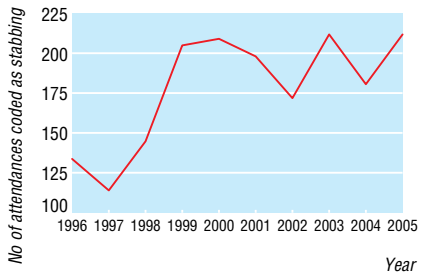
Letters

Stabbing: data support public perception

Editor—Last year Hern et al published an editorial on knife crime and clearly the problem has not gone away.[1] A quick search of the *Times* website finds 90 hits on the single search term "stabbing" in the past three months alone. Several recent deaths have fuelled the perception that forensic knife injuries have become an epidemic, resulting in a knife amnesty and government discussion of new punitive measures. An increase in such injuries is supported by data from regional police forces and the Home Office, with 1200 reported attacks in London last year and 30% of homicides caused by knife injury.[2] Crimes defined as "more serious wounding or other act endangering life" almost doubled nationally from 1995 to 2005.[3]

We audited forensic knife injuries at this hospital, one of Europe's busiest emergency departments, to establish the size of this problem in a representative urban area (east London). We extracted data on forensic knife injuries (excluding deliberate self harm) from a detailed prospectively recorded database of all trauma calls from July 2004 to June 2006 (these reflecting more severe injuries). Overall there were 309 forensic knife injuries; 259 patients were admitted, 184 were operated on, and eight died. The chest was the most common area injured (183/309 patients, 6/8 deaths). Most patients were men (297/309), and mean age was 28 (range 15-74).

To give a measure of changing incidence over a longer time of a greater range of severity of injury, we also performed an audit of all cases coded as "stabbing" on the patient administration system during the 10 year period from July 1997 to June 2006 (figure).



Numbers of attendances coded as stabbing at Royal London Hospital

Over both periods, the data show an increase in the overall incidence of stabbings. Furthermore, increased need for surgical intervention in the prospective study may reflect increasing severity of injury. These data therefore seem to support the general perception that knife injuries are increasing.

Tom König *trauma fellow*
Charles H Knowles *senior lecturer in surgery*
c.h.knowles@qmul.ac.uk

Alison West *trauma nurse specialist*
Alastair Wilson *director, accident and emergency*
Frank Cross *consultant vascular and trauma surgeon*
Trauma Service, Royal London Hospital, Whitechapel, London E1 1BB

Competing interests: None declared.

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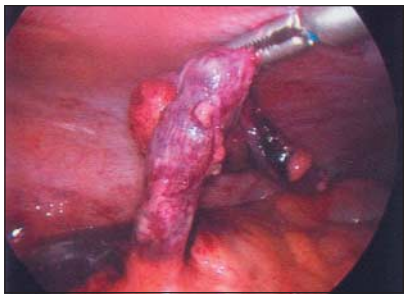
Acute appendicitis

Leaving normal looking appendices

Editor—In their clinical review of acute appendicitis Humes and Simpson point out that complications can occur after removal of a normal appendix.[1] To decrease the rate of negative appendicectomies, the use of diagnostic laparoscopy followed by either laparoscopic or open appendicectomy may be beneficial. Diagnostic laparoscopy allows the doctor to leave a normal looking appendix, identify alternative pathologies, or accurately site a small incision for open appendicectomy.

We audited 187 diagnostic laparoscopies for suspected acute appendicitis over two years in a district general hospital where diagnostic laparoscopy is routine and found 141 diagnostic laparoscopies (75%) proceeded to laparoscopic appendicectomy while the remaining 46 patients (25%) had a macroscopically normal appendix, and no appendicectomy was performed. Hospital stay and complications following laparoscopic appendicectomy were favourable compared with open appendicectomy, and outcomes were similar regardless of grade of operating surgeon. Controversy persists over the safety of leaving a "normal" looking appendix as it may be inflamed in up to 10% of cases although the clinical significance of this is uncertain.[2]



The European Association of Endoscopic Surgeons recommends using diagnostic laparoscopy combined with laparoscopic appendicectomy for the management of suspected acute appendicitis.[3] Many UK district general hospitals lack expertise and a camera holder for out of hours laparoscopic appendicectomy, making open appendicectomy the only option. Growing evidence is supporting the routine use of diagnostic laparoscopy, and we think that, combined with laparoscopic appendicectomy, it should be an integral part of surgical training. Our experience shows that this is safe and feasible. Public awareness is growing, and patients may soon demand that they be given a choice.

