZioPharm, and has received research support from Daiichi-Sankyo. TF has served on the Speakers Bureau for Schering-Plough and Dojime. The other authors declare that they have no conflict of interest.

Acknowledgments
TFC, LN, and MHC were supported by the Translational Research Fund for Cancer and Cardiology at Children’s Hospital Boston. MHC was also supported by a Swaim Across America Fellowship and the Long-Term Survivorship Grant from the Dana-Farber Cancer Center. The phase II trial of sunitinib efficacy was funded, in part, by Pfizer, and the cardiovascular study was funded by Department of Cardiology, Children’s Hospital Boston. This work was also supported by grants from the National Heart, Lung, and Blood Institute (HL61688 and HL67371 to TF) and grants from the Finnish Heart Foundation and the Finnish Cultural Foundation (to RK). MAR is supported by a grant from the National Heart, Lung, and Blood Institute, American Heart Association, and Thomas Smith Award. SMD is supported by National Institutes of Diabetes and Digestive and Kidney Diseases and David M Bray Scholars in Medicine Award. Grant support for this work was derived in part by philanthropic support from the following sources: the Virginia and Daniel K Ludwig Trust for Cancer Research, the Quick Family Fund for Cancer Research, the Stutman GIST Cancer Research Fund, and Leslie’s Links. We thank Joseph Loscalzo for his advice with this work and Elliott Antman for helpful comments in relation to the report. We appreciate the assistance of Mami Hirata and Elaine Monteiro in data collection. We would also like to thank Yung Chung and Shao Meng Chen for their support.

References
26 Osusky KL, Hallahan DE, Fu A, Ye F, Shyr Y, Geng L. The receptor tyrosine kinase inhibitor SU11248 impedes endothelial cell migration, tubule formation, and blood vessel formation in vivo, but has little effect on existing tumor vessels. Angiogenesis 2004; 7: 225–33.
Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study

QUASAR Collaborative Group*

Summary

Background The aim of the QUASAR trial was to determine the size and duration of any survival benefit from adjuvant chemotherapy for patients with colorectal cancer at low risk of recurrence, for whom the indication for such treatment is unclear.

Methods After apparently curative resections of colon or rectal cancer, 3239 patients (2963 [91%] with stage II [node negative] disease, 2291 [71%] with colon cancer, median age 63 [IQR 56–68] years) enrolled between May, 1994, and December, 2003, from 150 centres in 19 countries were randomly assigned to receive chemotherapy with fluorouracil and folinic acid (n=1622) or to observation (with chemotherapy considered on recurrence; n=1617). Chemotherapy was delivered as six 5-day courses every 4 weeks or as 30 once-weekly courses of intravenous fluorouracil (370 mg/m²) with high-dose (175 mg) L-folinic acid or low-dose (25 mg) L-folinic acid. Until 1997, levamisole (12 courses of 450 mg over 3 days repeated every 2 weeks) or placebo was added. After 1997, patients who were assigned to receive chemotherapy were given fluorouracil and low-dose folinic acid only. The primary outcome was all-cause mortality. Analyses were done by intention to treat. This trial is registered with the International Clinical Trial Registry, number ISRCTN82375386.

Findings At the time of analysis, 61 (3·8%) patients in the chemotherapy group and 50 (3·1%) in the observation group had missing follow-up. After a median follow-up of 5·5 (range 0·10–6) years, there were 311 deaths in the chemotherapy group and 370 in the observation group; the relative risk of death from any cause with chemotherapy versus observation alone was 0·82 (95% CI 0·70–0·95; p=0·008). There were 293 recurrences in the chemotherapy group and 359 in the observation group; the relative risk of recurrence with chemotherapy versus observation alone was 0·78 (0·67–0·91; p=0·001). Treatment efficacy did not differ significantly by tumour site, stage, sex, age, or chemotherapy schedule. Eight (0·5%) patients in the chemotherapy group and four (0·25%) in the observation group died from non-colorectal cancer causes within 30 weeks of randomisation; only one of these deaths was deemed to be possibly chemotherapy related.

Interpretation Chemotherapy with fluorouracil and folinic acid could improve survival of patients with stage II colorectal cancer, although the absolute improvements are small: assuming 5-year mortality without chemotherapy is 20%, the relative risk of death seen here translates into an absolute improvement in survival of 3·6% (95% CI 1·0–6·0).

Introduction Colorectal cancer is the second most common malignant disease in developed countries, with 1 million new cases and 500000 deaths worldwide every year.1 Cytotoxic chemotherapy, after apparently complete resection, can lower the risk of recurrence, but there has been debate over which patients benefit from such adjuvant treatment and which drug regimens are most effective. A 1-year course of fluorouracil plus levamisole11 was widely recommended as standard treatment for stage III (node positive) colon cancer in the early 1990s.12 However, subsequent evidence has established that a 6-month regimen of fluorouracil coupled with folinic acid13 is at least as effective,14–16 and that adding levamisole to fluorouracil regimens does not improve outcome.17–19 The benefits from adjuvant fluorouracil and folinic acid are supported by a clear pharmacological rationale20 and by definitive evidence that folinic acid enhances the activity of fluorouracil in advanced disease.21

Chemotherapy with fluorouracil and folinic acid has, therefore, become widely used for stage III (node positive) colon cancer. However, there remains uncertainty whether stage II (node negative) patients derive sufficient benefit from adjuvant chemotherapy to justify the toxicity, costs, and inconvenience of treatment.22 Furthermore, although the effect of adjuvant chemotherapy is assumed to be similar in rectal and colon cancer, there is little direct randomised evidence to support this. Giving fluorouracil concurrently with radiotherapy does seem to improve survival over radiotherapy alone,23 but this could be due to synergy between radiotherapy and fluorouracil. Most previous trials of fluorouracil and folinic acid have included only patients with colon cancer, and a Dutch trial of fluorouracil and levamisole showed benefit in colon but not rectal cancer.1 Consequently, there has been doubt among many clinicians whether patients with rectal cancer—whether node positive or negative—benefit from adjuvant chemotherapy. The QUASAR (QUick And Simple And Reliable) trial was designed to provide large-scale randomised evidence on the value of adjuvant chemotherapy with fluorouracil and folinic acid with fluorouracil and folinic acid.
Methods

Patients

Patients were eligible if they were thought to have had a complete resection of colon or rectal cancer with no evidence of distant metastases, and if they had no definite contraindications to chemotherapy. No prior chemotherapy was allowable other than a 1 week post-operative portal vein infusion of fluorouracil. Written consent was sought before randomisation, and after a full written and verbal explanation of the treatment options had been given. Ethics approval for the study was given by the local research ethics committee at each hospital.

Procedures

QUASAR adopted a pragmatic trial design, with local clinical teams categorising patients as having either a clear or an uncertain indication for adjuvant chemotherapy. The indication for chemotherapy was decided by each patient’s clinicians, after consultation with the patient, rather than by any per-protocol definition. In practice, lymph node status was the key discriminant, with 70% of those deemed to have a clear indication for chemotherapy having stage III disease, while 91% of those with an uncertain indication had stage II disease. Data for the patients with a clear indication for chemotherapy have been reported elsewhere. Patients with an uncertain indication for chemotherapy were randomly assigned to receive adjuvant chemotherapy or to observation, but with chemotherapy considered in the event of recurrence. A minimised randomisation procedure was used to ensure that allocations were balanced with respect to age, tumour site, stage, portal vein infusion or not, pre-operative radiotherapy or not, planned post-operative radiotherapy or not, and chemotherapy schedule (weekly or every 4 weeks). Randomisation was done by telephone call to a central office. Until October, 1997, those allocated to receive chemotherapy were simultaneously randomly allocated to receive fluorouracil plus either high-dose or low-dose folinic acid, each combined with levamisole or placebo. Subsequently, all patients allocated to receive chemotherapy were given fluorouracil plus either high-dose or low-dose chemotherapy.

Chemotherapy consisted of 30 doses of fluorouracil (370 mg/m² intravenously) combined with either high-dose (175 mg intravenously) or low-dose (25 mg intravenously) L-folinic acid. L-folinic acid, the active isomer, is equivalent, pharmacologically, to double the dose of racemic folinic acid. It was recommended that chemotherapy be given in six 5-day courses every 4 weeks, but a 30-week schedule of once weekly administration was also allowable. The dose of fluorouracil for subsequent courses was reduced if substantial toxicity occurred after the previous course. Levamisole (50 mg or matching placebo) was given three times daily for 3 days repeated every 2 weeks for 12 courses. Chemotherapy and levamisole or placebo treatment started in the same week, if possible within 6 weeks of surgery. Use of radiotherapy for rectal cancers, and all other aspects of patient management, were left to the discretion of the responsible physician.

To facilitate large-scale recruitment, QUASAR adopted a streamlined trial design with no extra investigations and minimal extra workload for participating clinicians. Important prognostic data were collected at randomisation. Collaborators were required to notify the trial office of any serious unexpected adverse experiences believed to be due to chemotherapy. But, apart from this, there was just one yearly follow-up form that requested brief details of serious toxicity, recurrence, and death. In the UK, this information was supplemented by use of national mortality records with extra information sought from clinicians on the causes of deaths without recorded recurrence. Flagged patients from England and Wales were assumed to be alive as of January, 2005, unless notified otherwise. A postal follow-up of the status of all patients was done in January, 2004. For analyses of recurrence, and for survival analyses for patients who had not been successfully flagged, analyses were censored at March, 2004, if a follow-up reply was received or at last follow-up otherwise.

Dispensing pharmacists were asked to record the doses and schedule of fluorouracil and folinic acid until 1998,
when central supplies of folinic acid were discontinued. Health economic data, compliance, treatment toxicity, and quality of life were measured in a substudy (n=700, from selected centres in the West Midlands) through patient questionnaires (European Organisation for Research and Treatment of Cancer QLQ-30® with colorectal cancer, a resource usage module, and the hospital anxiety and depression scale) completed before chemotherapy and then at 3, 6, 15, and 27 months. Detailed toxicity data were recorded at the same time points from patient notes. Pathological reports were requested retrospectively from all patients. At the time of submission, 650 such reports had been received; these reports were reviewed centrally.

To assess cost-effectiveness as cost per quality-adjusted life-year (QALY), the average life-years gained through improved survival with chemotherapy were estimated by use of UK national mortality statistics and the QALYs lost during chemotherapy by assigning a utility score to quantify the reduction in health-related quality of life while undergoing chemotherapy.

Statistical analysis
Target recruitment was at least 2500 patients, which would give a more than 80% chance of detecting a 5% improvement in survival (eg, from 75% to 80%) between chemotherapy (any) and control, at a significance level of less than 0·05. The decision to close recruitment was made by the trial steering committee without knowledge of interim results. The primary outcome measure was all-cause mortality. Secondary outcomes were death from colorectal cancer, and recurrence. Analyses were by intention to treat and used standard log-rank methods. Tests for heterogeneity of treatment effect between subgroups were as described by the Early Breast Cancer Trialists’ Collaborative Group, using recurrence as the most statistically sensitive outcome measure. Prior hypotheses were that the monthly 5-day schedule would be more effective than the once-weekly schedule and that chemotherapy within 6 weeks of surgery would be more effective than later.

Analyses were done with SAS version 9.1. This trial is registered with the International Clinical Trial Registry, number ISRCTN82375386.

Role of the funding source
The general structure of the study was designed by the UK Coordinating Committee on Cancer Research (London, UK; now the National Cancer Research Institute), and managed, analysed, and reported independently of the funding body or any companies, who had no representative in its organisation and who, like the steering committee, remained blind to the results as they accumulated. All authors had access to all the data and had final responsibility for the decision to submit for publication.

Results
Between May 25, 1994, and Dec 24, 2003, 3239 patients were entered into the uncertain indication arm of QUASAR by 332 clinicians from 150 centres in 19 countries. Figure 1 shows the trial profile. Patients were well balanced with respect to baseline characteristics (table). The median age of the patients was 63 (IQR 56–68) years; 1979 (61%) were men; 2291 (71%) had colon cancer; 260 (8%) had stage III, 2963 (91%) stage II, and 16 (0·5%) stage I disease. Of the 628 patients with data for vascular invasion and T stage, 81 (13%) had vascular invasion, 78 (13%) had T4 tumours, and 32 (5%) had both. If allocated, chemotherapy was scheduled for

### Table: Baseline characteristics of randomised patients

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (n=1622)</th>
<th>Observation (n=1617)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>8 (0·5%)</td>
<td>8 (0·5%)</td>
</tr>
<tr>
<td>II</td>
<td>1483 (91%)</td>
<td>1480 (92%)</td>
</tr>
<tr>
<td>III</td>
<td>131 (8%)</td>
<td>129 (8%)</td>
</tr>
<tr>
<td><strong>Site</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>1148 (71%)</td>
<td>1143 (71%)</td>
</tr>
<tr>
<td>Rectum (or both)</td>
<td>474 (29%)</td>
<td>474 (29%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1006 (62%)</td>
<td>973 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>616 (38%)</td>
<td>644 (40%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>185 (11%)</td>
<td>185 (11%)</td>
</tr>
<tr>
<td>50–59</td>
<td>427 (26%)</td>
<td>428 (26%)</td>
</tr>
<tr>
<td>60–69</td>
<td>678 (42%)</td>
<td>673 (42%)</td>
</tr>
<tr>
<td>70+</td>
<td>331 (20%)</td>
<td>332 (21%)</td>
</tr>
<tr>
<td>Range in years</td>
<td>23–86</td>
<td>23–84</td>
</tr>
<tr>
<td>Median age</td>
<td>63 (56–68)</td>
<td>63 (56–68)</td>
</tr>
<tr>
<td><strong>Other adjuvant therapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-operative radiotherapy</td>
<td>102 (6%)</td>
<td>101 (6%)</td>
</tr>
<tr>
<td>Postoperative radiotherapy</td>
<td>133 (8%)</td>
<td>131 (8%)</td>
</tr>
<tr>
<td>Portal vein infusion</td>
<td>6 (0·4%)</td>
<td>5 (0·3%)</td>
</tr>
<tr>
<td><strong>Intended chemotherapy schedule</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-day course every 4 weeks</td>
<td>769 (47%)</td>
<td>765 (47%)</td>
</tr>
<tr>
<td>Once weekly</td>
<td>853 (53%)</td>
<td>852 (53%)</td>
</tr>
<tr>
<td><strong>Chemotherapy allocated</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil-high-dose folinic acid +levamisole*</td>
<td>141 (9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fluorouracil-high-dose folinic acid +placebo*</td>
<td>143 (9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fluorouracil-low-dose folinic acid +levamisole*</td>
<td>142 (9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fluorouracil-low-dose folinic acid +placebo*</td>
<td>141 (9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fluorouracil-high-dose folinic acid†</td>
<td>20 (1%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fluorouracil-low-dose folinic acid†</td>
<td>20 (1%)</td>
<td>NA</td>
</tr>
<tr>
<td>Fluorouracil-low-dose folinic acid†</td>
<td>105 (6%)</td>
<td>NA</td>
</tr>
<tr>
<td>No chemotherapy</td>
<td>NA</td>
<td>1617</td>
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</tbody>
</table>

Data are n (%) or median (IQR). *Randomised between high-dose and low-dose folinic acid and between levamisole and placebo. †Randomised between high-dose and low-dose folinic acid.
5 days every 4 weeks for 1534 (47%) patients and once a week for 1705 (53%). Chemotherapy was mainly fluorouracil plus low-dose folinic acid (1318 of 1622 patients, 81%) without levamisole (1337 of 1622 patients, 82%), with 0·3% also receiving a postoperative portal vein infusion of fluorouracil. 198 (21%) of the 948 patients with rectal cancer or both rectal and colon cancer had received pre-operative radiotherapy, 202 (28%) of these patients were scheduled for postoperative radiotherapy.

3% (45/1622) of patients allocated chemotherapy did not start (figure 1). Of those who did, pharmacy record cards were available for 742 (47%), with 428 (58%) receiving their full chemotherapy and 558 (77%) at least 80%. In those receiving chemotherapy every 4 weeks, the cumulative dose of fluorouracil was higher for those aged under 70 years than for older patients (17·9 g vs 15·6 g, p<0·0001; webtable 1); by contrast, of the patients receiving once-weekly chemotherapy, there was no difference in cumulative dose between those aged under 70 years and older patients (18·3 g vs 18·0 g, p=0·09). Radiotherapy use was similar in the chemotherapy and observation groups.

2793 (86%) patients in QUASAR were entered from the UK, of whom 2712 (97%) were successfully flagged with the national death registry, and were thus assumed to be alive as of January, 2005, unless notified otherwise. Replies to the postal follow-up have been received at the time of this report for 2306 (90%) of the 2558 patients still alive. 111 (4%) of the 2558 patients alive had missing follow-up—ie, not flagged or no recent follow-up received. The median follow-up of the surviving patients is 5·5 (range 0–10·6) years.

Over the whole study period, there were 311 deaths in the chemotherapy group and 370 in the observation group. The relative risk of dying from any cause with chemotherapy versus observation was 0·82 (95% CI 0·70–0·95; p=0·008; figure 2). The numbers of deaths from causes other than colorectal cancer were similar in the chemotherapy and observation groups: 152 (4·7%) died in the chemotherapy group versus 160 (4·3%) in the observation group (p=0·7; webtable 2). The relative risk of dying from colorectal cancer was 0·81 (95% CI 0·68–0·96; p=0·008; figure 2). The numbers of deaths from other causes were similar in patients with stage II and in those with stage III cancer, and in patients with colon and those with rectal cancer (figure 3). There was also no significant difference in the effect size between men and women, once-weekly chemotherapy and chemotherapy every 4 weeks, or in time from surgery to randomisation (figure 3). The relative risk of dying from colorectal cancer was 0·82 (95% CI 0·68–0·96; p=0·01) in those with stage II cancer, and 0·78 (95% CI 0·66–0·93; p=0·004) and 0·68 (95% CI 0·52–0·88; p=0·004) in those with rectal cancer (figure 4). There was no reduction in recurrence for patients aged over 70 years, but this apparently lesser treatment benefit with increasing age did not reach statistical significance.

The proportional reduction in recurrence with chemotherapy versus observation alone was much the same in patients with stage II and in those with stage III cancer, and in patients with colon and those with rectal cancer (figure 3). There was also no significant difference in the effect size between men and women, once-weekly chemotherapy and chemotherapy every 4 weeks, or in time from surgery to randomisation (figure 3). The relative risk of recurrence with chemotherapy compared with observation alone in patients with stage II cancer was 0·78 (95% CI 0·66–0·93; p=0·004) and 0·68 (95% CI 0·52–0·88; p=0·004) in those with rectal cancer (figure 4). There was no reduction in recurrence for patients aged over 70 years, but this apparently lesser treatment benefit with increasing age did not reach statistical significance.

There were 293 recurrences in the chemotherapy group and 359 in the observation group. The relative risk of recurrence with chemotherapy versus observation over the whole study period was 0·78 (95% CI 0·67–0·91; p=0·001; figure 2). There was significant heterogeneity in treatment effect by period of follow-up, with 149 (9·2%) recurrences in the chemotherapy group in the first 2 years after randomisation, compared with 227 (14·0%) in those in the observation group (p=0·004). The relative risk of recurrence in the first 2 years with chemotherapy versus observation was 0·64 (95% CI 0·52–0·78; p=0·0001; figure 3). Subsequently, there was no benefit, or loss of benefit, with 144 (12·8%) of 1127 patients in the chemotherapy group and 132 (12·7%) of 1040 patients in the observation group experiencing a recurrence after 2 years (p=0·94).
Comparison of the proportional reductions in recurrence in the 2 years after randomisation, where the most extreme effect of chemotherapy is seen (figure 3), showed a similar, borderline significant pattern of decreasing benefit with age (p=0.05; webfigure 1). The relative risk of recurrence in the 2 years after randomisation was 0.71 (95% CI 0.54–0.92; p=0.01) for patients with stage II colon cancer.

### Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Events/patients (Chemotherapy)</th>
<th>Events/observation (O–E)</th>
<th>Var</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>199/1148 (17.3%)</td>
<td>230/1143</td>
<td>-19.6 107.2</td>
<td>0.83 (0.65–1.07)</td>
</tr>
<tr>
<td>Rectum or both</td>
<td>94/474 (19.8%)</td>
<td>129/474</td>
<td>-21.6 55.6</td>
<td>0.68 (0.48–0.96)</td>
</tr>
</tbody>
</table>

Interaction between two groups χ²₁=1.5; p=0.21

### Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Events/observation (O–E)</th>
<th>Var</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>2/8 (25.0%)</td>
<td>0.6 0.7</td>
<td>0.81 (0.63–1.08)</td>
</tr>
<tr>
<td>Stage II colon</td>
<td>164/1073 (15.3%)</td>
<td>-17.6 89.5</td>
<td>0.69 (0.46–1.04)</td>
</tr>
<tr>
<td>Stage II rectum</td>
<td>70/410 (17.1%)</td>
<td>-15.1 41.2</td>
<td>0.73 (0.46–1.15)</td>
</tr>
<tr>
<td>Stage III</td>
<td>58/131 (44.3%)</td>
<td>-10.0 31.3</td>
<td>0.73 (0.46–1.15)</td>
</tr>
</tbody>
</table>

Heterogeneity between four groups χ²₃=6.6; p=0.09

### Sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Events/observation (O–E)</th>
<th>Var</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>177/1006 (17.6%)</td>
<td>-25.0 98.2</td>
<td>0.78 (0.60–1.01)</td>
</tr>
<tr>
<td>Women</td>
<td>116/616 (18.8%)</td>
<td>-15.6 64.7</td>
<td>0.79 (0.57–1.08)</td>
</tr>
</tbody>
</table>

Interaction between two groups χ²₁=0.0; p=0.93

### Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Events/observation (O–E)</th>
<th>Var</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 years</td>
<td>23/185 (12.4%)</td>
<td>-3.6 13.0</td>
<td>0.76 (0.37–1.55)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>65/428 (15.2%)</td>
<td>-15.3 39.9</td>
<td>0.68 (0.45–1.02)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>129/678 (19.0%)</td>
<td>-26.4 74.0</td>
<td>0.70 (0.52–0.94)</td>
</tr>
<tr>
<td>70+ years</td>
<td>76/331 (21.0%)</td>
<td>4.5 35.7</td>
<td>1.13 (0.74–1.75)</td>
</tr>
</tbody>
</table>

Heterogeneity between four groups χ²₃=3.1; p=0.09

### Schedule

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Events/observation (O–E)</th>
<th>Var</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once a week</td>
<td>145/853 (17.0%)</td>
<td>-10.7 77.2</td>
<td>0.87 (0.65–1.17)</td>
</tr>
<tr>
<td>Every 4 weeks</td>
<td>148/769 (19.2%)</td>
<td>-30.3 85.6</td>
<td>0.70 (0.53–0.93)</td>
</tr>
</tbody>
</table>

Interaction between two groups χ²₁=0.17; p=0.69

### Time to treatment

<table>
<thead>
<tr>
<th>Time to treatment</th>
<th>Events/observation (O–E)</th>
<th>Var</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery to randomisation &lt;6 weeks</td>
<td>146/816 (17.9%)</td>
<td>-27.5 86.5</td>
<td>0.73 (0.55–0.96)</td>
</tr>
<tr>
<td>Surgery to randomisation 6+ weeks</td>
<td>145/799 (18.1%)</td>
<td>-13.8 75.5</td>
<td>0.83 (0.62–1.12)</td>
</tr>
</tbody>
</table>

Interaction between two groups χ²₁=0.39; p=0.59

### Time from randomisation

<table>
<thead>
<tr>
<th>Time from randomisation</th>
<th>Events/observation (O–E)</th>
<th>Var</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 0–1</td>
<td>149/1622 (12.2%)</td>
<td>-41.8 94.0</td>
<td>0.64 (0.49–0.84)</td>
</tr>
<tr>
<td>Years 2–4</td>
<td>127/1127 (11.3%)</td>
<td>5.9 58.4</td>
<td>1.11 (0.79–1.55)</td>
</tr>
<tr>
<td>Years 5+</td>
<td>172/564 (3.0%)</td>
<td>-4.9 10.5</td>
<td>0.63 (0.28–1.99)</td>
</tr>
</tbody>
</table>

Heterogeneity between three groups χ²₃=11.3; p=0.004

Test for trend over three groups χ²₁=4.1; p=0.04

Unstratified

<table>
<thead>
<tr>
<th>Chemotherapy better</th>
<th>293/1622 (18.1%)</th>
<th>359/1617 (22.2%)</th>
<th>-40.7 162.9</th>
<th>0.78 (0.64–0.95)</th>
</tr>
</thead>
</table>

Relative risk and 99% CI

Relative risk and 95% CI

Figure 3: Relative risk of recurrence with chemotherapy by site, stage, sex, age, chemotherapy schedule, and timing

See Online for webfigure 1.
and 0·57 (95% CI 0·38–0·89; p=0·007) for patients with stage II rectal cancer (figure 5). For patients aged under 70 years, the relative risk of recurrence in the 2 years after randomisation was 0·59 (95% CI 0·43–0·82; p=0·0008) for those with stage II colon cancer and 0·58 (95% CI 0·38–0·93; p=0·01) for those with stage II rectal cancer (webfigure 2).

Subgroup investigations of mortality were less reliable than for recurrence because of the lesser treatment effect, but followed a similar pattern (figure 6). The relative risk of death from any cause in patients with stage II cancer was 0·84 (95% CI 0·68–1·00; p=0·046) and 0·77 (95% CI 0·54–1·00; p=0·05) for those with rectal cancer (figure 4).

Serious, unexpected adverse events were rare: eight (0·5%) patients in the chemotherapy group and four (0·25%) of those in the observation group died from non-colorectal cancer causes within 30 weeks of randomisation (webtable 2). Only one of these deaths was deemed to be possibly chemotherapy related. Quality-of-life measurements directly related to expected toxicity (diarrhoea, nausea, vomiting, mouth pain, fatigue, appetite loss, and social functioning) were worse in those patients in the chemotherapy group than in those in the observation group (p<0·001 for all categories), but only during chemotherapy. Chemotherapy patients with clinician-rated grade 3/4 toxicity reported worse global quality of life than did those with lesser or no toxicity. The only material difference between chemotherapy regimens was between schedules with more grade 3/4 toxicity with the four-weekly than the once-weekly schedule. The proportion of patients with grade 3/4 nausea (6% of 200 patients vs 1% of 227 patients), oral adverse events (10% vs 0%), diarrhoea (11% vs 5%), neutropenia (7% vs 1%), and any grade 3/4 toxicity (31% vs 10%) was significantly greater with 4-week courses of chemotherapy than with once-weekly delivery (p<0·001 for all adverse events; webtable 3).

Resource usage, other than for chemotherapy administration, did not differ between patients randomised to chemotherapy and observation. The cost of delivering QUASAR chemotherapy was estimated to be between £2000 and £3000 per person. A utility score for QUASAR chemotherapy was not measured directly, but in view of the minor effect of chemotherapy on quality of life, was estimated to be 0·7 during the 6 months of chemotherapy—ie, a loss of about 8 weeks of full health life. Sensitivity analyses indicate that the two chief determinants of cost per QALY are the size of survival

Figure 4: Effect of chemotherapy on (A) recurrence and (B) survival for stage II patients and on (C) recurrence and (D) survival for patients with rectal cancer.

See Online for webfigure 2

See Online for webtable 3
benefit from chemotherapy and the life expectancy (ie, age) of the patient (webfigure 3). For patients under the age of 70 years, there was a net gain of a few months of QALYs even with the lowest estimate of treatment efficacy. By the age of 80 years, only at the highest estimate of treatment efficacy was a small net benefit seen.

**Discussion**

The results presented here indicate that, relative to observation alone, adjuvant chemotherapy with fluorouracil and folinic acid lowers the risk of all-cause mortality in patients with colorectal cancer who have had successful resection of the cancer, and who have an uncertain indication for chemotherapy, by almost a fifth. Of particular interest is the evidence of an improvement in survival with chemotherapy for patients with stage II cancer. Although this improvement was of borderline statistical significance, the survival benefit is supported by a significant reduction in recurrence, by evidence that 3-year disease-free survival is a good surrogate for overall survival, by unequivocal evidence from previous trials of a survival benefit for stage III patients, by evidence from pooled analyses of other randomised trials, and from individual studies that suggest that the proportional reductions in mortality and recurrence from adjuvant chemotherapy based on fluorouracil are much the same in patients with stage II and III disease. The data presented here are also consistent with previous trial evidence, a meta-analysis of which found a mortality risk ratio of 0.87 (95% CI 0.73–1.01; p=0.07) for patients with stage II disease.

There is also evidence that, relative to observation alone, the risk of death or recurrence in patients with rectal cancer who received adjuvant chemotherapy was lowered, indicating that the previously reported lack of benefit in this subgroup was probably falsely negative. In QUASAR, the effect of chemotherapy on recurrence was larger, albeit not significantly so, in patients with stage II rectal cancer than it was in those with stage II colon cancer. The reduction in stage II colon cancer did not reach statistical significance (figure 3), but this could be explained by the the limited statistical sensitivity of such subgroup investigations, particularly when subdividing analyses by disease stage and then again by site. Comparisons of recurrence rates in the first 2 years after randomisation—the period when the full effect of chemotherapy is seen—are statistically more reliable than are comparisons of all events. The relative risks of recurrence in the first 2 years were similar in patients with stage II colon cancer and in those with stage II rectal cancer (figure 5).

Although probably real, the survival benefit from chemotherapy for a patient with stage II colorectal cancer is small: if 5-year mortality without chemotherapy is 20%, a reduction in the relative risk of death of 18% (95% CI 5–30) translates into an absolute improvement in overall survival of 3·6% (1·0–6·0). One encouraging finding is that—by contrast with a recent trial report—chemotherapy seems to prevent a proportion of recurrences and deaths, rather than just delaying them, which makes the life-years gained more substantial, especially for younger patients. For example, for a 55-year-old, who would have a life expectancy of 30 more years if not dying of their cancer, reducing their 5-year risk of cancer death by 3·6% (eg, from 20% to 16·4%) would increase their life expectancy by about a year. By contrast, a sustained 3·6% improvement in survival for a 75-year-old, with a life expectancy of about 10 years, would increase their life expectancy by only 4 months. If a 2-month deduction is made for loss of quality-adjusted life during chemotherapy, the average QALYs gained are 10 versus 2 months. Furthermore, the results presented here suggest that the proportional reduction in mortality with chemotherapy is less for older patients. However, this finding could be a false negative, since other studies have reported benefit for...
patients over the age of 70 years.\textsuperscript{10,11}

Current recommendations are that patients with stage II disease who have a higher than average risk of tumour recurrence—eg, those with stage T4 disease or vascular invasion, about 30% of the QUASAR study population—should be offered chemotherapy.\textsuperscript{12} Pathological data were available for only 20% of the study population, and so any difference in efficacy between those with high-risk stage II disease and those with low-risk stage II disease could not be investigated.

### Figure 6: Relative risk of death with chemotherapy by site, stage, sex, age, chemotherapy schedule, and timing

<table>
<thead>
<tr>
<th>Site</th>
<th>Deaths/patients Chemotherapy</th>
<th>Events in chemotherapy group</th>
<th>Relative risk and CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>208/1148 (18.1%)</td>
<td>-19.5 112.2</td>
<td>0.84 (0.66-1.07)</td>
</tr>
<tr>
<td>Rectum or both</td>
<td>103/474 (21.7%)</td>
<td>-15.0 58.0</td>
<td>0.77 (0.55-1.08)</td>
</tr>
</tbody>
</table>

**Stage**

- **Stage I**
  - Chemotherapy: 0/8 (0.0%)
  - Observation: 2/8 (25.0%)
  - Relative risk: 0.86 (0.66-1.12)

- **Stage II colon**
  - Chemotherapy: 173/1073 (16.1%)
  - Observation: 198/1073 (18.5%)
  - Relative risk: 0.86 (0.66-1.12)

- **Stage II rectum**
  - Chemotherapy: 79/410 (19.3%)
  - Observation: 95/407 (23.3%)
  - Relative risk: 0.80 (0.54-1.19)

- **Stage III**
  - Chemotherapy: 59/131 (45.0%)
  - Observation: 75/129 (58.1%)
  - Relative risk: 0.69 (0.44-1.07)

**Sex**

- **Men**
  - Chemotherapy: 203/1006 (20.0%)
  - Observation: 234/973 (24.0%)
  - Relative risk: 0.84 (0.66-1.07)

- **Women**
  - Chemotherapy: 110/616 (17.9%)
  - Observation: 136/644 (21.1%)
  - Relative risk: 0.79 (0.57-1.10)

**Age**

- **<50 years**
  - Chemotherapy: 20/185 (10.8%)
  - Observation: 23/185 (12.4%)
  - Relative risk: 0.85 (0.39-1.87)

- **50–59 years**
  - Chemotherapy: 63/428 (14.7%)
  - Observation: 83/427 (19.4%)
  - Relative risk: 0.76 (0.49-1.16)

- **60–69 years**
  - Chemotherapy: 133/610 (21.7%)
  - Observation: 171/673 (25.4%)
  - Relative risk: 0.74 (0.55-0.99)

- **70+ years**
  - Chemotherapy: 95/331 (28.7%)
  - Observation: 93/332 (28.0%)
  - Relative risk: 1.02 (0.70-1.48)

**Schedule**

- **Once a week (intent)**
  - Chemotherapy: 154/853 (18.1%)
  - Observation: 174/852 (20.4%)
  - Relative risk: 0.88 (0.66-1.17)

- **Every 4 weeks (intent)**
  - Chemotherapy: 157/769 (20.4%)
  - Observation: 196/765 (25.6%)
  - Relative risk: 0.76 (0.58-1.00)

**Time to treatment**

- **Surgery to randomisation <6 weeks**
  - Chemotherapy: 155/816 (19.0%)
  - Observation: 196/818 (24.0%)
  - Relative risk: 0.82 (0.63-1.07)

- **Surgery to randomisation 6+ weeks**
  - Chemotherapy: 154/799 (19.3%)
  - Observation: 170/788 (22.0%)
  - Relative risk: 0.81 (0.61-1.07)

**Time from randomisation**

- **Years 0-1**
  - Chemotherapy: 98/1622 (6.0%)
  - Observation: 129/1617 (8.0%)
  - Relative risk: 0.75 (0.54-1.06)

- **Years 2-4**
  - Chemotherapy: 154/1227 (12.6%)
  - Observation: 155/1218 (12.4%)
  - Relative risk: 0.95 (0.71-1.27)

- **Years 5+**
  - Chemotherapy: 59/608 (8.8%)
  - Observation: 85/629 (13.2%)
  - Relative risk: 0.67 (0.44-1.03)

**Heterogeneity**

- **Between four groups χ² = 0.3; p = 0.60**
- **Sex**
- **Age**
- **Schedule**
- **Time to treatment**
- **Time from randomisation**

**Test for trend over groups χ² = 1.2; p = 0.28**

**Relative risk and 95% CI**

![Figure 6: Relative risk of death with chemotherapy by site, stage, sex, age, chemotherapy schedule, and timing](https://www.thelancet.com)
However, the similar proportional reductions with chemotherapy in the risk of recurrence in patients with stage II disease and those with stage III disease suggest that the proportional reductions in the risk of recurrence in high-risk and in low-risk stage II disease will also be similar. Thus, because pathological variables are only moderately prognostic of outcome in stage II disease, they are only moderately useful as discriminants of treatment benefit. For example, preliminary analyses of pathological data from QUASAR suggest that the 5-year risks of death for an untreated patient with stage II disease with and without high-risk features are about 30% and 20%, respectively (data not shown). The absolute benefit from an 18% reduction in mortality would be 5 - 4% in those with high-risk features and 3 - 6% in those without, which might both be considered sufficient to justify well-tolerated QUASAR-type chemotherapy, at least for younger patients. Reliable predictors of sensitivity to chemotherapy would constitute a more useful means to help individualize adjuvant therapy. QUASAR includes a substudy of stored cancer tissue that will help clarify the role of high-risk factors in stage II disease and, hopefully, identify tumour markers that will enable targeting of treatment at the most responsive patients.