Faheez Mohamed *specialist registrar, general surgery*
University Hospital of North Durham, Durham DH1 5TW
faheez@btinternet.com

Kevin K Khoo *clinical research fellow*
Wansbeck General Hospital, Ashington, Northumberland NE63 9JJ

Competing interests: None declared.

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Weighing up risks and benefits of investigations and treatments

Editor—A few issues arise from Humes and Simpson's review of acute appendicitis.[1] It is important to clinically assess the right groin and hip, particularly in paediatric patients as transient synovitis or irritable hip and septic arthritis are common[2] and are differential diagnoses that must be considered for atypical presentations. Children are often referred with abdominal pain where the gait of the patient has not been assessed and a painful limp can often be missed in a patient examined only in the supine position.

Radiological investigations for appendicitis have progressed and computed tomography may be used in the UK in adults, particularly to rule out right sided colonic pathologies such as cancers and diverticular disease, however for children where radiation exposure is certainly more of an issue, advocating computed tomography scans on the basis of higher diagnostic precision has potential risks for the children in question. As so much of the diagnosis of acute appendicitis is clinical judgment, admission and repeated examination is an important diagnostic tool that is often undervalued, now that more sophisticated imaging is available, but still should not be ignored.

Longer term complications of open appendicectomy include bowel obstruction secondary to adhesions. A recent long term follow-up study showed that patients who underwent appendicectomy subsequently had a relatively low overall direct risk of readmission (0.9%).[3] However, this procedure accounted for 30% of all abdominal procedures and 7% of all patient readmissions during the five years following lower abdominal surgery, for the study in question. Appendicectomy therefore may contribute significantly to the overall burden of adhesion related readmissions. The healthcare cost of adhesion related readmission is huge—in 1994 this amounted to $1.4bn (currently £700m; €1100m).[4] This potential burden of readmission from open appendicectomy may be reduced with the use of laparoscopic surgery.

A recent meta-analysis[5] that included 11 randomised trials and over 6000 paediatric patients demonstrated that wound infection was significantly reduced with laparoscopic versus open appendectomy (1.5% *v* 5%; odds ratio 0.45 (95% confidence interval 0.27 to 0.75)), as was ileus (1.3% *v* 2.8%; odds ratio 0.5 (0.29 to 0.86)), both of which could further reduce the readmission rates and cost of complications subsequent to the treatment of appendicitis.

Sanjay Purkayastha *clinical research fellow*
s.purkayastha@imperial.ac.uk

Sudipta Purkayastha *visiting professor*
Paraskeva Paraskevas *senior lecturer*
Department of Biosurgery and Surgical Technology, Imperial College, London W2 1NY

Competing interests: None declared.

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Acute appendicitis or acute appendicectomy?

Editor—Over 40 years ago, I studied the clinical pathology of the appendix and the epidemiology of appendicectomy. I would like to comment on four complementary issues.[1] Firstly, around 1960 the 4/1000 death rate ranged from 1/2600 for uncomplicated appendicitis in young adults, to 1/9 for patients older than 50 with a perforated appendix. Death rates for male patients were double those for female patients. Deaths from a normal appendicectomy were 1/5000 in young adults.[2] In my own study of 1412 appendicectomies, surgeons differed over whether to risk removing normal appendixes or leave abnormal ones in, and deaths from higher and lower operative approaches balanced almost exactly. However, morbidity from the more conservative approach was higher due to more readmissions, and more patients continued to complain of pain in the right iliac fossa.[3]

Secondly, 37 of 45 patients with recurrent or chronic appendicitis had iron deposits in their appendixes, a histological finding that correlated with recent pain in the right iliac fossa.[4] In 119 patients with mesenteric adenitis, cure by surgery was also likely for those whose appendixes were positive for iron. Is the concept of neuroimmune appendicitis a helpful addition to an already idiosyncratic diagnostic area?