The optimum chemotherapy regimen for stage II disease is unclear. 20% of patients in QUASAR received levamisole or high-dose folinic acid, or both, and this has no relevant effect on interpretation of the study findings because neither the addition of levamisole nor use of a higher dose of folinic acid had any effect on the efficacy of the combination of fluorouracil and folinic acid. Treatment every 4 weeks had a larger effect on recurrence than did the once-weekly regimen; however, the once-weekly regimen was less toxic. Furthermore, the two schedules seemed to have similar efficacy in patients in QUASAR who had a clear indication for treatment. If treatment every 4 weeks is more effective than the once-weekly schedule then the benefits from an optimum chemotherapy regimen will be larger than reported here. Similarly, enhanced survival benefits might be achieved with newer chemotherapy regimens that are more efficacious at preventing recurrence than is the combination of fluorouracil and folinic acid. However, whether these newer regimens produce a worthwhile extra survival benefit has yet to be established. Furthermore, safety is a major consideration in choosing adjuvant chemotherapy, in particular for patients at low risk of recurrence. There have been five toxicity-related deaths—all receiving treatment every 4 weeks—in almost 6000 patients treated with chemotherapy in QUASAR, considerably fewer than reported with newer chemotherapy regimens.

The small but definite benefit from well-tolerated chemotherapy found here should provide helpful new information for discussions between patients and physicians on the potential benefits of chemotherapy, and allow the patient to make a better informed decision to proceed with, or refuse, the offer of chemotherapy. Longer follow-up of QUASAR, and meta-analysis with other studies, is needed to resolve whether chemotherapy produces worthwhile benefits for those aged over 70 years, and further trials are needed to define the optimum chemotherapy regimen.

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**Conflict of interest statement**

None of the writing committee members have any conflict of interest to declare.

**Acknowledgments**

We thank the patients who participated in QUASAR, without whose help this study would not have been possible. QUASAR was funded principally by the UK Medical Research Council, the Imperial Cancer Research Fund, the Cancer Research Campaign (now merged as CRUK), and the Department of Health. Randomisation and other support was provided by the BHF/CR UK/MRC Clinical Trial Service Unit, Oxford. Additional sponsorship (for meeting costs) was provided by Lederle (now Wyeth-Ayerst), who also donated L-folinic acid, and by the Mark Hardy Research Fund. Levamisole was donated by Janssen Pharmaceuticals.

**References**


Tuberculosis is still a leading cause of death in low-income and middle-income countries, especially those of sub-Saharan Africa where tuberculosis is an epidemic because of the increased susceptibility conferred by HIV infection. The effectiveness of the Bacille Calmette Guérin (BCG) vaccine is partial, and that of treatment of latent tuberculosis is unclear in high-incidence settings. The routine diagnostic methods that are used in many parts of the world are still very similar to those used 100 years ago. Multidrug treatment, within the context of structured, directly observed therapy, is a cost-effective control strategy. Nevertheless, the duration of treatment needed reduces its effectiveness, as does the emergence of multidrug-resistant and extensively drug-resistant disease; the latter has recently become widespread. The rapid expansion of basic, clinical, and operational research, in addition to increasing knowledge of tuberculosis, is providing new diagnostic, treatment, and preventive measures. The challenge is to apply these advances to the populations most at risk. The development of a comprehensive worldwide plan to stop tuberculosis might facilitate this process by coordinating the work of health agencies. However, massive effort, political will, and resources are needed for this plan to succeed.

Introduction

Tuberculosis has troubled humankind throughout history. It has been a leading cause of death throughout the world, and still is in low-income and middle-income countries. The limitations of existing methods of prevention, diagnosis, and treatment of tuberculosis have been emphasised by the increased susceptibility of HIV-infected people to develop the disease, and by the emergence of drug-resistant strains. Overall, the worldwide burden of tuberculosis is still growing. Improvement in the control of the disease in many regions of the world is offset by the effect of HIV in the resource-poor health systems of sub-Saharan Africa. The challenge is to apply advances to the populations most at risk.

Epidemiology

The most recent estimates of the worldwide epidemic of tuberculosis are for 2004, when there were 8·9 million new cases and 1·7 million deaths. The worldwide annual incidence of tuberculosis is about 10% and 40% of new and previously treated patients, respectively.9 Eastern Europe has the highest prevalence: multidrug-resistant tuberculosis is found in about 10% and 40% of new and previously treated patients, respectively.1

Extensively drug-resistant (XDR) tuberculosis is, by definition, resistant to at least rifampicin and isoniazid, in addition to any quinolone and at least one injectable second-line agent (capreomycin, amikacin, kanamycin).

HIV infection is also strongly associated with the transmission of tuberculosis between adults in sub-Saharan Africa.6 High transmission rates of tuberculosis cause large numbers of children to be infected, which is concerning not least because of the rapid disease progression and the difficulties with diagnosis in this group.1

Multidrug-resistant tuberculosis is defined as resistance to rifampicin and isoniazid, with or without other drug resistance. Treatment for multidrug-resistant tuberculosis is longlasting, less effective, costly, and poorly tolerated. Estimates are that more than 4% of patients with tuberculosis worldwide are multidrug resistant, with more than 40% of these patients having been previously treated for tuberculosis.5 Eastern Europe has the highest prevalence: multidrug-resistant tuberculosis is found in about 10% and 40% of new and previously treated patients, respectively.1

We focused on tuberculosis in adults; readers are referred to a review of tuberculosis in children. The search strategy was a 5 year review of PubMed (2001–2006), the Cochrane library (2001–2006), and Embase (2001–2006). We searched with the terms “tuberculosis” and “Mycobacterium tuberculosis”. To compile table 2, we searched with the terms “tuberculosis”, “human”, “genetic”, and “susceptibility”. We mainly 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 the ones we regarded as relevant. Review articles are cited to provide readers with more details and references than this Seminar can accommodate. Our reference list was modified on the basis of comments from peer reviewers.
In one outbreak of tuberculosis in HIV-infected patients, XDR patients constituted 24% of all multidrug-resistant individuals.10 This level of resistance makes tuberculosis essentially untreatable, and 52 of 53 patients with tuberculosis died after a median of only 16 days.10 In 85% of patients with XDR tuberculosis in this study, the strain of *Mycobacterium tuberculosis* had the same genetic background, indicating recent transmission, and 67% had been admitted within the previous 2 years, raising the possibility of nosocomial transmission. This outbreak emphasises the need for new antimycobacterial drugs, increased surveillance, and caution in hospitals when nursing patients with suspected multidrug-resistant tuberculosis.11 In the absence of satisfactory practices to ensure adherence to medication, drug resistance will continue to emerge.

**Host–pathogen interaction**

A complex interaction exists between host and pathogen that can last for decades. One paradox of tuberculosis is that the pathogen resides and multiplies within macrophages. The availability of genome sequences of mycobacteria,12–15 the ability to delete and reintroduce genes into mycobacteria reliably, and the advent of microarray technology have moved *M tuberculosis* to the forefront of bacterial genomics. A mechanism by which *M tuberculosis* has evolved is via the loss or duplication of genomic segments. Clinical isolates of this organism have up to 5·5% of their genes deleted.16 *M leprae* manifests such reductive evolution even more strikingly; less than 50% of its genes are functional.17 Some deletions in the genes of *M tuberculosis* seem to have only happened once, and thus provide useful phylogenetic markers.17 This information, together with the sequence of *M bovis*, has allowed us to explore the relationship between *M tuberculosis* and humankind in history. The origin of tuberculosis in human beings was thought to have taken place via the domestication of cattle, suggesting that *M bovis* was the progenitor of *M tuberculosis*. However, *M tuberculosis* and *M bovis* share a common ancestor, and thus *M bovis* did not give rise to *M tuberculosis*.18,19 Additionally, the analysis of unique sequence deletions, in 875 strains from 80 countries has indicated that *M tuberculosis* arose and migrated together with human beings from Africa.20 Remarkably, evidence exists that six specific lineages of *M tuberculosis* have adapted to specific populations. Thus, for example, the east African–Asian lineage appears most commonly in individuals of Indian origin, even when they migrate to the UK or USA.21 One lineage of tuberculosis that seems to buck the trend is the east Asian lineage, which is more commonly known as the W/Beijing family of strains; it is successful worldwide, and possibly increasing in frequency.22 W/Beijing strains predominate in southeast Asia, but are widely distributed in the Indian subcontinent and in South Africa.23,24 They have also been associated with several outbreaks of drug-sensitive and drug-resistant tuberculosis in the USA and Europe.25–27 These strains have been believed to be hypermutable, as a consequence of mutations in DNA-repair genes of the *mut* (methylnalonyl coenzyme A mutase) family,28 although this observation...
has been challenged.79 Additionally, W/Beijing strains have been found to have greater virulence than other strains, in both human beings and animal models. One mechanism that underlies the greater virulence seems to be the production of an immunosuppressive phenolic glycolipid in the presence of an intact polyketide synthase 15/1 (pks 15/1) gene, which is a genetic feature of W/Beijing strains.10,30 In another lineage (east African–Indian), the deletion that characterises the lineage has been associated with an immune-subverting phenotype that potentially increases the ability of this strain to persist and cause outbreaks in populations.12

Several components of the mycobacterial cell wall have immunomodulatory activity, including phenolic glycolipid, phosphatidylinositol mannosides, lipoproteins, and lipopeptides.13 These molecules are recognised by the Toll-like receptors (TLRs) and other innate receptors on macrophages and dendritic cells, which trigger both protective and pathogenic immune responses.14 The combination of TLR2 and TLR1 recognises phosphatidylinositol mannosides and the 19-kDa lipoprotein in the cell wall.15,16 In combination with TLR2, TLR9 also contributes to the best possible host resistance.17 The role of TLR4 in tuberculosis is controversial, with some studies of knock-out mice showing that TLR4 is very important in tuberculosis,18,19 but others indicating little effect.20,21 Ligation of TLR2 and TLR1 by mycobacterial cell wall components promotes antimycobacterial immunity, although the final effector pathway remains unclear. In mice, the key intracellular pathway seems to be activation of inducible nitric oxide synthase and p47 GTPase by the cytokine interferon-γ, which is produced by T cells.22 Whether nitric oxide contributes to the intracellular defence against mycobacteria in man is still unclear. TLR2 and TLR1 ligation in mononuclear phagocytes activates 1-α hydroxylase, which converts 25-hydroxyvitamin D3 into 1,25 dihydroxyvitamin D3.23,24 Activated vitamin D has pleiotropic immune effects, including the induction of antimicrobial peptides such as the cathelicidin LL-37.25 Deficiency of vitamin D is associated with tuberculosis in immigrants to the UK.4 Overall, these findings suggest not only a novel mechanism of intracellular killing, but also the possibility of prevention of tuberculosis by vitamin D supplementation.

Mice have 23 genes encoding immunity-related GTPases, which are subdivided into five families (Inga, Irgb, Irgc, Irgd, and Irgm). Only two homologues exist in human beings, IRGC and IRGM.6 A report suggested that the activity of IRGM is associated with autophagy,48 which is a cellular homeostatic mechanism whereby cytoplasmic remnants and bacteria are taken into the endoplasmic reticulum, with consequent death of intracellular mycobacteria.49 Other novel regulatory and effector pathways of the host defence against mycobacteria include the uptake of apoptotic macrophages by dendritic cells, thereby enabling efficient T-cell recognition of tuberculosis antigens present in macrophages at the surface of dendritic cells,50 and the uptake of apoptotic neutrophils by macrophages, after which potent antimicrobial peptides are released from the neutrophils into the macrophage vacuoles that contain the mycobacteria.51 Thus, cells that eat other cells, or themselves, seem to be a way of dealing with this unwanted intruder.

Potent defence mechanisms need induction and regulation. Knowledge of essential protective immune regulatory cytokines has come from the analysis of rare mutations that confer susceptibility to mycobacteria, and serendipitously by postmarketing surveillance of biological therapies for autoimmune disease. In a remarkable series of studies done during the late 1990s, mutations in the interleukin-12- and interferon-γ-driven type-1 cytokine pathway proved to predispose to severe atypical mycobacterial infections (table 1).

These studies were coincident with an increased interest in the host genetic determinants of susceptibility. A moderate genetic component in susceptibility to tuberculosis exists,52 and several studies have examined it. Three whole-genome-based approaches have yielded moderate linkage to various chromosomal regions, which have been different in each population studied.53-55 Case-control studies are better suited to detect weak effects, and various associations have now been described. Table 2 lists some of the associations that have been replicated in more than one study, together with some studies that show novel pathways that might be implicated in pathogenesis.

The host genetic component of susceptibility seems to be distributed in many genes, and the genes implicated seem to vary between populations, which is consistent with the emerging evidence that Mycobacterium tuberculosis itself might be population specific. Integrated studies of host and pathogen genetic variability are desirable; such studies will need to be very large, and thus expensive.

The immune control of tuberculosis has also been emphasised by the association between biological therapies that neutralise tumour necrosis factor and the rapid reactivation of tuberculosis.56,57 These observations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon γ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>receptor 1</td>
<td>Point mutation at nucleotide</td>
<td>Severe atypical mycobacterial infection</td>
</tr>
<tr>
<td></td>
<td>395, which introduces a stop</td>
<td></td>
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<tr>
<td></td>
<td>codon</td>
<td></td>
</tr>
<tr>
<td>Interferon γ</td>
<td>Homozygous dinucleotide</td>
<td>Infection of M fortuitum and M avium</td>
</tr>
<tr>
<td>receptor 2</td>
<td>deletion at nucleotides</td>
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</tr>
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<td></td>
<td>27/8 and 27/9, resulting in</td>
<td></td>
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<tr>
<td></td>
<td>a premature stop codon</td>
<td></td>
</tr>
<tr>
<td>Interleukin 12p40</td>
<td>Large homozygous deletion</td>
<td>BCG infection</td>
</tr>
<tr>
<td>Interleukin 12R1 receptor subunit</td>
<td>Various missense mutations and deletions</td>
<td>Severe mycobacterial and salmonella infections</td>
</tr>
<tr>
<td>STAT1</td>
<td>Point mutation at nucleotide</td>
<td>Disseminated BCG or M avium infection</td>
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<td>2116</td>
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</table>

Table 1: Mendelian susceptibility to mycobacteria
have confirmed the crucial role of tumour necrosis factor in protective granuloma formation. Less certainty exists about the key factors in the downregulation of the immune response, which is not only needed to restrict immunopathological changes, but also might be exploited by the pathogen to subvert the immune response. Factors that might be implicated include T-cell apoptosis, the action of regulatory T cells, or type-2 T-helper cells opposing the effects of type-1 cells. Type-2 T-helper cells produce interleukin 4, but appreciable secretion of this cytokine in response to M tuberculosis antigens has not frequently been shown. However, interleukin 4 is highly active even in small amounts, and its antagonistic splice variant (interleukin 4 delta 2) is associated with protection in several studies.

How does M tuberculosis survive for so long in such an immune barrage? Two large-scale studies that used microarray screening of mutated mycobacteria after passage in mice and cells give some insight. In the first analysis, Sassetti and Rubin mutated almost every non-essential gene of M tuberculosis, and reported that 194 genes are needed for growth in mice. With similar genetic techniques, Stewart and colleagues examined the effect of a random mutation in BCG on intracellular growth and on the ability to resist phagosomal acidification, a key aspect of early immune evasion in slow-growing mycobacteria. Although the studies differed in some conclusions, several striking similarities exist. First, both studies identified membrane-associated proteins as important, especially those of the mce (mycobacterial cell entry) operon, which had previously been ascribed a role in virulence. Second, small-molecule transporters—including those used in ion, aminoacid, and disaccharide transport—are important early in the infection to bacterial replication. Thus, the rapid aerobic growth of mycobacteria early in infection seems to be carbohydrate dependent. Later in infection and during latency, bacilli can switch to using lipids as a source of energy. Both studies also found that kefB, a K+ efflux channel, protects bacilli against electrophile toxic effects by lowering intracellular pH. These studies, therefore, not only shed light on pathogenesis, but also on potential new drug targets.

**Diagnosis**

Bacteriological diagnosis of tuberculosis continues to rely on the detection of acid fast bacilli on microscopic examination and on culture. In tuberculous meningitis, where conventional smear diagnosis has a low yield, a study that is more than 50 years old showed that yields approaching 50% can be obtained by centrifugation of 5–10 ml of cerebrospinal fluid followed by longlasting microscopic examination. This simple technique is seldom used. Fluorescent microscopy is faster and more sensitive than conventional carbolfuchsin methods, but is not sensitive or widely available in resource-limited settings. Liquid culture in automated systems has considerably shortened the time and labour required for positive culture; however, this technique is expensive. An affordable, rapid diagnostic test that has better sensitivity than smear examination is highly desirable, but remains elusive. Nevertheless, substantial advances have been made, notably in the diagnosis of latent infection and the rapid diagnosis of drug resistance.

Many studies have assessed the value of in-house nucleic-acid amplification tests for the diagnosis of tuberculosis, but the absence of reproducibility makes the assessment of these tests difficult. However, several commercial nucleic-acid amplification tests for tuberculosis are available. These tests generally have high specificity. Sensitivity is high in smear-positive sputum, where tests have little value other than confirming that the acid-fast bacilli are M tuberculosis. However, their sensitivity in sputum that is smear negative or in extrapulmonary specimens is moderate (table 3). Moreover, a Vietnamese study reported that smear examination with the technique from the study cited above was at least as sensitive as the nucleic-acid amplification test in cerebrospinal fluid. Thus, the diagnostic role of
nucleic-acid amplification tests in smear-negative sputum or extrapulmonary disease is limited by their moderate sensitivity—so that cultures usually still need to be done. Furthermore, the cost of nucleic-acid amplification tests is too high for routine use in developing countries.

The attenuating deletion that defines BCG (designated region of difference 1, *RD1*) contains two highly antigenic proteins, the 6-kDa early secretory antigenic target (ESAT-6) and culture filtrate protein-10 (CFP-10).[^353][^354] The fact that these antigens are largely restricted to the *M. tuberculosis* complex, and their ability to stimulate T cells, form the basis for novel assays that assess the presence of tuberculosis infection, by detection of the release of interferon-γ by T cells in response to these antigens in vitro.[^355] The limitations of the TST are well recognised; false positives occur because the purified protein derivative contains many antigens that are present in BCG and non-pathogenic mycobacteria, and false negatives occur in immunocompromised patients, early in primary tuberculosis, and in disseminated tuberculosis.

In three studies, Lalvani and colleagues[^356][^357][^358] showed that ESAT-6-based and CFP-10-based enzyme-linked immunospot (ELISpot analysis) is about 90% sensitive for active tuberculosis and more specific than the TST in BCG-vaccinated individuals, correlates better than the TST with exposure to a point source of infection, and seems less compromised than the TST by the presence of HIV infection.[^359] Although the test cannot differentiate active from latent infection, in some clinical circumstances (for instance in children, or when cells from pleural fluid are assayed) knowledge that *M. tuberculosis* infection is present can aid the diagnosis of active disease.[^360][^361][^362] This knowledge has led to the development and marketing of the commercially available T-SPOT.TB test (Oxford Immunotec, UK) for tuberculosis infection. Two other commercial tests based on the same principle exist: QuantiFERON TB Gold (QFG) and QuantiFERON TB Gold in tube (QFGIT, both made by Cellestis, Carnegie, Australia). QFG has been extensively assessed in immunocompetent adults,[^363] in whom sensitivity and specificity seem similar to those of the T-SPOT.TB test. Preliminary reports showing that the sensitivity of interferon-γ release assay is impaired by immunosuppression[^364][^365] are not in agreement with a recent analysis suggesting that these tests might have an important role in the identification of HIV-infected people at risk of developing active tuberculosis.[^366] The QFGIT test has the advantage of in-tube incubation of whole blood without the need for a CO₂ incubator, but studies are so far too few to draw definitive conclusions. More detailed assessment of all these tests in high-incidence settings, people infected with HIV, and children is needed. Also, whether these tests are more accurate than the TST at predicting the risk of subsequent tuberculosis needs to be established; if this is true, these tests would allow more accurate prescription of preventive therapy against tuberculosis.

The diagnosis of drug resistance by conventional methods takes 6–8 weeks, or even longer if solid media are used. However, the microscopic examination of growth in wells that are filled with liquid culture medium, with or without the addition of drugs, enables the rapid (within 10 days) detection of drug resistance.[^367][^368] This technique is potentially applicable in resource-limited settings, but is labour intensive.

Resistance to rifampicin is almost invariably a marker for multidrug resistance, and several techniques are available to detect it rapidly. Rapid detection of rifampicin resistance by molecular methods (line probe assay) is sensitive and specific on culture-positive isolates.[^369] Although sensitivity is lower in clinical specimens,[^370] line probe assays are useful for the early detection of multidrug-resistant tuberculosis, enabling early initiation of therapy and appropriate infection control measures. Bacteriophage assays, in which the uptake of bacteriophages into mycobacteria is used as an index of mycobacterial growth, have similar performance characteristics, but specificity is variable.[^371]

When tuberculosis and HIV are comorbid, tuberculosis is often sputum-smear negative. Resource-poor settings have restricted access to mycobacterial culture and almost no access to nucleic-acid amplification tests. Therefore, clinical diagnoses, supported by radiology, are commonly made in developing countries. WHO has issued guidelines for the diagnosis of smear-negative and extrapulmonary tuberculosis, in settings with high prevalence of HIV.[^372] Additionally, international standards for tuberculosis care have recently been drawn up.[^373] Case definitions for smear-negative pulmonary tuberculosis have been developed, with mixed results in African studies.[^374] Expanded case definitions, including extrapulmonary tuberculosis, performed well with positive predictive values of around 90% for most of the case definitions in an HIV-infected population.[^375] However, clinical case definitions can never be completely accurate; therefore, they should be coupled with an objective assessment of response to treatment.[^376] Patients who fail to respond should be referred for further investigation.

**Treatment**

Conventional short-course therapy has remained unchanged for decades. The most frequently recommended and effective combination is isoniazid, rifampicin,
pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampicin for 4 months.121 This regimen is very effective for treatment of patients with tuberculosis, including patients with HIV infection.122 The internationally recommended tuberculosis control strategy is directly observed treatment short course (DOTS). DOTS is based on five elements: political will, case detection, standardised observed therapy, effective drug supply, and monitoring and evaluation. The intervention is based on achieving the maximum benefit of existing methods for diagnosis and treatment, and is a highly cost-effective standardised observed therapy, effective drug supply, and directly observed treatment short course (DOTS). DOTS nationally recommended tuberculosis control strategy is including patients with HIV infection.152 The inter-

very effective for treatment of patients with tuberculosis, standard doses.161,162 Higher doses of rifampicin are of patients with pulmonary tuberculosis treated with standard doses.161,162 Higher doses of rifampicin are associated with improvements in outcomes and in early bactericidal activity.163 More data are needed to recommend a change in practice, and higher doses are being included in future research of newer regimens.

New antitubercular drugs are needed to improve the treatment of patients with multidrug-resistant tuberculosis, and might enable the duration of treatment to be shortened. Some new compounds with antimycobacterial activity exist,165 and some licensed antimicrobials have good activity. However, the chances of the generation of a successful new compound by 2010 have been estimated to be slim, and would need a commitment of up to US$400 million.164

Among antimicrobial agents already licensed, some of the newer fluoroquinolones, notably moxifloxacin and gatifloxacin, have good in-vitro activity against M tuberculosis. The substitution of isoniazid by moxifloxacin reduces the time to bacillary clearance and cure in the mouse model of tuberculosis.165,166 Furthermore, intermittent therapy with rifapentine, moxifloxacin, and pyrazinamide is more potent than it is with rifampicin, isoniazid, and pyrazinamide in the same animal model.165 Moxifloxacin reduces the time to sputum culture conversion compared with ethambutol when added to conventional therapy.165 Earlier sputum culture conversion might enable the duration of treatment to be shortened, but this remains to be confirmed in clinical trials. One concern is that resistance to fluoroquinolones can develop rapidly, especially when these drugs are used as monotherapy to treat suspected bacterial infections of the lower respiratory tract before tuberculosis has been diagnosed.173,174 Moreover, some fluoroquinolones, including gatifloxacin, with promising antimycobacterial activity have been withdrawn postmarketing because of toxic effects.

The nitroimidazopyran PA-824 and the diarylquinoline R207910 are promising new antimycobacterial drugs.173,174 Both have novel mechanisms of action, and have activity against isolates that are resistant to other drugs. Both agents have begun early clinical trials.

Tuberculosis is characterised by immunopathological changes; indeed, a competent immune response is needed to produce pulmonary cavitation, which is a feature of adult tuberculosis but seldom seen in advanced HIV infection. The course of treatment can also be complicated by paradoxical deterioration,25 which has recently received great attention because of its frequency and severity in HIV-infected patients treated with antiretroviral therapy. Although adjuvant corticosteroid therapy predisposes to tuberculosis, it is sometimes also used to suppress inflammation in tuberculosis and in paradoxical reactions. However, evidence to support this therapy only exists for tuberculous meningitis, and possibly pericarditis.175,176

No clear evidence that steroids improve the outcome of tuberculous pleural effusions exists.178

In HIV-infected patients, steroids have been shown to be beneficial in tuberculous meningitis, although the overall prognosis is still extremely poor.178 Steroid use in pleural tuberculosis was associated with a higher incidence of Kaposi’s sarcoma.179 An additional concern is
that steroid therapy of HIV-associated pulmonary tuberculosis is associated with a transient increase in HIV viral load.180

Particularly in view of the advent of XDR tuberculosis, investigators are asking whether the immune response to tuberculosis can be modified or augmented to assist clearance of bacilli. In addition to the possible antibacterial effects of vitamin D outlined above, preliminary clinical studies of inhaled interferon γ in patients with multidrug-resistant tuberculosis are being followed up.181 The most widely tested immunomodulatory agent is immunisation with killed \textit{M vaccae}, which showed some promise in early studies.182 However, two clinical trials subsequently showed little evidence of additional efficacy above DOTS, although one study showed a little more rapid sputum clearance in the group treated with \textit{M vaccae} than in the control group.183-185 Further research into the relation between the immune response and the successful treatment of both active and latent tuberculosis may lead the way to more targeted interventions.186,187

**Treatment of latent tuberculosis infection**

Preventive therapy reduces tuberculosis incidence in HIV-positive and HIV-negative individuals.118 It is a successful component of tuberculosis control in Europe and North America, where special attention is also given to the prevention of tuberculosis in patients who receive immunosuppressive therapies.189 Diffi culty in the identification of those at risk, uncertainty about effectiveness in higher-transmission settings, and concerns about cost-effectiveness and acquired drug resistance have limited the implementation of preventive therapy in resource-poor countries. Notwithstanding the theoretical and operational defi ciencies of TST, the greatest benefi t is in patients who are positive to the skin test. The best-studied regimen is 6–12 months of isoniazid is inadvertently given to patients with subclinical or unrecognised tuberculosis. A systematic review reported a non-signifi cant trend (relative risk 1.45, 95% CI 0.85–2.47) of increased resistance to isoniazid when tuberculosis arose despite preventive therapy.190

The well recognised hepatotoxicity of antitubercular drugs is a very important consideration in the treatment of latent infection, because it increases the risk–benefi t ratio. Several randomised controlled trials have shown that short courses (2 or 3 months) of rifampicin and pyrazinamide were well tolerated by HIV-positive people, and as effective as standard courses of isoniazid (6 or 12 months) for the prevention of tuberculosis.191 However, two subsequent trials in HIV-negative people showed that severe derangement of liver function occurred fi ve to ten times more often with rifampicin and pyrazinamide than it did with isoniazid;192,193 many clinicians used rifampicin and pyrazinamide to prevent tuberculosis in people without HIV infection before the trials were done, resulting in several cases of severe hepatotoxicity.194 Indeed, in HIV-negative people, preventive treatment with rifampicin and pyrazinamide is reported to cause more hepatotoxicity than treatment of tuberculosis with rifampicin, pyrazinamide and isoniazid.195 This finding shows that data obtained in clinical trials cannot be extrapolated to different populations. Investigators are seeking to understand better the biology of latent infection, with the long-term aim of developing new drugs for latent tuberculosis.196,197

<table>
<thead>
<tr>
<th><strong>Type</strong></th>
<th><strong>Evidence of effectiveness</strong></th>
<th><strong>Developmental stage</strong></th>
<th><strong>Notes</strong></th>
<th><strong>Reference</strong></th>
</tr>
</thead>
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<tr>
<td>Modified vaccinia Ankara BS\texttext{A}</td>
<td>Live attenuated vector</td>
<td>Mice, guineapigs</td>
<td>Phase II</td>
<td>199,200</td>
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<tr>
<td>72f fusion protein</td>
<td>Subunit</td>
<td>Guineapigs</td>
<td>Phase I</td>
<td>Delivered in AS02 adjuvant</td>
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<tr>
<td>rBCG30</td>
<td>Recombinant BCG</td>
<td>Guineapigs</td>
<td>Phase I</td>
<td>A recombinant BCG that overexpresses antigen BS\texttext{A}</td>
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<tr>
<td>ESAT-6-BS\texttext{B} fusion</td>
<td>Subunit</td>
<td>Guineapigs, macaques</td>
<td>Phase I</td>
<td>Delivered in IC31 adjuvant</td>
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<tr>
<td>ESAT-6-\texttext{TB10.4} fusion</td>
<td>Subunit</td>
<td>Mice</td>
<td>Preclinical</td>
<td>Delivered in IC31 adjuvant</td>
</tr>
<tr>
<td>Δ\texttext{Cyl}rBCG</td>
<td>Attenuated recombinant BCG</td>
<td>Mice</td>
<td>Preclinical</td>
<td>A recombinant BCG without the urease \texttext{C} gene and expressing listeriolysin</td>
</tr>
</tbody>
</table>

**Table 4: Novel vaccines against tuberculosis**

Vaccination

Meta-analyses of BCG vaccinations have not been entirely uniform in their conclusions,116 but consensus exists that BCG provides some protection, especially against severe tuberculosis in children. The duration of protection seems to be variable. BCG does not seem to reduce the transmission of tuberculosis, which is a serious shortcoming. A more effective vaccine might greatly improve tuberculosis control.117

BCG confers some protection against tuberculosis in animal models.198 During the past 10 years, vaccinologists have developed various novel vaccines with equal or greater efficacy than BCG in animals (table 4). Some of these candidates are now in phase I or II clinical trials,
and the STOP-TB partnership intends to bring one such candidate into clinical use by 2015.265 Because childhood BCG vaccination has some effectiveness, a pragmatic consensus has emerged that novel vaccines should be assessed by how much more immunity they confer than does BCG. Vaccination after infection might reduce reactivation, and is being considered as a possibility.

However, two serious bottlenecks exist in tuberculosis vaccine research. First, efficacy trials need to enrol many individuals and to follow them up for a long time, because disease manifests only in a minority of people infected with *M tuberculosis*, and can do so many years after a vaccine is given. Second, convincing in-vitro correlates of a protective immune response are needed. Despite considerable advances in the understanding of immunity to mycobacteria, and in particular of the role of T cells that produce interferon γ, enumeration of these cells has not emerged in studies as a definitive single marker of immunity. A recent report suggests that the absence of interferon-γ-secreting T cells that respond specifically to antigens from RD1 might be a marker of resistance to primary tuberculosis induced by BCG vaccination.266 Reliable correlates of protection might be established only during the course of a vaccine trial, by comparing the responses after vaccination in those who remained disease-free with those who developed the disease.

**Control of HIV-associated tuberculosis**

While we await new drugs and vaccines, a pressing need to address a tuberculosis catastrophe exists: the HIV-driven epidemic in sub-Saharan Africa. The ways to cope with this epidemic are restricted, and poor health infrastructure limits their implementation. Antiretroviral treatment has been shown to reduce the incidence of tuberculosis,207–209 but the risk of developing tuberculosis is still much higher than in HIV-negative individuals. Furthermore, the net gain in life expectancy provides more years in which the patient can contract tuberculosis. A recent model has shown that antiretroviral therapy and treatment of latent tuberculosis infection had a very modest effect on tuberculosis incidence;210 the only preventive strategy that substantially affected incidence of tuberculosis was reduced HIV incidence. The detection and cure of active tuberculosis were the most effective interventions.211 Other interventions that might lower incidence include secondary preventive therapy, and preventive therapy combined with antiretroviral therapy. In locations where the tuberculosis epidemic is driven by HIV, access to mycobacterial culture or nucleic-acid amplification tests would, in a mathematical model, greatly reduce tuberculosis prevalence and mortality, with a more modest reduction in tuberculosis incidence.212 A combined approach with all the available interventions is reasonable because of the scale of the epidemic, but precious resources should be directed towards those interventions with the greatest effect.

Co-administration of antiretroviral and antitubercular therapy is not straightforward for three reasons: drug interactions between antiretroviral drugs and rifamycins; shared toxicities; and the immune reconstitution inflammatory syndrome.213 Available data suggest that patients who have been given antiretroviral and antitubercular therapy are at increased risk of adverse drug reactions, but the studies are retrospective and do not enable accurate attribution of the risks conferred by HIV infection, antiretroviral therapy, or other concomitant medications.214

Rifampicin is a potent inducer of cytochrome P450 enzymes, and the drug efflux pump P-glycoprotein. Two classes of antitubercular drugs, protease inhibitors, and non-nucleoside reverse transcriptase inhibitors are substrates of cytochrome P450, and their metabolism is enhanced when rifampicin is taken. Additionally, protease inhibitors are substrates of P-glycoprotein, induction of which reduces absorption of protease inhibitors from the intestine, and enhances first-pass metabolism. These interactions can result in subtherapeutic concentrations of antitubercular drugs, increasing the risks of disease progression and drug resistance. The reductions in protease-inhibitor concentrations are substantial when rifampicin is administered, and co-administration is possible only with high doses of the poorly tolerated protease inhibitor ritonavir, an inhibitor of P-glycoprotein and cytochrome P450.215 An alternative strategy is to replace rifampicin with rifabutin, a weak inducer of cytochrome P450, that does not greatly alter most protease-inhibitor concentrations. However, rifabutin is at present unaffordable in developing countries. The concentrations of the non-nucleoside reverse transcriptase inhibitors are less affected by rifampicin, and co-administration is possible, especially with efavirenz. Some authorities recommend increasing the dose of efavirenz, but this measure does not seem necessary.216,217 The non-nucleoside reverse transcriptase inhibitor nevirapine is widely used in developing countries, but few data exist on co-administration with rifampicin, and an increased dose of nevirapine might be necessary.218

![Figure 2: Typical features of the immune reconstitution inflammatory syndrome](image-url)
Patients with tuberculosis commonly develop the immune reconstitution inflammatory syndrome after starting antiretroviral therapy (figure 2). This syndrome is characterised by aberrant immunopathological immunity to tuberculosis. Tuberculosis that was improving under treatment can worsen; non-apparent tuberculosis can be unmasked. Diagnosis is difficult, because immune reconstitution inflammatory syndrome in patients with tuberculosis has protean manifestations. The differential diagnosis includes tuberculosis that is deteriorating because of incomplete adherence or drug resistance, other opportunistic diseases, and drug hypersensitivity. Little is known about the cause or management of immune reconstitution inflammatory syndrome in patients with tuberculosis; however, in a preliminary report, it has been associated with large expansions of T cells that produce interferon Y. Improvement of severe immune reconstitution inflammatory syndrome with corticosteroids has been shown, but these drugs are not without risks in HIV-infected individuals. Immune reconstitution inflammatory syndrome in patients with tuberculosis is common in those with the most serious depletion of CD4+ T cells when they start antiretroviral therapy, and when the interval between the beginning of antituberculosis therapy and that of antiretroviral therapy is short (<2 months). Some recommend that antiretroviral therapy is deferred until the intensive phase of antituberculosis therapy is complete; however, a risk exists of increased morbidity and mortality in patients with advanced HIV disease. Clinical trials are underway to establish the optimum timing of initiation of antiretroviral therapy in patients with tuberculosis.

Conclusions
Tuberculosis, especially when combined with HIV, remains a formidable problem. Increase in drug resistance threatens the advances that have been made by wider implementation of rational multidrug therapy through the DOTS strategy. Nevertheless, basic and applied research activity is more intense than ever, and clear progress towards better preventive measures, diagnostic tests, and drug treatment options exists. Increased political will within the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of the international health community is essential to tackle this disease head on, which is shown by the creation of a comprehensive worldwide plan. The political will to deal with this initiative is essential, because the global control plan needs massive effort and resource to decrease incidence in all regions of the world.

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

Acknowledgments
Our work is supported by the Wellcome Trust, European Union, the Medical Research Council of South Africa, and Secure the Future (Bristol Myers Squibb). None of these agencies had any role in the writing or decision to publish this Seminar. We thank the World Health Organisation for their permission to reproduce figure 1 and Graeme Ayton Mentejies for the photographs in figure 2.