Thirdly, I found no evidence that appendicitis ran in families, but appendicectomy did. Another indication that appendicectomy was a decision sometimes influenced by non-biomedical factors was that surgeons of all operative approaches were more likely to remove appendixes from nurses and from colleagues' children.[5]

Fourthly, in 65 of 870 certified deaths from appendicitis, no evidence was found of either appendicitis or an appendicectomy. In 88 of my own series of appendicectomies, discharge classifications of appendicitis were entered despite no histological evidence of appendicitis.

Two decades later, I found that the same issues applied to the use of antibiotics by general practitioners. Whether in surgery or in general practice, any theoretical model for clinical practice must allow for the interaction of both biomedical and behavioural science. The challenge to clinical practice of modern evidence based medicine and clinical guidelines is to find out how to celebrate and incorporate the right balance between these two interdependent sciences to counter increasingly discontinuous and target centred care.

John G R Howie *emeritus professor of general practice*
University of Edinburgh, Edinburgh EH8 9DX
john.howie00@btinternet.com

Competing interests: None declared.

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Acute renal failure from contrast medium

Beware patients taking metformin …

Editor—Mathew et al highlight the dangers of contrast induced nephropathy in a patient with type 2 diabetes mellitus.[1]

Such patients are often treated with the biguanide metformin, which is excreted by the kidney. Even with normal renal function, metformin should be withheld for 48 hours from the time of the radiological study if intravenous iodinated contrast media is to be given, with close monitoring of renal function before restarting.[2] This is to prevent, in the context of contrast induced nephropathy, high serum metformin concentrations, which could lead to lactic acidosis. A review of published cases of metformin induced lactic acidosis shows that 8% occur in presence of contrast induced nephropathy.[3] This risk increases in diabetic patients with pre-existing renal impairment. With known renal impairment, metformin should be stopped 48 hours before the study, to allow monitoring of the renal function, and low osmolar contrast media should always be used.[2]

Remember also that patients with multiple myeloma have multiple risk factors for acute renal failure, including hypercalcaemia, dehydration, infection, and urinary light chains, and that contrast (particularly with older contrast agents) may be a further insult to the kidney.[4]

John A Sayer *clinical lecturer in medicine (nephrology)*
School of Clinical Medical Sciences, University of Newcastle upon Tyne, Newcastle upon Tyne NE2 4HH
j.a.sayer@ncl.ac.uk

Competing interests: None declared.

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… and remember simple and cheap measures

Editor—Mathew et al describe some of the risk factors and consequences of contrast induced nephropathy, a condition increasingly encountered after elective and emergency cardiac angiography and angioplasty.[1] The role of *N*-acetylcysteine in preventing this common condition is often underemphasised. Many good prospective randomised controlled trials support its use, as do most meta-analyses, but the strength of overall conclusions is often hindered by the heterogeneity of the study protocols of the included trials. A dose dependent relation with both oral and intravenous administration has clearly shown a reduction of contrast induced nephropathy in patients undergoing cardiac angiography.[2 3]

Pre-hydration is simple, cheap, carries minimal risk, and should be routinely used

despite the lack of a large prospective randomised controlled trial of hydration versus no hydration. Correction of subclinical dehydration may be the principal benefit. However, the route and type of fluid prescribed seem to be important in preventing contrast induced nephropathy. Intravenous isotonic fluid (0.9% saline) is more effective than half isotonic fluid (0.45% saline),[4] and intravenous administration is more effective than oral.[5] Most benefit is seen in high risk groups.

Amit Patel *senior house officer in cardiology*
Heart Hospital, London W1G 8PH
amit.patel@doctors.org.uk

Competing interests: None declared.