References


Seminar


Chronic Diseases 3

Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use

Perviz Asaria, Dan Chisholm, Colin Mathers, Majid Ezzati, Robert Beaglehole

In 2005, WHO set a global goal to reduce rates of death from chronic (non-communicable) disease by an additional 2% every year. To this end, we investigated how many deaths could potentially be averted over 10 years by implementation of selected population-based interventions, and calculated the financial costs of their implementation. We selected two interventions: to reduce salt intake in the population by 15% and to implement four key elements of the WHO Framework Convention on Tobacco Control (FCTC). We used methods from the WHO Comparative Risk Assessment project to estimate shifts in the distribution of risk factors associated with salt intake and tobacco use, and to model the effects on chronic disease mortality for 23 countries that account for 80% of chronic disease burden in the developing world. We showed that, over 10 years (2006–2015), 13·8 million deaths could be averted by implementation of these interventions, at a cost of less than US$0·40 per person per year in low-income and lower middle-income countries, and US$0·50–1·00 per person per year in upper middle-income countries (as of 2005). These two population-based intervention strategies could therefore substantially reduce mortality from chronic diseases, and make a major (and affordable) contribution towards achievement of the global goal to prevent and control chronic diseases.

Introduction

80% of global deaths from chronic diseases—mainly cardiovascular disease, cancer, chronic respiratory disease, and diabetes—are in low-income and middle-income countries. Demographic changes in these countries are expected to increase the proportion of deaths attributable to these causes from just over half in 2002 to 61% by 2015.1

The WHO Comparative Risk Assessment project estimated the number of deaths from chronic diseases which could potentially be averted if the distributions of major risk factors were reduced.2 In this and the following paper of the Series, we aimed to assess selected intervention strategies—for which scaled-up coverage can be justified on the basis of sufficient information and evidence1—to see what contribution they could make towards achievement of the goal to reduce rates of mortality from chronic diseases worldwide by an additional 2% per year for the next 10 years.3 We used the WHO’s framework for classification of individual and population-based interventions as core, expanded, or optimum (in terms of their effectiveness, cost, acceptability, and feasibility).1 In this paper, we address two population-based strategies: salt reduction and tobacco control. The next paper in this Series assesses interventions for treatment of individuals at high risk of cardiovascular disease.4 Taken together, these population-level and individual-level strategies could be the first elements of a package of chronic disease prevention and control, to which other interventions could be added.

This analysis complements other efforts, including those related to the Millennium Development Goals, to estimate the cumulative financial and health consequences of scaling up coverage for intervention strategies.2–6 The purpose, methods, and perspective of such analyses are distinct from the economic assessment of the cost-effectiveness of interventions (which aims to identify increased efficiency or best buys across the health sector, and which covers a broader set of potential costs and effects).1,3,4 Other research has assessed the cost-effectiveness of salt-reduction and tobacco-control strategies in the context of low-income and middle-income countries, and shown that both are highly efficient uses of societal resources.10–13

Key messages

- 23 countries have 80% of the burden of chronic disease in low-income and middle-income regions of the world
- In these countries, 13·8 million deaths could be averted over 10 years from 2006 to 2015 (8·5 million by a salt-reduction strategy and 5·3 million by implementation of four elements of the WHO Framework Convention on Tobacco Control)
- Most deaths averted would be from cardiovascular diseases (75·6%), followed by deaths from respiratory diseases (15·4%) and cancer (8·7%)
- The cost of implementing these two interventions would be less than US$0·40 per person per year in low-income and lower middle-income countries, and US$0·50–1·00 per person per year in upper middle-income countries (as of 2005)
- Although large absolute numbers of deaths could be averted with these selected interventions, they nevertheless account for only a small fraction of the total burden of chronic disease deaths
Modifiable risk factors and interventions

Reduction in salt consumption

Two meta-analyses of randomised controlled trials that examined the long-term effects of salt reduction in people with and without hypertension have shown that moderate reductions in salt intake (of 2–4·6 g per day) can reduce absolute systolic blood pressure by a small but important amount.14,15 One of these meta-analyses showed that the size of the decrease in blood pressure was correlated with that of the reduction in salt intake.19 Furthermore, similar reductions in salt intake can cause even greater decreases in blood pressure in people with higher baseline blood pressures.14,15 These studies add to observational evidence that blood pressure increases rapidly with age in populations which have a high average intake of salt,6,17 whereas communities in which salt consumption is very low do not have an age-related increase in blood pressure.6,18 Four prospective studies that directly examined the effects of sodium intake on cardiovascular mortality showed positive associations between dietary sodium intake and increased risk of stroke19,20 and coronary heart disease.21,22 WHO recommends a salt intake of no more than 5 g per day.23

In low-income and middle-income countries, salt is used predominantly to preserve meat and fish, and in seasoning or sauces used during cooking and at the table.14 Simple changes in diet—such as avoiding salty food and not adding salt at the table—can reduce sodium intake by about 3–4·5 g per day, which is equivalent to about 30% of the average daily intake.25,26 Such reductions have been achieved in intensive, short-term community-based interventions in China, Jamaica, and Nigeria.27,28 However, a controlled trial of a community-health-promotion programme in Ghana—where salt intake is comparatively low—did not cause a change in salt intake (despite a reduction in mean systolic blood pressure).29 Modification of the salt content of foods such as soy sauce and miso are also feasible,30 as is salt substitution.31

We modelled the effect of a 15% reduction in salt consumption on blood pressure in 23 low-income and middle-income countries that account for 80% of the burden of chronic diseases in developing countries (table 1 and webtable 1). This reduction would be achieved by a voluntary reduction in the salt content of processed foods and condiments by manufacturers, plus a sustained mass-media campaign aimed to encourage dietary change within households and communities.12,13,30,31 We modelled only the blood-pressure-dependent effects of sodium intake on cardiovascular mortality, and did not quantify reductions in other mortality outcomes that are mediated by blood pressure (eg, renal failure) or by other mechanisms (eg, gastric cancer32).

Reduction in tobacco use

The WHO Framework Convention on Tobacco Control (FCTC) has proposed a set of policies to reduce demand for tobacco.33,34 We selected some of the FCTC’s population-based control measures: increased taxes on tobacco products to reduce smoking prevalence; enforcement of smoke-free workplaces; requirements for FCTC-compliant packaging and labelling of tobacco products combined with public awareness campaigns about the health risks of smoking; and a comprehensive ban on tobacco advertising, promotion, and sponsorship.

Table 1 shows the estimated change in the real price of tobacco and in smoking prevalence that would result from implementation of these four FCTC policies. Weftables 2 and 3 show a detailed breakdown by country, with relevant demographic and administrative characteristics.14–16

We did not do the same analyses for the FCTC’s two other population-based policies for reduction of demand for tobacco—regulation of the contents of tobacco products and regulation of tobacco product disclosures (Articles 9 and 10 of the FCTC)—because of information constraints on effect size and resource-need estimates. However, we did include an additional cost estimate for a national household survey every 3 years to ascertain population-wide changes in smoking prevalence, since this underpins many of the modelled intervention strategies.

<table>
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<th>30–44 years</th>
<th>45–59 years</th>
<th>60–69 years</th>
<th>70–79 years</th>
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<tr>
<td>Reduction in salt intake (g per day)*</td>
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<td>1·69 (0·46)</td>
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<tr>
<td>Decrease in mean systolic blood pressure (mm Hg)†</td>
<td>1·24 (0·26)</td>
<td>1·70 (0·37)</td>
<td>2·34 (0·52)</td>
<td>2·83 (0·64)</td>
<td>3·46 (0·82)</td>
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<td>Increase in real price of tobacco§</td>
<td>43·2% (15·8%)</td>
<td>43·2% (15·8%)</td>
<td>43·2% (15·8%)</td>
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<tr>
<td>Change in smoking prevalence caused by non-price interventions</td>
<td>12% (0·7%)</td>
<td>12% (0·7%)</td>
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<td>12% (0·7%)</td>
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<td>Change in smoking prevalence caused by combined price and non-price interventions</td>
<td>20·8% (0·6%)</td>
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<td>20·8% (0·6%)</td>
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Data are mean (SD). *15% decrease in mean sodium intake. †Values are for the final year of the intervention (2015). §Population-level tobacco policies were assumed to apply equally to all categories of smokers. Increase in real price sufficient to reduce smoking prevalence by 10%.

Table 1: Effect sizes of salt-reduction and tobacco-control interventions for different age-groups in 23 countries (2006–15)
Analytical framework
For each of the 23 countries, and for all years between 2006 and 2015, we used methods from the WHO Comparative Risk Assessment project to estimate the effects of successful implementation of the two strategies.\(^\text{37}\) We calculated the proportion of chronic disease deaths from specific causes (see webtable 4) that could be averted if the distributions of mean systolic blood pressure and tobacco exposure were shifted to lower levels (the “potential impact fraction”) for different age-groups and sexes in adults.\(^\text{37}\) Technical details are in a webappendix.\(^\text{3,38–42}\) We then calculated the absolute numbers of deaths that would be averted for each disease outcome of interest by multiplying the potential impact fraction by total mortality from that disease outcome in the corresponding year. We added these results to give the total mortality that could be averted over 10 years. Cause-specific mortality data for diseases related to blood pressure and tobacco for 2006–15 were from updated projections in the Global Burden of Disease project.\(^\text{1}\)

Assessment of distributional shifts in risk-factor exposures
Salt interventions
We used data from the Intersalt study, which had the most comprehensive and consistent cross-population estimates of urinary salt excretion to date, to estimate projected salt intake if future consumption continued to follow recent trends (business-as-usual salt intake).\(^\text{7}\) Accurate longitudinal data for trends in salt consumption in low-income and middle-income countries are scarce, although recent reviews of mean salt consumption within populations showed that, with the exception of a few countries, mean sodium intakes have changed little over the past 20 years.\(^\text{17}\) We therefore ran the models on the basis that, in the absence of any interventions, salt consumption would stay constant. We obtained baseline blood pressure levels in 2006 and business-as-usual projections of mean systolic blood pressure to 2015 from the WHO Global InfoBase.\(^\text{46}\)

We then calculated the effects of the predicted reduction in salt intake on population mean systolic blood pressure. We used the relationship between change in sodium intake and change in systolic blood pressure for specific age-groups and sexes with different starting blood pressures, which were obtained by Law and colleagues from comparisons between populations.\(^\text{7,23,44–46}\) The Intersalt study also estimated these effects, but not for different age-groups or sexes.\(^\text{3}\) It therefore potentially underestimated the effects of dietary salt reduction in older people, for whom starting blood pressures are higher. We used coefficients from the series of studies by Law and colleagues\(^\text{47}\) in the primary analysis, and uncorrected coefficients from the Intersalt study in the sensitivity analysis.

We obtained relative risks of mortality as a result of reduced mean systolic blood pressure from the WHO Comparative Risk Assessment study.\(^\text{6}\) On the basis of a review of the time taken for risk reversal after a sustained reduction in blood pressure,\(^\text{4}\) we expected that risk reversal would be achieved 3 years after salt intake was reduced for hypertensive and cerebrovascular diseases (where risk reversal is defined as the diminishing excess risk among those who had formerly been exposed to the same levels as those who were never exposed). By contrast, for coronary heart disease and other cardiovascular disease outcomes, two-thirds of the risk reversal would take place in the first 3 years, and the rest over the subsequent 7 years.\(^\text{44}\)

Tobacco interventions
We calculated baseline exposure to tobacco for each age-group and sex from the accumulated smoking history and the phase of the tobacco-exposure epidemic in each country with projected rates of mortality from lung cancer for 2006–15 as an indicator of tobacco-associated hazardous effects in continuing and former smokers.\(^\text{1,39,40}\) We expressed business-as-usual tobacco exposures as “smoking impact ratios” (the prevalence of smokers within the study population who had accumulated smoking histories that were equivalent to those of a reference population for whom increased risk had been measured previously; webappendix).\(^\text{48}\)

We modelled the increases in taxation that would be sufficient to reduce smoking prevalence by 10% on the basis of data on tobacco taxation from recent World Bank and WHO studies (Yurekli A, International Development Research Centre, Canada, and Onder Z, Bilkent University, Turkey; personal communication).\(^\text{47}\) The total price elasticity of demand (percentage change in demand in response to a 1% increase in price) for tobacco products in low-income and middle-income countries ranges between −0.4 and −1.2.\(^\text{49}\) Half or more of the estimated effect on the demand for tobacco products results from a reduction in smoking prevalence,\(^\text{49}\) and the rest is attributable to reduced smoking intensity in continuing smokers. To be conservative, we calculated that the prevalence elasticity (percentage change in smoking prevalence in response to a 1% change in price) was half of the total price elasticity of demand. We did not account for changes in mortality in continuing smokers due to decreases in smoking intensity, which are likely to be smaller than mortality reductions due to smoking cessation, and thus we slightly underestimated the total effect of tobacco-control policies. We moderated all estimates of the health impact of higher tobacco taxes to account for the proportion of the tobacco market that evades taxation as a result of smuggling.

For non-price interventions, we estimated that comprehensive bans on smoking in the workplace would reduce smoking prevalence by 3–8%,\(^\text{30}\) in the context of the labour-participation rate in each country. We did not analyse the effects of enforcement of indoor-air laws on public transport. We calculated that dissemination of
health information (warnings about tobacco) would reduce smoking prevalence by 2%, although the effects could be higher in low-income and middle-income countries where the harmful effects of tobacco smoke are less well known. We estimated that media campaigns could be higher in low-income and middle-income countries where the harmful effects of tobacco smoke are less well known. We estimated that media campaigns would reduce smoking prevalence by 7%, and bans on tobacco advertising would reduce it by 2%. Effects of price and non-price interventions on the prevalence of smoking were analysed individually and in combination (table 2 and webtable 2). We assumed that proportional reductions in smoking prevalence would apply equally to all categories of smoker.

We used relative risks of death as a result of tobacco exposure from published analyses of the reference population. We also calculated the reversibility of the relative risk of tobacco-related mortality, according to the time since cessation of smoking, from a reanalysis of data on the reference group. We adjusted reversibility estimates for non-lung-cancer mortality outcomes to account for the rapid reversal of tobacco-related cardiovascular mortality risk after cessation of smoking, and the slower reversal of risk of death from chronic obstructive pulmonary disease.

Financial costs of implementation

Our selected population-based interventions will not require expenditures by patients or health-care providers. However, the interventions will depend on programmatic resource inputs for planning, implementation, and monitoring. Examples of activities with substantial resource consequences include: national and provincial meetings for strategic planning and monitoring of the programmes; national surveillance at the household level to assess changing rates of consumption of salt and tobacco; human resources for programme management, communication, enforcement, and regulation; awareness campaigns through mass-media channels; and supplies and equipment (including transport costs). Apart from vehicles, we did not include the costs of any capital items, such as land purchase or office construction.

We calculated resource needs on the basis of previous analyses of tobacco-control and salt-reduction strategies in different regions. The human resources needed at national, provincial, and district levels in different regions have been previously calculated, taking into account the capacities of these regions to raise taxes or to introduce and enforce new tobacco-control measures.

We assessed the capacity of the 23 countries in our study to implement the interventions as either weak, moderate, or strong (webtable 3). For mass media, we included the costs of television and radio advertising, newspaper advertisements, wall posters, and information leaflets. We based our estimates on a tested approach to communication for behavioural impact, which included specific proposals for the frequency and intensity of TV, radio, and newspaper advertisements needed to effect behavioural change.

To take account of expected synergies for implementation of a range of tobacco-control strategies, we combined the resource needs for legislation, promotion, and enforcement of indoor-air laws and a comprehensive ban on tobacco advertising into one estimate. Similarly, we estimated the joint resource needs associated with dissemination of health information and advertising to counter that of tobacco companies. Webtable 5 shows estimates for specific resource inputs in the categories of strategic development and assessment, human resources, and media and communications activities for a salt-reduction programme. Resource inputs for tobacco-control measures were likewise estimated (data not shown). Necessary quantities of office supplies and equipment for full-time employees of each programme are available elsewhere. We did not estimate any future reductions in health-care use that might result from a reduced incidence of cardiovascular disease.
Since these interventions are nationally applicable instruments of public policy, we worked on the basis that the full costs of implementation would apply over 10 years (ie, we did not envisage that they would be gradually scaled up). All costs are expressed in US dollar prices for the year 2005. Prices of resource items, such as salaries, per diems, equipment costs, and mass-media emissions, were obtained from the WHO-CHOICE database, which uses gross national income per person (plus other explanatory variables) to predict country-specific unit costs.

**Sensitivity analysis**

We assessed the effects of doubling the reduction in salt consumption to achieve a 30% decrease from baseline values, and of decreasing salt intake to the limit recommended by the WHO of 5 g per day. We also tested the sensitivity of the results by substitution of alternative coefficients for the conversion of salt intake to changes in blood pressure, from the Intersalt study (webtable 6). For tobacco interventions, we incorporated higher and lower estimates of the effects of non-price interventions, and the effect of an increase in the real price of tobacco to a cost that would reduce smoking participation rates by 20%. We also assessed how resource needs would be affected if each country had a weak or a strong capacity for implementation and if input prices were 20% higher or lower.

**Deaths averted**

Our findings show that over 10 years (2006–15), 13.8 million deaths could be averted if the selected measures to reduce tobacco and salt exposure were implemented (figure 1). 8.5 million deaths would be averted by implementation of the salt-reduction strategy alone, and 5.5 million by implementation of the four elements of the WHO FCTC alone. Most of the deaths averted (75·6%) would be from cardiovascular diseases, followed by deaths from respiratory disease (15·4%) and cancer (8·7%) (table 2).

58·7% of deaths averted would be in men, which stems from their higher and longer exposures to tobacco in low-income and middle-income countries. Deaths averted in men older and younger than 70 years would be about equal, whereas for women, many more deaths (71%) would be averted at older ages (>70 years), which reflects the later onset of cardiovascular mortality in women and the greater benefit of salt reduction in older age-groups for whom starting blood pressures are higher.

Most deaths would be averted in China and India (4.5 million and 3.1 million, respectively), as would be expected from the sizes of their populations. However, figure 2 shows that the highest gains in crude avertable mortality rates per 100 000 population older than 30 years would be in Russia (166) and in eastern European countries (Ukraine [153] and Poland [160]). These results reflect the very high rates of cardiovascular disease in

![Deaths averted per 100 000 population older than 30 years (2006-15)](image-url)

*Figure 2: Deaths averted per 100 000 population older than 30 years (2006-15)*
these populations, and their high baseline blood pressure and exposure to tobacco. Rates of avertable mortality for salt interventions alone were similarly high in these countries. Avertable mortality rates for tobacco interventions were highest for Poland, Vietnam, China, and Indonesia. The main reason so many deaths could be averted in Poland and Indonesia is that underlying tobacco exposures (and smoking impact ratios) are high, and therefore tobacco-reduction strategies could achieve large gains in these countries. In Vietnam and China, where tobacco exposures (as measured by smoking impact ratio) are lower, the high rates of potentially avertable mortality can be largely explained by the high death rates from tobacco-related causes—thus, small absolute decreases in tobacco exposure could still avert many deaths.