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Benign prostatic hyperplasia

Caveat for finasteride should be discussed before prescribing

Editor—Patel and Chapple recommend finasteride as one drug in combination therapy of benign prostatic hyperplasia.[1] Finasteride was evaluated for chemoprevention of prostate cancer in a seven year, placebo controlled study of 18 882 men at low risk of developing prostate cancer.[2] Patients who received finasteride (5 mg/day) had a 25% lower incidence of prostate cancer. However, they also had a higher incidence and a greater proportion of high grade cancers. This is unlikely due to finasteride artifact.[3] Since finasteride lowers serum levels of prostate specific antigen (PSA), it may also delay a prostate biopsy in asymptomatic men, allowing proliferation of high grade cancer.[4] The authors have rightfully cautioned readers to use lower reference values of PSA when screening patients taking finasteride. This caveat should be discussed with patients before prescribing finasteride for benign prostatic hyperplasia.

Hussam Ammar *attending physician*
drmalani@yahoo.com

Ashok K Malani *attending physician, internal medicine*
Chakshu Gupta *physician, laboratory medicine and pathology*
Heartland Regional Medical Center, 5325 Faraon Street, St Joseph, MO 64506, USA

Competing interests: None declared.

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Authors' reply

Editor—A recent expert European consensus group (in which the senior author (CRC) was a key participant) reviewed the data from both the prostate cancer prevention trial and the medical therapy of prostatic symptoms study.[1–3] The consensus was that the studies provide additional support for the use of finasteride in managing men with lower urinary tract symptoms and benign prostatic hyperplasia and that the increased incidence of diagnosed high grade cancer in the finasteride treated group compared with placebo is probably a consequence of a relative detection bias in the finasteride group caused by a reduction in prostate volume.

Treatment with finasteride therefore enhances detection of high grade disease, in addition to reducing the overall seven year prevalence of prostate cancer by 24.8% compared with placebo ($P<0.001$). The group concluded that discussing chemoprevention using finasteride with men concerned about prostate cancer (family history, abnormal prostate specific antigen (PSA) value) may be appropriate and that the consensus findings need to be disseminated to other healthcare professionals and guidelines on prostate cancer updated.

Anand K Patel *research registrar*
Christopher R Chapple *professor of urology*
c.r.chapple@sheffield.ac.uk
Urology Research, J Floor, Royal Hallamshire Hospital, Sheffield S10 2JF

Competing interests: CRC has acted as a consultant or received research funding (or both) from Pfizer, Astellas, Abbott, and Recorati Pharmaceuticals. AKP has no competing interests to declare.

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Society's advice on low weight and IVF was ignored by media

Editor—In his report on the guidance issued by the British Fertility Society, O'Dowd says that the society recommended obese women should be denied fertility treatment.[1] In this, he shows the same bias as much of the rest of the media. The guidance issued by the BFS actually states that women at both extremes of weight (BMI <19 or >29) should be referred for dietetic advice, warned of pregnancy risks and, if appropriate, provided with access to further interventions including psychological.

The media furore has focused exclusively on the obesity advice, ignoring the advice about underweight women. An array of published studies shows associations between eating disorders, intrauterine growth retardation, preterm delivery and poor pregnancy outcome.[2] Subfertility in women with eating disorders is a homoeostatic response to inadequate nutrition, but failure to appreciate this has led to cases of conception as a result of artificial ovulation induction, with poor outcomes.[3] A survey of obstetricians in Sydney showed that few made any reference to body weight records during prenatal visits, with fewer than 50% asking about body weight control and disordered eating.[4] A subsequent study in the United Kingdom showed considerable deficits in knowledge of eating disorders' reproductive pathology among obstetricians.[5]

We regret that the selective reporting of the guidelines led to a missed opportunity to raise awareness of the profound effects of eating disorders on reproductive pathology, both on fertility and on the outcome of pregnancy.

Helen C Murphy *clinical lecturer in psychiatry*
hmurphy@sgul.ac.uk
St George's, University of London, London SW17 0RE

John F Morgan *director*
Yorkshire Centre for Eating Disorders, Leeds Mental Health NHS Trust, Newsam Centre, Seacroft Hospital, Leeds LS14 6WB

Competing interests: None declared.

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Possible cause of false normal B-12 assays

Editor—In response to Devalia,[1] we report a further eight cases of serum samples from patients with megaloblastic anaemia or subacute combined degeneration of the cord in whom current assays have failed to detect cobalamin deficiency. The cobalamin results were well within the manufacturers' reference range and not to do with cut-off point. The table shows results from two cases of megaloblastic anaemia, which subsequently responded to cobalamin treatment, in which pretreatment serum was available for analysis by several methods.