Potential impact fractions
Potential impact fractions for tobacco-control interventions (deaths averted by the interventions as a proportion of total possible deaths from chronic diseases) were highest in Indonesia, Poland, Thailand, and South Africa. In these countries, high tobacco exposures are combined with large price elasticities for tobacco products; thus, the moderate increases in real price that we modelled would manifest as many deaths averted. Potential impact fractions for salt-reduction interventions were highest in the Philippines, China, and Egypt; this reflects high baseline salt intakes in these societies. The scope to increase the intensity of the interventions can be seen by comparison of the potential impact fractions that would be achieved with the modelled intensity of interventions (7%) with those that might be achieved if exposure to risks from tobacco and blood pressure were reduced to the best possible levels (31%).

Financial cost estimates
Figure 3 and webtable 7 show the estimated financial costs associated with implementation of the selected interventions. Total expenditure for implementation of both strategies would range from $0.14 to $0.38 per person per year in low-income and lower middle-income countries, and from $0.52 to $1.04 per person per year in upper middle-income countries (webtable 7). The ranges in each group are primarily caused by differences in the prices or unit costs of programme inputs (such as salaries). Across all 23 countries, the mean implementation cost per person was $0.36, which on average was equivalent to 0.5% of government spending on health; for the nine low-income countries studied, the proportion was 4.7%. Expressed in terms of total costs, which largely reflected the range of population sizes (37 to 1282 million), expected expenditure needs ranged from less than $10 million per year in Democratic Republic of the Congo, Ethiopia, Burma, and Ukraine, to more than $200 million per year in China and India.

Most of the combined cost (67–80%) would arise from implementation of the population-based interventions of the FCTC. Half of this would be spent on legislation for and enforcement of comprehensive advertising bans and clean indoor-air laws (figure 3). The cheapest component of the FCTC package would be enactment of
revised levels of taxation on tobacco products ($0·02–0·17 per person). The main costs of the strategy to reduce salt consumption would be awareness campaigns through mass-media outlets and regulation of food products by public-health officers, with a total cost ranging from $0·04 to $0·32 per person for the countries analysed. In terms of expenditure categories, the largest cost would be the human resources needed for management and supervision of tobacco-control and salt-reduction programmes (over 50% of total costs), most of which would be incurred at the provincial and district levels.

Results of sensitivity analysis

Table 3 shows the sensitivity of estimates for avertable mortality and impact fraction to variations in the reduction of exposure to risks from tobacco and salt that could be achieved, and in the effectiveness of non-price interventions for tobacco control. Moreover, the results varied according to the coefficients used to calculate the conversion of changes in salt intake to reduced blood pressure (webtable 6). We calculated that the number of deaths that would be averted by salt interventions would be more than two-thirds lower with coefficients from the Intersalt study than with those used in our analysis. However even by this conservative estimate, simple measures to reduce salt consumption by 15% would avert 2·4 million deaths. The most pessimistic scenario for all interventions combined would avert almost 7 million deaths between 2006 and 2015; the most favourable would avert 35·3 million deaths over the same period.

In a best-case cost scenario—in which input prices were 20% less than predicted, and resource requirements reflected a strong capacity for implementation—mean expenditure estimates for the 23 countries would be 40% lower ($0·21 per person). By contrast, in the worst case—in which input prices were 20% more than predicted and the implementation environment was weak—expenditure estimates for the 23 countries would be 40% higher ($0·50 per person). In this worst-case scenario, investment per person would need to be $0·15–0·30 in low-income countries, and $0·50–1·70 in middle-income countries.

Discussion

Our investigation has highlighted the continuing high toll of tobacco deaths in regions where the tobacco epidemic is developing fastest, and the large number of potentially avertable deaths from cerebrovascular and hypertensive diseases in regions of high salt consumption. Our results show that 13·8 million deaths from chronic diseases could be averted over a 10-year period (2006–15) in 23 low-income and middle-income countries by implementation of a few population-based interventions. This potential health gain amounts to 38% of the global goal for reduction of chronic disease proposed by WHO in 2005, and just under 60% of the global goal for the 23 low-income and middle-income countries in our analysis. The addition of individual-level interventions with a multidrug regimen on the basis of opportunistic contact with the health service, as discussed in the next paper in this Series,6 could raise this figure to about 32 million deaths averted, which indicates the feasibility of achieving the global goal in these countries.

To show the potential effects of these interventions, we have modelled them for 23 countries which account for
most of the burden of chronic disease in developing regions of the world. But the interventions should be feasible in all low-income and middle-income countries. As expected, the largest absolute avertable burdens would be in the most populous countries in the world (China and India). However, when the effects of the interventions on chronic disease burdens in individual countries were considered, we showed that Poland, Indonesia, and the Philippines would have most to gain from implementation. The only potentially adverse effect of the interventions would be an increase in prevalence of iodine-deficiency diseases from reduced consumption of iodised salt. However, if salt could be supplemented with sufficient iodine to protect people who ate 5 g of salt per day, rather than the existing estimated intake of 10 g per day, the prevalence of iodine deficiency should not increase.24

The two interventions we selected would not reduce exposure to salt and tobacco to the minimum. Furthermore, the diseases under consideration are affected by many additional risk factors that fall beyond the scope of the selected intervention strategies. Previous analyses have shown that at least 45–50% of the chronic disease burden in low-income and middle-income countries can be attributed to a combination of known risk factors.25,26 Thus, the intensity of the selected interventions could be expanded incrementally to reduce risk-factor exposures to lower levels, and new interventions could be added to tackle risk factors (such as obesity) which would not be addressed by our package, as evidence for their effectiveness becomes available.

Others have attempted to assess the global costs associated with scaling up health interventions.27 For example, the cost of providing universal access to basic health services has been estimated to exceed $30 per person per year.28 We used the same method as these other costing exercises, and obtained much lower expenditure estimates. The selected interventions should be cheap, because they are made at the population level; are easy to introduce and maintain; and should not incur patient-level health-care expenditures. In the case of tobacco taxation, implementation costs would be largely if not completely offset by the revenues that are generated.

These interventions might also avert the costs of future health care, because of fewer events that cause admission to hospital. For example, economic studies that have taken the future health-care costs of salt reduction into account have assessed that interventions become cost-saving under plausible assumptions.29,30 We omitted these potential offsets because this was a financial (rather than an economic) analysis (for example, averted events imply economic savings with respect to inpatient bed days but would actually be unlikely to reduce financial outlays because freed bed-space would quickly be redeployed to address other acute health needs). The main limitations of our analyses stem from the underlying uncertainties in the data sources we used. Because data about salt consumption in low-income and middle-income countries were not available for many of the countries modelled, they had to be inferred from regional estimates. Furthermore, we did not have time trends for these data. Projections of mortality and exposure trends for smoking impact ratio and for blood pressure were, from necessity, based on many explicit assumptions. The ultimate effects of reduction in tobacco exposure were underestimated because the effects of reduction in smoking intensity were not modelled. Furthermore, because of the short timeframe of our study, we excluded the effects on smoking uptake in young people and their future mortality. We examined the sensitivity of our estimates to further feasible reductions in exposure distributions. A more ambitious approach, which would aim to reduce dietary salt to the recommended intake of 5 g per day and to increase the real price of tobacco to a cost that would result in a 20% fall in smoking prevalence, would avert 18·1% of deaths from the causes of chronic disease that we considered, compared with the 7·1% achieved with the selected set of interventions. Finally, our model assessed the number of deaths that would be averted in each year during the period 2006–15; we did not dynamically account or adjust for deaths of people who survived into subsequent years as a result of the specified interventions. Analysis of the global goal presented in the first paper of this series suggests that such people might survive for 18 years on average.31

A small number of population-based interventions, which could be implemented without great cost or the need for structural change to the health system, especially in the 20 out of 23 countries that are signatories to the FCTC, could make a major contribution to the goal of reducing rates of death from chronic diseases by an additional 2% per year. Although the absolute numbers of deaths that would be averted with these selected interventions are substantial, they nevertheless account for only a small fraction of the total burden of deaths from chronic diseases. This point emphasises the need for a combination of individual-level and population-level interventions, implemented in line with the best available evidence and in a stepwise manner that progresses from core to expanded optimum strategies, to slow the looming threat of chronic disease epidemics in low-income and middle-income countries.

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

Acknowledgments
We thank Regina Guthold and Kathleen Strong from the WHO Global InfoBase for generating the projections of blood pressure estimates, and Armando Peruga, Tom Gaziano, Shah Ebrahim, Anthony Rodgers, Douglas Bettcher, Jonathan Brown, and Alastair Gray for their written review and feedback. The views expressed are those of the authors and not necessarily those of WHO.
References


35. Lawes CMM, Feigin VL, Rodgers A. Estimating reductions in blood pressure following reductions in salt intake by age, sex and WHO region. Auckland, New Zealand: Clinical Trials Research Unit, University of Auckland, 2002.


61 Day NE. Epidemiological studies should be designed to reduce correction needed for measurement error to a minimum. BMJ 1997; 315: 484.


66 Abegunde DO, Mathers CD, Adam T, Ortegon M, Strong K. The burden and costs of chronic diseases in low-income and middle-income countries. Lancet 2007; published online Dec 5. DOI:10.1016/S0140-6736(07)61696-1.
Prevention of cardiovascular disease in high-risk individuals in low-income and middle-income countries: health effects and costs

Stephen S Lim, Thomas A Gaziano, Emmanuela Gakidou, K Srinath Reddy, Farshad Farzadfar, Rafael Lozano, Anthony Rodgers

In 2005, a global goal of reducing chronic disease death rates by an additional 2% per year was established. Scaling up coverage of evidence-based interventions to prevent cardiovascular disease in high-risk individuals in low-income and middle-income countries could play a major part in reaching this goal. We aimed to estimate the number of deaths that could be averted and the financial cost of scaling up, above current coverage levels, a multidrug regimen for prevention of cardiovascular disease (a statin, aspirin, and two blood-pressure-lowering medicines) in 23 such countries. Identification of individuals was limited to those already accessing health services, and treatment eligibility was based on the presence of existing cardiovascular disease or absolute risk of cardiovascular disease by use of easily measurable risk factors. Over a 10-year period, scaling up this multidrug regimen could avert 17·9 million deaths from cardiovascular disease (95% uncertainty interval 7·4 million–25·7 million). 56% of deaths averted would be in those younger than 70 years, with more deaths averted in women than in men owing to larger absolute numbers of women at older ages. The 10-year financial cost would be US$47 billion ($33 billion–$61 billion) or an average yearly cost per head of $1·08 ($0·75–$1·40), ranging from $0·43 to $0·90 across low-income countries and from $0·54 to $2·93 across middle-income countries. This package could effectively meet three-quarters of the proposed global goal with a moderate increase in health expenditure.

There were an estimated 35 million deaths from heart disease, stroke, cancer, and other chronic diseases worldwide in 2005. 80% of these deaths were in low-income and middle-income countries, and this proportion is projected to increase further in the coming decades. A major driver of the rising burden is the epidemiological transition, especially ageing of populations. Underlying social, environmental, and economic changes have led to increasing levels of major chronic disease determinants such as tobacco smoking, inadequate physical activity, unhealthy diets, excess bodyweight, and suboptimum levels of blood pressure, cholesterol, and plasma glucose. Proven cost-effective strategies are available for reducing exposure to chronic disease risk factors in low-income and middle-income settings, including both population-wide and individual high-risk approaches. Scaling up these interventions is essential for achieving the goal of an additional 2% yearly reduction in rates of chronic disease deaths over the next 10 years. Demonstrating the potential health effects and cost of scaling up is essential to build the political will for action, develop investment plans, and mobilise resources. The second paper in this Series covered the evidence base for preventing chronic disease, and the third paper covered population-wide strategies for preventing chronic disease. In this paper, we consider individual approaches, defined as interventions in which the primary actors are individual people and their health-care professionals. The individual-based strategies with the greatest accumulated evidence of effectiveness are drugs to prevent cardiovascular disease: blood pressure-lowering drugs, cholesterol-lowering drugs, and aspirin. Although these interventions are cost effective in low-income and middle-income countries and are available in most markets, their current coverage in high-risk individuals in these settings remains low. There is also likely to be abuse and waste in many settings. This situation represents a substantial lost opportunity for reducing the rising burden of chronic diseases.

Key messages

- A global goal of reducing chronic disease death rates by an additional 2% per year was established in 2005
- Treatment of high-risk individuals with aspirin, blood pressure-lowering drugs, and cholesterol-lowering drugs to prevent cardiovascular disease is effective and cost effective. However, coverage in low-income and middle-income countries is low
- Scaling up a multidrug regimen targeted at individuals with existing cardiovascular disease or who are at high absolute risk of cardiovascular disease could avert almost 18 million deaths over the next 10 years in 23 low-income and middle-income countries
- The financial cost would be an average yearly cost of $1·08 per head, ranging from $0·43 to $0·90 across low-income countries and from $0·54 to $2·93 across middle-income countries
- This cost could effectively meet three-quarters of the proposed global goal with a moderate increase in health expenditure.
Unlike high-technology approaches, a simple multi-drug regimen of aspirin, blood pressure-lowering drugs, and cholesterol-lowering drugs for individuals at high-risk of cardiovascular disease could more easily be brought to scale in low-income and middle-income countries, since it could be delivered mainly through primary health care or outpatient settings. Scale-up could be further facilitated by limiting screening of patients to those already accessing health services (opportunistic screening), and identifying high-risk individuals with an absolute risk approach.17 Most people at high risk can be easily identified by their history of having had a heart attack, stroke, or other major vascular event. Others can be identified with easily measurable risk factors (eg, age, sex, blood pressure, body-mass index, tobacco use) that do not require expensive and time-consuming laboratory testing. Although ultimately these medicines could be combined into a single pill,18–20 evidence for a combination pill is not yet definitive, nor is a cheap combination pill of aspirin and drugs for lowering blood pressure currently available.21 In the meantime, the scaling up of proven individual drugs for prevention of cardiovascular disease should not be delayed.

Our aim was to establish the number of deaths between 2006 and 2015 that could be averted and the financial cost of scaling up a multیدrug regimen for prevention of cardiovascular disease in a selection of low-income and middle-income countries. Countries were included in the analysis if they were classified as low-income or middle-income countries, and they accounted for at least 0·7% of the global disability-adjusted life-years (DALYs) attributable to chronic diseases for such countries.4 23 countries, accounting for 80% of global chronic disease deaths in all low-income and middle-income countries, were included (table 1). We adhered to the costing principles used in other studies that have estimated the worldwide costs of scaling-up health service delivery for other conditions.22,23 A public provider perspective for costs was used, with costs reported in 2005 US$ over the period 2006 to 2015.

**Definition of high-risk individuals**

We defined high-risk individuals as those aged between 40 and 79 years who have had non-fatal coronary heart disease or a cerebrovascular event. Individuals within the same age range and without established disease were also deemed high-risk if they had an estimated absolute risk of dying from coronary heart disease or a cerebrovascular event of 15% or more over the next 10 years. Absolute risk was determined from country-specific risk charts, constructed as part of this analysis (see below), that relied on easily measurable risk factors only. Individuals with existing cardiovascular disease would receive aspirin, an angiotensin-converting-enzyme inhibitor, a β blocker, and a statin, whereas for those without existing cardiovascular disease but who are at high risk, a thiazide would replace the β blocker.24 There is much debate about the choice of first-line blood pressure-lowering drugs in those without existing cardiovascular disease. The drugs listed here are simply illustrative and the general principle is that most people need two blood pressure-lowering agents. We assumed that patients who were initially without existing disease and were treated, but subsequently had an incident cerebrovascular event or non-fatal coronary heart disease, would be switched over to the regimen for those with existing disease. Individuals who were treated and adherent were assumed to be treated indefinitely.

**Simulation model**

A microsimulation model (webappendix) was used to create for each country a series of 10,000 individual life histories for each 5-year age-group and sex-group over the period 2006 to 2015. This simulation was done using information on the population distribution of risk factors, correlations between risk factor levels, associations between risk factors and disease, and population-level estimates of ischaemic heart disease, cerebrovascular events, and other mortality (table 2).27,29–31 Age-specific and sex-specific trends in risk factor rates and mortality during this period were included by using information

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**Table 1:** Countries that account for 80% of global chronic disease deaths in low-income and middle-income countries

<table>
<thead>
<tr>
<th>Country</th>
<th>CMH health system strength category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>3</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>2</td>
</tr>
<tr>
<td>Brasil</td>
<td>4</td>
</tr>
<tr>
<td>Burma</td>
<td>2</td>
</tr>
<tr>
<td>China</td>
<td>4</td>
</tr>
<tr>
<td>Colombia</td>
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</tr>
<tr>
<td>Democratic Republic of the Congo</td>
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</tr>
<tr>
<td>Egypt</td>
<td>4</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>4</td>
</tr>
<tr>
<td>India</td>
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</tr>
<tr>
<td>Indonesia</td>
<td>3</td>
</tr>
<tr>
<td>Iran</td>
<td>4</td>
</tr>
<tr>
<td>Mexico</td>
<td>4</td>
</tr>
<tr>
<td>Nigeria</td>
<td>4</td>
</tr>
<tr>
<td>Pakistan</td>
<td>2</td>
</tr>
<tr>
<td>Philippines</td>
<td>4</td>
</tr>
<tr>
<td>Poland</td>
<td>4</td>
</tr>
<tr>
<td>Russia</td>
<td>4</td>
</tr>
<tr>
<td>South Africa</td>
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<td>Thailand</td>
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<td>Turkey</td>
<td>4</td>
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<tr>
<td>Ukraine</td>
<td>4</td>
</tr>
<tr>
<td>Vietnam</td>
<td>4</td>
</tr>
</tbody>
</table>

CMH=Commission on Macroeconomics in Health. Categories of health system strength range from 1 to 4, where 1 is the most constrained and 4 the least constrained.