Only two of the five methods found extremely low levels of cobalamin despite severe clinical deficiency. The Bayer centaur assay detected one of the two case samples as low. These competitive binding immunoassays are no boil and rely on alkaline hydrolysis and dithiothreitol or monothioglycerol treatment to release cobalamin from transcobalamin and denature intrinsic factor antibody.

Pretreatment serum cobalamin concentrations in two cases with false normal cobalamin results in current commercial assays

	Abbott Architect	Bayer Advia Centaur	Beckman Coulter Access	Diagnostic products Corporation Immulite 2000	Roche Elecsys E170 E2010	Intrinsic factor antibody Launch Diagnostics
Reference range (pg/ml)	189-883	211-911	180-914	193-982	191-663	0-5.9*
Reference range (pmol/l)	139-651	156-672	133-674	143-725	141-489	
Case 1 (pg/ml)	<60	145	356	310	81	244*
Case 2 (pg/ml)	<60	217	317	360	70	>100*

*u/ml.

We postulate that intrinsic factor antibody present in the patient serum at high titre fails to be denatured by the alkaline hydrolysis and dithiothreitol treatment and persists into the binding stage, resulting in antibody interference rather than heterophilic antibody interference. The incidence is estimated at 1:3000 requests, and whether some assays are more vulnerable to this effect than others is not yet clear.

Manufacturers are urged to test assays pre-release with high titre anti-intrinsic factor antibody serum samples. Clinicians are urged to be vigilant for these potentially dangerous "false normal" cobalamin results. Laboratories should not report cobalamin assays in isolation from intrinsic factor antibody and other haematological data. Pretreatment serum should be stored in any suspected cases for homocysteine and methylmalonic acid concentrations and for anti-intrinsic factor antibody titres to confirm that the megaloblastic anaemia or neuropathy is indeed due to cobalamin deficiency. A therapeutic trial of cobalamin will prevent delay in treatment and adverse clinical consequences. Such cases should be notified to the Medicines Health Care Related Products Agency (www.mhra.gov.uk) and UKNEQAS Haematinics (ukneqas.haematinics.org.uk).

Malcolm S Hamilton *director*
m.s.hamilton@talk21.com

Sheena Blackmore *deputy director*
Anne Lee *scheme scientist*
United Kingdom External Quality Assessment Scheme, UKNEQAS Haematinics, Department of Haematology, Good Hope NHS Trust, Sutton Coldfield B77 7RR

Competing interests: None declared.

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More on switching statins

Comments from Pfizer

EDITOR—Moon and Bogle claim that all statins are the same except for the cost.[1] NHS costs need to be managed but should not be the sole driver of clinical decision making.

New guidelines recommend that cholesterol <4 mmol/l is the optimal target for patients with cardiovascular disease, diabetes, or high risk primary prevention.[2] Data modelled from the CURVES study showed less than 33% of patients would reach this level with simvastatin 40 mg.[3]

The summary of product characteristics for simvastatin states that patients may be intolerant of simvastatin, not at target with current treatment, or have contraindications or dosing restrictions with simvastatin, such as patients with severe renal impairment.

The authors suggest that atorvastatin, 10 mg and 20 mg, is as effective as simvastatin 40 mg. However, both studies quoted show that atorvastatin 20 mg is more efficacious than simvastatin 40 mg in cholesterol reduction.

The authors argue that the cardiovascular outcomes data are similar for atorvastatin 10 mg and simvastatin 40 mg. The unpublished in-house meta-analysis quoted includes studies different in design, population, end points, and outcomes that should not be combined in meta-analysis.[4] Meaningful conclusions cannot reliably be drawn from such data.

The authors use the 3T study comparing atorvastatin and simvastatin to claim no difference but it assessed lipid lowering, not cardiovascular events.[5] More patients achieved target cholesterol level on atorvastatin than simvastatin. The authors admit that the study was underpowered for analysis of cardiovascular events. Their claim of no difference in this comparison is statistically invalid.

A national decision on mass switching ignores the added resources and costs that such a programme would need. A more sophisticated approach to initial selection, switching, and combination of statins is required for cardiovascular risk management.

Kate Lloyd *medical director*
Pfizer, Tadworth, Surrey KT20 7NS
Kate.Lloyd@Pfizer.com

Competing interests: KL is medical director of Pfizer in the United Kingdom.

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Authors' reply

EDITOR—Statins all work by blocking the same enzyme but differ in their potency. Higher doses of less potent statins can equal or better lower doses of more potent statins. This is true for simvastatin 40 mg and atorvastatin 10 mg or 20 mg.

Switching from atorvastatin 10 mg or 20 mg to simvastatin 40 mg represents the largest single drug saving ever available to the NHS. This saving can be used to treat more patients, thereby reducing the overall cardiovascular disease burden.

Simvastatin 40 mg is slightly superior to atorvastatin 10 mg and slightly inferior to atorvastatin 20 mg for cholesterol lowering. In 2005 atorvastatin 10 mg was prescribed 1.7 times more than atorvastatin 20 mg and because of this therapeutic substitution with simvastatin 40 mg would not be expected to alter the population lipid profile.[1–3]

Different statins have different effects on high density lipoprotein (HDL) cholesterol, however. Simvastatin 40 mg increases HDL more than any dose of atorvastatin. The atorvastatin negative dose-response curve for HDL elevation means that, for example, atorvastatin 80 mg is no better than 40 mg at modifying the total cholesterol:HDL ratio.[1 2]

Atorvastatin and simvastatin have the same metabolic pathways and drug interactions. Most interactions increase drug effect, so lower doses can be used—for example, simvastatin 10 mg in severe renal failure, avoiding atorvastatin after the negative 4D trial.[4]

At UCLH NHS Trust, our switching policy has reduced atorvastatin 10 mg or 20 mg prescriptions from 111 to two a month.[5] Many primary care trusts have also switched and are spending up to threefold less for statin prescriptions than non-switching primary care trusts (data available within PACT data analysis). Statin switching is also endorsed in the new government productivity metrics for statin prescribing.

The fiscal benefit of switching translates to a saving of £250m (€370m; £470m) per year in England. This simply cannot be ignored.

James C Moon *specialist registrar*
james.moon@uclh.nhs.uk
Department of Cardiology, Heart Hospital, UCL Hospitals NHS Foundation Trust, London W1G 8PH

Richard G Bogle *acting consultant in cardiology and clinical pharmacology*
Experimental Medicine and Toxicology, Imperial College London, London W12 0HS

Competing interests: RB has received lecture honorariums from AstraZeneca, Aventis, and Pfizer for speaking at educational meetings.

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Long term safety of statins should be monitored

EDITOR—We agree with Ravnskov et al that little is known about the adverse effects of high dose statins but also propose that little is known about the long term safety of more modest doses used at present.[1] Lifetime use of statins may equate to treatment for 30 years or more.[2] As said by the authors, multicentre, large scale trials have established efficacy of these agents but are much less reliable in detecting uncommon serious adverse outcomes such as cancer.

Recent studies provide reassurance about the safety of statins with respect to all cause carcinogenicity in the short term[3 4] and up to 10 years.[5] However, although the length of postmarketing surveillance remains quite short compared with the medically accepted latency period for cancer of 20 years,[2] it seems prudent to establish systems examining and linking large databases to allow extended follow-up for malignancy. Such monitoring can also help ascertain whether any class effect or dose response exists and whether certain categories of carcinogenicity are influenced by statins either favourably (as shown by some case-control studies) or deleteriously.

These data linkage systems should include a variety of stakeholders, among them regulatory authorities from different countries and the pharmaceutical industry, all cooperating in the provision of more robust information in this and other important areas of pharmacovigilance. Recent issues surrounding the long term uncertainty of cyclo-oxygenase-2 inhibitors and hormone replacement therapy have highlighted that drug safety must be proved rather than assumed, especially for drugs used very widely and long term.