See Online for webappendix
Table 2: Main model parameters

<table>
<thead>
<tr>
<th>Risk factor distribution</th>
<th>Description</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>Mean and SD (mm Hg) for country, sex, age, and calendar year</td>
<td>25</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Mean and SD (mmol/L) for country, sex, age, and calendar year</td>
<td>25</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>Mean and SD (kg/m²) for country, sex, age, and calendar year</td>
<td>25</td>
</tr>
<tr>
<td>Current daily smoking</td>
<td>Prevalence specific for country, sex, age, and calendar year</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Prevalence specific for GBD region, sex, and age</td>
<td>26</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>Prevalence specific for GBD region, sex, and age</td>
<td>26</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Prevalence specific for GBD region, sex, and age</td>
<td>26</td>
</tr>
<tr>
<td>Risk factor correlations</td>
<td>Correlation matrix for risk factors above specific for region, sex, and age</td>
<td>Datasets available to the authors</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factor-disease associations</th>
<th>Description</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>Sex-and-age specific relative risk per mm Hg increase for ischaemic heart disease and cerebrovascular disease</td>
<td>27</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Sex-and-age specific relative risk per mmol/L increase for ischaemic heart disease and cerebrovascular disease, adjusted for proportion of ischaemic versus haemorrhagic stroke</td>
<td>28</td>
</tr>
<tr>
<td>Current daily smoking</td>
<td>Age-specific relative risks of prevalent smoking for cerebrovascular disease</td>
<td>29</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Sex-specific relative risks of prevalent diabetes for ischaemic heart disease and cerebrovascular disease</td>
<td>30,31</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>Sex-specific relative risks of prevalent coronary heart disease for cerebrovascular disease and coronary heart disease death</td>
<td>32</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>Sex-specific relative risks of prevalent cerebrovascular disease for ischaemic heart disease and death from cerebrovascular disease</td>
<td>33</td>
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</table>

Mortality

<table>
<thead>
<tr>
<th>Coronary heart disease</th>
<th>Mortality rates (ICD10 codes I20-I25) specific for country, sex, age, and calendar year</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular disease</td>
<td>Mortality rates (ICD10 codes I60-I69) specific for country, sex, age, and calendar year</td>
<td>2</td>
</tr>
<tr>
<td>Other mortality</td>
<td>Mortality rates from causes other than ischaemic heart disease and cerebrovascular disease specific for country, sex, age, and calendar year</td>
<td>2</td>
</tr>
</tbody>
</table>

GBD=Global Burden of Disease.

Table 2: Main model parameters

from the WHO Global InfoBase and updated projections of the Global Burden of Disease database. The model was implemented in Stata 9.2 (Stata Corporation, Texas, USA). An individual’s yearly risk of coronary heart disease and cerebrovascular event was determined as a function of sex, age, continuous level of systolic blood pressure and total cholesterol, whether they currently smoke, and whether they have prevalent diabetes, coronary heart disease, or a cerebrovascular event. The 10-year combined risk of fatal coronary heart disease or cerebrovascular event for each individual in the simulation model was determined as a function of their yearly risk, assuming an exponential function.

Body-mass index is highly correlated with blood pressure, cholesterol, and diabetes. Previous studies, however, have shown no significant association between body-mass index and coronary heart disease and cerebrovascular events when adjusted for these factors. On this basis, it has not been included as an independent predictor of an individual’s risk of coronary heart disease and cerebrovascular events. In many low-income and middle-income countries, however, measuring blood cholesterol or plasma glucose for the diagnosis of diabetes might be too expensive or impractical. As such, although not included as an independent determinant of risk, we explicitly modelled each individual’s body-mass index by incorporating known correlations of body-mass index with blood pressure, cholesterol, and diabetes (webappendix). Body-mass index is then used in the absolute risk charts as a proxy for cholesterol and diabetes because it is more easily measured.

Inevitably countries will adopt different risk prediction strategies, and the basic approach described here is only suggestive and not prescriptive. With more sophisticated algorithms that better target those at high risk, such as approaches that include measurement of cholesterol, fasting plasma glucose, or urine dipstick testing for glycosuria, both the costs and benefits can be expected to increase.

Absolute risk charts were generated by categorising the simulated population according to sex, age, smoking status (current smoker, non-smoker), systolic blood pressure (<120, 120–139, 140–159, 160–179, 180+ mm Hg), and body-mass index (<22.5, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30+ kg/m²). Risk charts were constructed by categorising the mean 10-year risk of fatal coronary heart disease or cerebrovascular events for each combination of the above risk factor strata into (i) greater than or equal to 15%; and (ii) less than 15% (figure 1).

Current coverage and estimated scale-up

Current coverage of the individual drugs was established from available sources. For countries where estimates were not available, Global Burden of Disease regional averages of current coverage were used.

Scaling-up patterns used in this analysis are intended to suggest, not prescribe, how scale-up could be achieved. As with previous studies, the Commission on Macroeconomics in Health (CMH) index was used to classify countries into four levels of health systems strength, where CMH1 is the most constrained and CMH4 the least constrained (table 1). For countries for which there was no CMH value, we made assumptions based on total health expenditure per head.

For the most constrained countries (CMH1), we assumed a slow start due to a need for such countries to strengthen the health system in initial years before commencing scale-up of drug provision to the target coverage of 50% of those accessing health services by 2015 (figure 2). For CMH2 countries we assumed a sigmoid curve in line with the traditional shape of scale-up curves up to the target coverage of 50% of those accessing health services by 2015. Countries classified as CMH3 were assumed to need fewer initial investments; the model assumes an almost linear sigmoid pattern, only slowing down near the target coverage of 80% of those accessing health services by 2015. For the least constrained (CMH4) countries,
rapid linear scale-up up to the target coverage of 80% by 2010 was assumed to be feasible.

The proportion of the population accessing health services each year, by age, sex, and country was estimated by using information from the 2002 World Health Survey. For the 11 countries without World Health Survey results, the Global Burden of Disease regional population-weighted average was used.

**Estimation of effectiveness and adherence**

Effectiveness of the individual drugs in those with and without established disease was established in the same way as in modelling exercises from previously published studies (table 3). Since these studies indicated that the relative risk reduction of these drugs is roughly constant across major subgroups, the joint effect was estimated by multiplying the relative risks for each individual drug and applied to an individual’s estimated yearly probability of a fatal or non-fatal coronary heart disease or cerebrovascular event.

Studies of adherence under non-trial conditions to medication for cardiovascular disease prevention report long-term adherence rates of around 20–80%, with the rate of discontinuation highest in the first 12 months after the start of treatment. Individuals with established disease and those with smaller out-of-pocket medication payments are also more likely to be adherent. For the purposes of this analysis, we assumed that long-term adherence to the multidrug regimen in those with established disease would be 60% (varied between 40% and 80% in uncertainty analysis). For those without established disease we assumed a lower adherence rate of 40% (varied between 20% and 60% in uncertainty analysis). Of the individuals who discontinue treatment, we assumed that 70% of them would do so in the first year, 20% in the second year, and 10% in the third year of treatment.

**Estimation of costs**

Costs were divided into patient and programme costs with inputs defined in accordance with current standards of treatment and based on general experience of health system requirements. Patient costs refer to costs at the point of delivery and include service delivery costs related to screening individuals and delivering and monitoring the intervention, drug costs, and laboratory testing (table 4). An additional 2 min was assumed to be required to assess treatment eligibility in screened individuals. For each treated individual, two additional service delivery contacts (15 min each) per year were also included. For drug costs we used median buyer prices (including buyer prices for various government health agencies) reported in the Management Sciences for Health (MSH) database for the year 2005, with the low and high price used as the lower and upper ends of the uncertainty interval. A country-specific multiplier from the database WHO CHOosing Interventions that...
are Cost Effective (WHO-CHOICE)\textsuperscript{8} was used to account for drug transportation costs. Cost estimates do not account for storage, loss, or wastage of drugs. Laboratory tests for electrolytes, renal function, and liver function per treated individual per year were assumed to be needed.

Programme costs include those incurred at the administrative levels of districts, provinces, or countries. Programme costs include the additional yearly cost of national and provincial-level management teams responsible for administration, and for monitoring and assessment of the intervention. National and provincial-level workshops for strategic development and coordination purposes were assumed to take place every 2 years. In-service training of health-care workers to deliver the intervention was also done every year. Four 3-day training courses per health district per year with an average of 20 attendants were assumed. The cost of producing risk charts was also included. All programme costs were adjusted for the population-level coverage of the intervention. Country-specific unit prices for laboratory, service delivery, and programme-related costs were derived from the WHO-CHOICE database.\textsuperscript{50} Since the intervention relies on opportunistic screening, and therefore existing health care infrastructure and health workers, we did not consider the additional costs of recruiting and training new health workers or building new health facilities.

Probabilistic, multivariate uncertainty analysis was used to establish the effect of uncertainty in both effect and cost parameters on the main outcome measures. Best-case and worst-case scenario analyses were also done on the cost of drugs, reduction in risk of drugs, and patient adherence.

**Projected deaths averted**

The programme scale-up was estimated to avert a cumulative 17·9 million deaths (95% uncertainty interval 7·4 million–25·7 million) over the period 2006 to 2015 (figure 3). This number amounts to almost a fifth of cardiovascular disease deaths that would have otherwise occurred in these countries during this time. Three-quarters of those treated would be younger than 70 years (table 5). 56% of deaths averted would be in people younger than 70 years (table 5); when measured in life-years or health-adjusted life-years gained, an even larger proportion of the health benefit can be expected to accrue at middle-ages. 54% of deaths averted would be from coronary heart disease and 46% of deaths averted would be from cerebrovascular events. With their large population sizes and high underlying risk of cardiovascular disease, the largest absolute number of deaths averted over the next 10 years would be in India (5·8 million), China (4·8 million), and Russia (1·7 million).

**Projected financial cost of scaling up**

The average cost per treated individual per year is $55; this translates into an estimated cumulative 10-year cost of scale-up of $47 billion (95% uncertainty interval $33 billion–$61 billion; figure 4). This cost includes resources spent on medicines ($32·1 billion, 68% of total costs), health service delivery for screening and treatment...
The financial resources needed to scale-up this intervention are an average investment per year of around $5 billion, or $1·08 per head. Although this amount is not insubstantial, it is less than or similar to estimated resource needs for other interventions.\textsuperscript{22,23,13,14-15} This information provides a basis for developing country-specific agendas for action and investment plans by identifying the additional amount of resources that need to be mobilised. It suggests that in some settings monetary resources are not an insurmountable barrier to scaling up this strategy; low-income countries, however, will clearly need large amounts from external donors. In the Democratic Republic of the Congo, Burma, and Ethiopia, for example, this investment would represent around a tenth or more of current health expenditure.

There are several factors that any investment plan for this strategy should also consider. A key one will be ensuring access and supply of inexpensive cardiovascular medicines. This factor is crucial since drug costs, even at the generic-based median prices reported by MSH, account for two-thirds of the estimated resource needs. At the lowest drug price reported by MSH, the overall financial burden of this strategy could be substantially reduced to $0·56 per person per year. Availability of these multidrug regimens in the public sector, however, is low and, although availability is higher in the private sector, the price is substantially higher than prices reported by MSH and unaffordable for most individuals who need them.\textsuperscript{13} A range of policies is required at both international and country levels, such as promoting local manufacturing of generic products, pooling procurements, and price regulation, to ensure availability of inexpensive, high-quality cardiovascular medicines. Another crucial factor is the need for a functioning and effective primary health-care system to deliver this package.
particularly in the poorest settings, strengthening of the primary health-care system will be needed before scale-up can proceed. Related to this is the availability of human resources for health to screen and treat individuals. Non-physician health-care workers can be retrained to reliably and effectively assess and manage cardiovascular risks in primary health-care settings, even when there are no attending physicians.57 The additional time demands of the strategy described here are also not too onerous, particularly because the risk factors (history of disease, smoking status, height, weight, and blood pressure) used to identify high-risk individuals are often part of standard clinical examinations.

A related issue is who pays for the intervention. If the financial burden is predominantly borne by the patient, this will also have a negative effect on coverage and patients’ adherence,41 particularly in low-income settings. Long-term adherence, even in high-income settings, to cardiovascular prevention medication is typically low41–48 and its importance is highlighted by the sensitivity of the overall costs and health effects to this variable. Further research on mechanisms to improve patients’ adherence58,59 in developing countries could have a large effect on the success of the strategy proposed here.

The integration of service delivery of multidrug regimens for cardiovascular disease prevention with other ambulatory health services—ie, an opportunistic screening approach—aims to improve the cost-effectiveness and feasibility of this strategy, particularly during the early stages of scaling-up coverage. These benefits need to be balanced against a potential increase in health inequalities.60 This problem is not unique; for example, the effect of scaling up antiretroviral therapy is receiving increasing attention.61 Further research on the effect of different delivery methods for cardiovascular disease prevention on health inequalities are needed to inform implementation.

The acceptability of the proposed strategy for key stakeholders such as health-care professionals will probably be another key issue. Although there are legitimate concerns about large-scale medicalisation of the population, in the approach described here we focus only on those who are at highest risk in whom there is no controversy about indications for these medicines. The absolute risk stratification approach has been used for some time in settings such as New Zealand and western Europe;17 however, this approach is counter to established clinical practice in most low-income and middle-income countries that tend to focus on risk-factor thresholds, even though risk-based care is more effective and cost effective.6,9 Furthermore, although in this analysis we have kept the costs and demand on the health system to a minimum by limiting identification of high-risk individuals to easily measurable risk factors, some countries might choose to include cholesterol and blood sugar measurements, as is typically done in countries where the absolute risk approach is currently used. Countries might also choose to use waist circumference rather than body-mass index. Strategic development of an implementation plan that addresses these issues, in consultation with health practitioner groups, producers of national treatment guidelines, and civil society groups, will be an important component.

We have estimated the costs and health effects of scaling up a package of individual drugs. Combining these into one pill18–20 would reduce the complexity of a
multidrug regimen and potentially improve adherence as well as reducing production, distribution, and storage costs. Evidence for the efficacy of a combination pill is not definitive,10 nor is a four-drug combination currently available. Further information from current trials will provide eagerly awaited information on the effectiveness, safety, and adherence profile of a combination pill.

There are several limitations of the current analysis that should be considered. Although the best available data have been used, there is uncertainty, particularly in the least-developed settings where such data are scarce. For example, the estimates of patients’ adherence to medication used in this analysis are derived from studies in high-income settings, and these might not be easily transferable to low-income and middle-income country settings. We have, however, done extensive uncertainty analysis to quantify a plausible range. We have also not measured potential cost savings of avertting cardiovascular disease events that might offset the costs of this intervention, nor have we measured the potential costs of side-effects that might add to the costs of scaling up this intervention.

In terms of the scope and objectives of the analysis, the estimates provided here are intended to be suggestive, and not prescriptive, of how an individual high-risk approach for chronic disease could be scaled up. Country-specific approaches will, in reality, vary substantially from what is presented here. By focusing on aspirin, blood pressure-lowering drugs, and cholesterol-lowering drugs, our intention was not to discount the potential role of other individual approaches such as encouraging dietary, lifestyle, or other behavioural changes.10 Rather, we hoped to highlight the potential of a simplified and more easily scalable strategy for cardiovascular disease prevention in reducing the large health and economic burden attributable to chronic diseases in low-income and middle-income countries. The approach described here should also not be regarded as an alternative, but rather is complementary to population-wide approaches. For example, when the individual approach described here and the population-wide approaches described in the third paper in this Series7 are combined, they could essentially meet the proposed global goal.

Chronic disease deaths are projected to continue to rise in low-income and middle-income countries. Urgent attention should be paid to increasing efforts to prevent this rising burden. Scaling up an individual prevention approach, based on opportunistic screening, identification of high-risk individuals by easily measurable risk factors, and treatment with a multidrug regimen, could avert almost a fifth of all deaths from cardiovascular disease, and could be realised with a moderate increase in health expenditure.

Contributors
SSL designed and did the analysis and drafted the paper. AR, TAG, and EG contributed to the framework and design of the study. TAG analysed risk factor correlations for South Africa. EG and RL analysed risk factor correlations for Mexico. KSR analysed risk factor correlations for India. FF analysed risk factor correlations for Iran. Revisions were done by SSL with input from all authors.

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

Acknowledgments
We thank Regina Guthold and Kathleen Strong for providing data from the WHO Global InfoBase; Colin Mathers for data on mortality projections; Dan Chisholm for technical input on programme costs; Robert Beaglehole and Rod Jackson for input on the design of the study; and Robert Beaglehole, Dan Chisholm, and Ben Johns for comments and suggestions on drafts. EG thanks the Mexican Ministry of Health and the Grand Challenges in Global Health. FF thanks the Grand Challenges in Global Health.

References


Risk of authoritarianism: fibrinogen-transmitted hepatitis C in Japan

Hideo Yasunaga

In 1977, the US Food and Drug Administration revoked all licences for fibrinogen concentrate because of the risk for hepatitis infection and suspected lack of effectiveness. However, in Japan, fibrinogen concentrate was used routinely for treatment of obstetric bleeding until 1988. Even in 1997, academic texts by Japanese authorities in obstetrics still recommended that obstetricians use the product. An estimated 10 000 cases of hepatitis C infection are attributable to use of fibrinogen in Japan and are a result of authoritarianism that hindered effective policy changes. Scientists have a duty to refine repeatedly the quality of their evidence, and policymakers need to adjust existing policies continually to accord with the latest scientific evidence.

Introduction

In the 1980s, a plasma-derived factor VIII product brought tragedy to people with haemophilia in the form of HIV-1 infection. In Japan, about 40% (n=1800) of all patients with this blood disorder were infected with HIV-1, and lawsuits were brought against pharmaceutical company officers, a bureaucrat at the Ministry of Health and Welfare, and a prominent doctor.

AIDS, when caused by HIV-1-contaminated plasma derivatives, is called Yakugai-AIDS in Japan. Yakugai is a Japanese word with an original meaning of “health hazards due to pharmaceuticals”. However, this word no longer represents just adverse drug effects. Yakugai, as currently used, indicates cases in which the harmful effects of pharmaceuticals are disregarded by pharmaceutical companies, government, and doctors, resulting in the spread of health hazards caused by those products.

The social uproar that was caused by Yakugai-AIDS seemed to calm down for a time, but a new situation loomed. Until 1988, fibrinogen concentrate was used routinely in Japan, and about 10 000 cases of hepatitis C virus infection were estimated to have arisen in individuals who had been given this product. Most were women patients treated with fibrinogen for obstetric bleeding.