Steven J Haas *honorary research fellow*
steven.haas@med.monash.edu.au

Rosana Hage-Ali *research assistant*
Brian G Priestly *director, Australian Centre for Human Health Risk*
Andrew Tonkin *head, cardiovascular unit*
Lisa Demos *senior research fellow*
John J McNeil *head*
Monash University, Department of Epidemiology and Preventive Medicine, Central and Eastern Clinical School, Alfred Hospital, 89 Commercial Road, Melbourne, VIC 3004, Australia

Mark Nelson *chair, discipline of general practice*
School of Medicine, University of Tasmania, Private Bag 33, Hobart, Tasmania 7001, Australia

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Ageism in services for transient ischaemic attack and stroke

Clinical leadership is key in changing practice

EDITOR—Fairhead and Rothwell report substantial underinvestigation in routine clinical practice in elderly patients with transient ischaemic attack and stroke.[1] We found that brain imaging was performed only in a small proportion of older patients admitted with acute stroke.

The most common misconceptions were that imaging older adults after an acute stroke would not change management and therefore was a waste of resources. After the appointment of a clinical lead in stroke, we changed this practice by a continuing audit cycle, development of local acute stroke guidelines, and regular teaching sessions on the importance of appropriate prescribing of antiplatelet agents, risk of haemorrhage with indiscriminate use of antiplatelet agents, consequences of recurrent stroke, and prevention especially in older patients. The table shows that this sustained effort improved the rate of brain imaging in older patients.

Rates of brain imaging in patients admitted with acute stroke in 1997, 1998, and 2003 by age. Values are proportions (percentages)

Age (years)	1997 (n=347)	1998 (n=369)	2003 (n=349)
≤40	2/3 (67)	1/2 (50)	4/4 (100)
41-50	9/10 (90)	13/13 (100)	12/12 (100)
51-60	33/36 (84)	22/23 (96)	29/32 (91)
61-70	42/61 (68)	46/59 (78)	34/41 (83)
71-80	41/112 (34)	84/125 (67)	108/121 (89)
81-90	24/96 (25)	70/125 (56)	92/117 (78)
≥91	2/16 (12)	7/22 (31)	15/22 (68)

S H Guptha *consultant physician*
sunku.guptha@pbh-tr.nhs.uk

P Owusu-Agyei *clinical lead in stroke*
Peterborough and Stamford NHS Hospitals Trust, Edith Cavell Hospital, Peterborough PE3 9GZ

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1 Fairhead JF, Rothwell PM. Underinvestigation and undertreatment of carotid disease in elderly patients with transient ischaemic attack and stroke: comparative population based study. *BMJ* 2006;333:525-7. (9 September.)

Ageism or cost-benefit analysis?

EDITOR—Young comments that ageism will always prosper when resources are inadequate for the target population.[1] Is this really ageism, or is it application of a cost-benefit analysis—spending the limited resources where the greatest benefits will accrue?

I suspect that most "ageism" in the system is based on the belief that the greatest benefit over cost is obtained by a subconscious estimation of something like quality adjusted life years. There may be a further subconscious estimation of the economic contribution a patient may make. Doesn't sound too bad—so let's have a proper debate about how to measure benefit reasonably dispassionately.

The main problem I see is a failure to face up to reality: we cannot provide a perfect health service. Resources will always be inadequate: what we really need is transparency in admitting this and a fair system for allocating the resources available.

My guess is that the situation will get worse: healthcare costs will rise as research produces more treatments. I'd also guess that the money available will reduce as world resources become stretched—the recent rises in energy costs are indicative of what we will face in the future. We may need a fairer system much sooner than we hope.

Yes, there may be discrimination in our system. Yes, it may be unfair. Before we can deal with that, we must face up to the reality of resource restrictions, recognise the (potential) need for rationing, and devise fair systems for implementing it.

Too politically unpalatable? That vision leads to a future with continued pointless efforts to expose and deal with "unfair" discrimination, when the disease is much more fundamental.

Michael A McDowall *stroke registries coordinator*
University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU
m.a.mcdowall@ed.ac.uk

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1 Young J. Ageism in services for transient ischaemic attack and stroke. *BMJ* 2006;333:508-9. (9 September.)