The spread of hepatitis C virus infection was similar to Yakugai-AIDS in that it was caused mainly by use of virus-contaminated blood products. However, one thing was definitely different; although the factor VIII product was apparently effective for treatment of haemophilia, the effectiveness of fibrinogen against obstetric bleeding was suspect.

Disseminated intravascular coagulation is a severe complication of massive bleeding in obstetric disorders such as abruptio placentae. Use of coagulation factor concentrates in patients with this disorder is generally not advocated because they contain only selected coagulation factors, whereas affected individuals usually have a deficiency of all coagulation factors.4,5

This report aims to trace the medical history of fibrinogen concentrate use in Japan, to search for reasons for the inability to prevent the spread of hepatitis C virus infection, and to draw a lesson from this negative legacy of the past for current medical care and health policy.

Background to fibrinogen concentrate use in Japan

In 1964, in the wake of the furore surrounding the US Ambassador’s infection with hepatitis after a blood transfusion in Japan, the Japanese government adopted a policy of switching from commercial to donated blood. This strategy proved effective: the incidence of post-transfusion hepatitis in Japan was reduced from 50·9% to 16·2% per year.6 However, the government only decreed that the supply of blood should be from donations; no pronouncement was made about use of plasma-derived products. The Japan Blood Bank was formed into a pharmaceutical company named Midori Juji (Green Cross) and it started production of plasma-derived products from imported commercial blood.

The US Food and Drug Administration (FDA) approved use of unheated fibrinogen concentrate in 1947. However, after the late 1950s, fibrinogen-transmitted hepatitis cases were being reported repeatedly,7,8 and the FDA revoked all US licenses for fibrinogen concentrate in December, 1977.9 Reasons for this change included the high risk of hepatitis infection, availability of an alternative cryoprecipitate derived from one donor, and suspected lack of effectiveness of fibrinogen for disseminated intravascular coagulation.

In 1964, the Japanese Ministry of Health and Welfare approved use of unheated fibrinogen concentrate for secondary hypofibrinogenaemia, which was produced by Green Cross. Approval of this product was based on data from a case series of only 60 patients.10 Green Cross made plasma derivatives from pools of imported plasma taken from between 2000 and 20 000 donors. Until 1987, fibrinogen concentrate had been treated with viral inactivation measures including ultraviolet radiation and β propiolactone, but it was not heat treated. Fibrinogen use spread rapidly after approval, and the product was used as a haemostatic agent in clinical settings in obstetrics.

After the thalidomide tragedy in the 1960s,11 a reassessment system for medicines was introduced in Japan in 1971. However, fibrinogen was left out of this process, even though supportive evidence for this drug...
for the next 20 years included only case reports and expert opinion.

Green Cross received the information about the FDA’s withdrawal of approval for unheated fibrinogen concentrate as soon as it was implemented in 1977, but the company did not inform the Ministry of Health and Welfare. In the 1970s, pharmaceutical companies were not legally obliged to report information about foreign drugs to the Ministry. Furthermore, the Ministry of Health and Welfare did not have an independent information-gathering system for foreign data. In 1984, the Ministry asked Green Cross to provide basic data on fibrinogen for reassessment. In the information given, the FDA withdrawal was described; this instance was the first notification the Ministry claimed to have received of the FDA withdrawal. In 1985, the product underwent reassessment.

In January, 1987, a local outbreak of hepatitis infection greatly changed the situation for fibrinogen concentrate. An obstetrics clinic in Aomori Prefecture reported to the Ministry of Health and Welfare that seven of eight patients administered fibrinogen were stricken with non-A non-B hepatitis. Subsequently, nine women administered fibrinogen were reported to be infected. In April, 1987, Green Cross initiated a voluntary recall of unheated blood products and switched to heated products.

In June, 1987, the Investigation Committees for Re-evaluation of Human Blood Products, the members of which were specialists in transfusion or haematology, recommended to the Ministry of Health and Welfare that the indications for fibrinogen should be restricted to congenital hypofibrinogenaemia, since effectiveness of the drug against secondary hypofibrinogenaemia was unconfirmed. However, in September, 1987, the Japan Society of Obstetrics and Gynecology and the Japan Association of Obstetricians and Gynecologists protested against this decision. The reason given was that fibrinogen was used widely in clinical settings in obstetrics. Eventually, their request was accepted, and secondary hypofibrinogenaemia remained an indication.

Heat treatment was not effective enough to inactivate hepatitis C virus. In May, 1988, Green Cross reported 34 cases of hepatitis infection in patients administered heated products to the Ministry of Health and Welfare. In June, 1988, the company distributed a letter to all doctors and medical institutions warning them about fibrinogen-transmitted hepatitis.

The number of fibrinogen products that Green Cross supplied to medical institutions had continually risen since the 1960s until 1986, when it reached 76 500 products annually. However, this figure fell substantially to 58 300 in 1987 and 11 200 in 1988; few fibrinogen products have been used since 1989.

Choo and colleagues successfully isolated cDNA derived from the hepatitis C virus genome. Subsequently, Green Cross started donor screening for viral antibodies in 1990, and they enhanced safety by adding solvent and detergent treatment to plasma products in 1993; however, the demand for fibrinogen concentrate never recovered.

In 1995, the Investigation Committees for Re-evaluation of Human Blood Products pressed Green Cross to present further evidence on the effectiveness of fibrinogen for secondary hypofibrinogenaemia. However, Green Cross did not fulfil this request because of the striking decrease in sales for the product. Thus, secondary hypofibrinogenaemia was finally removed as an indication in 1998.

In 1990, a report of fibrinogen concentrate was published in Konnichi no chiryo shishin (Today's therapy), the most popular medical care manual for clinicians in Japan. After 1991, the description had disappeared, possibly because the product had seldom been used since 1989. However, until 1997, experts continued to write about fibrinogen in academic texts on obstetrics. One expert in 1980 said: “I cannot leave a patient dying from blood loss. I decided to carry out fibrinogen infusion.” After 1989, with a few exceptions, most academic books and reports on obstetrics still contained a note about fibrinogen infusion.

One text published in 1996 stated: “Fibrinogen poses a risk of hepatitis C virus infection”. However, most published works contained no indication of the hepatitis risk. After 1998, descriptions of fibrinogen concentrate in academic texts were no longer published.

Following the discussion session with experts on measures against hepatitis, instigated by the Ministry of Health and Welfare in 2000, the issue of fibrinogen and hepatitis C virus infection was again highlighted. In this session, a haematologist appealed for a survey to clarify the situation with respect to fibrinogen-transmitted hepatitis C virus infection. In response to this request, in March, 2001, the Ministry of Health and Welfare ordered Welfide—a company formed after the merger of Green Cross with Yoshitomi Company—to report on past use of fibrinogen, according to the Pharmaceutical Affairs Law (see next section).

Data for fibrinogen-transmitted hepatitis C virus infection in Japan

Screening for hepatitis B virus in donated blood started in 1972 in Japan, but this process only reduced the incidence of post-transfusion hepatitis infection from 16·2% to 14·3% a year. The presence of so-called non-A non-B hepatitis was already recognised at this time—eg, Prince and co-workers reported that 36 (71%) of 51 cases of post-transfusion hepatitis were caused by an unidentified agent other than hepatitis B virus. Incidence of post-transfusion hepatitis infection was reduced to 2·1% a year in Japan after screening for the hepatitis C virus antibody was introduced in 1990. Case reports of fibrinogen-transmitted hepatitis have been published occasionally in Japanese journals (table).
Presumably, hepatitis C virus infection was caused mainly by inappropriate use of injection needles or transfusion of tainted blood or blood products. In Japan, there are an estimated 885 000 carriers of hepatitis C virus, age 16–69 years (0·95% of the population), with 86% being older than 40 years.\textsuperscript{24}

Welfide reported in 2001 that the estimated number of fibrinogen products used since 1980 was about 538 300 and about 283 515 patients had been given the product—204 541 by intravenous infusion and 78 974 as a tissue glue to treat surgical bleeding. In a survey of 1849 hospitals, the estimated incidence of hepatitis C virus infection was 4·6% (180/3922) in patients who were administered fibrinogen intravenously and 1·5% (48/3297) in those to whom the product was used as tissue glue for surgical bleeding. Applying these rates to Welfide’s estimates, the approximate number of people developing fibrinogen-transmitted hepatitis infection was about 10 600 (9400 in infusion, 1200 in surgery), although this number can only be regarded as a rough estimate.\textsuperscript{25}

In 2004, the Ministry of Health, Labour, and Welfare (formerly the Ministry of Health and Welfare) published the names of 7004 medical institutions that had been supplied with fibrinogen and recommended that people who suspected they had hepatitis C virus infection to voluntarily take a test, which incidentally was not free. The exact number of patients with fibrinogen-transmitted hepatitis C still remains unclear.

According to the findings of a survey done by Amemiya between 1983 and 1985, 198 (0·20%) of 98 372 pregnant women had confirmed or suspected disseminated intravascular coagulation or massive bleeding (>2000 mL) at delivery.\textsuperscript{26} Applying this proportion to the number of livebirths across Japan in 1985 (n=1 431 577) suggests that efforts to stop bleeding would be judged indulgent if patients who had a Japanese doctor’s licence knew of the presence of non-A non-B hepatitis and the disease was the result of an act of betrayal by the doctors in whom they trusted.

Most of the above-mentioned data have only been reported in Japanese. In view of the epidemiological importance of this issue, this fact is surprising.

**Discussion**

**Lack of epidemiological data**

Before the 1980s, Japanese medical care was characterised by paternalism. Japanese people at that time were not sceptical or critical of treatments used in hospitals and clinics. Most doctors did not even inform patients of the names of the drugs that they were administering. Many patients are thought to have become asymptomatic carriers of hepatitis C virus without even knowing they had received the infecting drug.

Since the Medical Practitioners Law obliges medical institutions to store medical records for only 5 years, few past medical records remain for patients given fibrinogen. This difficulty has resulted in an inability to retrospectively trace individuals’ disease history and to obtain convincing data for the incidence of fibrinogen-transmitted hepatitis. These issues indicate the importance of lifelong storage of medical records for undertaking retrospective epidemiological surveys.

**Excessive use of fibrinogen**

One of the reasons that fibrinogen has been administered so excessively is that it is an easy and user-friendly treatment. Fibrinogen concentrate, prepared by dissolving powder in water, can be stored for a long time at room temperature.

Another reason for such excessive use could be that clinicians had a sense of urgency to save a patient who was bleeding in front of them and wanted to feel that they had tried everything. They might not have thought that efforts to stop bleeding would be judged indulgent if their patient developed hepatitis in the future.

In the 1980s, clinicians in general had different expectations and requirements to those of doctors today. In the 1980s, fibrinogen was believed to be a standard treatment for obstetric bleeding. Obstetricians might have found appropriate assessment of the risks and benefits of fibrinogen difficult to achieve because the prestigious textbooks they relied on misled them. However, everyone who had a Japanese doctor’s licence knew of the presence of non-A non-B hepatitis and the possibility of infection, even in the 1980s. If risk of infection were to be taken into consideration, fibrinogen should have been used only in cases when improvement was impossible by other treatment options. However, Japanese doctors used the product as their first choice, not last. They should have thought about their application of fibrinogen. For patients who became victims of hepatitis C virus infection, becoming stricken with the disease was the result of an act of betrayal by the doctors in whom they trusted.

In the 1980s, Japan used a third of the world’s plasma-derived products, and most of their supply

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**Table: Case reports of fibrinogen-transmitted hepatitis**

<table>
<thead>
<tr>
<th>Year</th>
<th>Location</th>
<th>Patients (n)</th>
<th>Treatment/procedure</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1981</td>
<td>Tokyo University Hospital</td>
<td>83</td>
<td>Cardiac surgery 14 given blood and unheated fibrinogen</td>
<td>Developed non-A non-B hepatitis</td>
</tr>
<tr>
<td>1987</td>
<td>Aomori Prefecture</td>
<td>9 women (age 23–36 years)</td>
<td>Obstetric procedure 9 given unheated fibrinogen 5 received blood transfusion</td>
<td>Developed non-A non-B hepatitis</td>
</tr>
<tr>
<td>1987</td>
<td>Nagano Prefecture</td>
<td>5 women (age 27–38 years)</td>
<td>Obstetric bleeding 5 given heated fibrinogen 2 received blood transfusion</td>
<td>Developed non-A non-B hepatitis</td>
</tr>
<tr>
<td>1986–87</td>
<td>...</td>
<td>13</td>
<td>13 given unheated or heated fibrinogen</td>
<td>Had hepatitis C virus RNA in blood sample</td>
</tr>
</tbody>
</table>
dependend on imports.26 When Japanese medical institutions used blood products, the costs were reimbursed by public medical insurance, and when they purchased a plasma-derived product at a lower price than the official reference price, the difference was a profit for the medical institution. Such a system could have also contributed to Japan’s overuse of plasma-derived products.

Risk of authoritarianism
Generally, people become anxious when they are informed that something that is present one day will disappear tomorrow. They want to avoid being deprived of something that they consider essential. Although specialists in transfusion and haematology said that fibrinogen for secondary hypofibrinogenemia was not effective, obstetric experts protested against restricting the indication because they widely used the product. The typical opinion of obstetric experts in the 1980s was that they used fibrinogen for a bleeding patient, the haemorrhage stopped, which meant fibrinogen was effective. Indeed, negligence or inability to obtain sound information on the long-term risks of non-A non-B hepatitis resulted in clinicians’ biased judgment about use of fibrinogen. To make matters worse, policymakers overemphasised the opinions of the obstetric experts and based their decisions accordingly. They should have been open to the opinions of a wide range of specialists, including haematologists, virologists, and epidemiologists.

Medical scientists must try ceaselessly to raise the quality of evidence. If an expert opinion is suspect, specialist clinicians should make efforts to provide better information. To keep to an opinion and impose it on others without making such efforts will result in harmful authoritarianism.

Maintaining such dominance can cause stagnation or, in some cases, retrogression of medical science. The greatest concern relating to authoritarianism is that it leads to an overestimation of the benefits of medical care and disregards or neglects the risks involved. When risks should be kept below a certain level, authoritarianism is a dangerous factor.

Diffusion of the latest scientific knowledge into clinical practice is sometimes slow. However, people who administer drugs must always prepare a safety system so that valid judgments can be made about both the effectiveness and the risk of drugs, thereby increasing the protection to patients from drug disasters. A principle of medical professionalism is the primacy of patients’ welfare. The principle of preventing drug disasters is that effectiveness should be strictly assessed and risks should be fully considered. The main role of the medical profession in this respect is to present scientific evidence. To appropriately evaluate an expert opinion from one domain, policymakers must hear opinions from workers in other research areas.

Conclusion
To prevent fibrinogen-transmitted hepatitis in Japan, all that had to be done was to stop using fibrinogen. This step was not impossible but it was something that the Japanese authorities failed to do. The commercialism of pharmaceutical companies, the bureaucracy of the Ministry of Health and Welfare, and the inability of the medical system to stand up to these organisations were not the only causes; the authoritarianism of the medical profession was the fundamental reason. The negative legacy of fibrinogen-transmitted hepatitis C virus in Japan is the result of authoritarianism that hindered an effective policy change that was in accordance with science. A tragedy caused by the stagnation of policy innovation, as was seen in this case, could potentially happen in almost any country in the future. To avoid such a disaster, scientists need to refine continuously the quality of their evidence, and policymakers must review existing policy repeatedly and adjust these policies to the latest scientific evidence.

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

Acknowledgments
I thank Tomoaki Imamura and Kazuhiko Ohe for helpful discussions and editorial assistance.

References


In December, 2006, a 26-year-old woman was sent to our medical admissions unit by her general practitioner (GP). She had consulted her GP because she felt light-headed on standing, as though she were about to faint. For several days, she had been increasingly tired, had aching muscles, and felt feverish; hours before contacting her GP, she had started to feel discomfort, then pain, in her upper abdomen; she had vomited two or three times that day. She had previously been in good health, and took no medications. Examination by the GP revealed nothing of note. By the time the patient arrived at our unit, she felt increasing pain in her upper abdomen, and she had not passed urine for 5 h. She had no other urinary or gastrointestinal symptoms; she had menstruated 4 days previously. She had no symptoms of focal infection, and had not recently been struck or injured.

On examination, the patient had no fever; her heart rate was 120 beats per min, and her blood pressure 110/70 mm Hg. Capillary refill was slow, at 3 s. She was clammy. Her upper abdomen was moderately tender, with no guarding. Bowel sounds were present. We swiftly administered intravenous fluids; catheterisation confirmed that very little urine was left in the bladder. Chest and abdominal radiography showed nothing of note. Blood tests showed a severe leucocytosis (22·7×10⁹ cells per L), consisting mainly of lymphocytes (14·1×10⁹ cells per L). The patient had a mild normocytic anaemia (haemoglobin concentration 102 g/L). Concentrations of alanine aminotransferase and alkaline phosphatase were high, at 251 U/L and 312 U/L respectively. A blood film showed atypical lymphocytes, consistent with infectious mononucleosis (figure). A Paul-Bunnell test was positive.

In view of the hypovolaemia and abdominal pain, CT of the abdomen was requested—and showed a ruptured spleen, with blood throughout the abdomen. We did an emergency splenectomy, from which the patient made a good recovery. Before discharge, the patient was vaccinated against Streptococcus pneumoniae, Haemophilus influenzae type b, and Neisseria meningitidis strain C, and prescribed prophylactic phenoxymethyl penicillin. When last seen, in February, 2007, the patient was well.

In the UK, an estimated 75% of university students are seropositive for Epstein-Barr virus. The infection is usually asymptomatic, but can manifest as infectious mononucleosis—sometimes known as the kissing disease, after a common route of viral transmission. Typical symptoms include malaise, fever, and sore throat. Neurological and psychiatric complications, such as meningitis, encephalitis, and depression, sometimes occur. In an estimated 0·1–0·2% of patients diagnosed with infectious mononucleosis, the spleen ruptures, often after a blow to the abdomen. People with infectious mononucleosis are therefore advised to avoid contact sports. However, spontaneous rupture also occurs. Usually, when the spleen ruptures in a patient with infectious mononucleosis, the organ is removed. However, preservation of the spleen may be preferable, particularly in children, who are more likely than adults to develop sepsis after splenectomy. Prospective studies are required.

References