comment

NHS England estimates that a fifth of beds are used by patients who will spend more than three weeks in hospital

ACUTE PERSPECTIVE David Oliver

Dealing with long ward stays

HS hospitals are consistently running at over 90% bed occupancy, compromising patient safety and bed management and leaving no capacity to deal with surges in demand or infection outbreaks.

NHS England estimates that a fifth of beds are used by patients who will spend more than three weeks in hospital. Its chief executive, Simon Stevens, has pledged to reduce these long stays by a quarter. And the NHS plan for 2018-19 includes a commitment to "improve patient flow inside hospitals," focusing specifically on "stranded" and "super stranded" patients who have been in hospital for over seven or 21 days, respectively.

Long stays result from a whole range of factors. These may include avoidable delays in assessment, investigation, treatment decisions, or referrals to community services or rehabilitation; and patients may remain medically unstable or still require the full facilities of the general hospital.

They may also result from delayed transfers of patients who are medically fit to leave but are waiting to access out-of-hospital care. In 2016-17, bed days from delayed transfers of care hit a record high of 2.25 million. This was a 25% increase on the previous year, and the National Audit Office has calculated that the real number of stranded patients is far higher than that officially recorded.

Since that peak, the number of delayed transfers of care has fallen. After a government target for tackling these, and an additional £2bn in earmarked social care funding, the overall number



fell by 12% in 2017-18. I worry whether the turnaround we've seen in the past 12 months can be sustained. Stepdown care is likely to be even harder to access given the financial challenges in clinical commissioning groups and local authorities, recent reductions in care home places, cuts in provision of social care packages, and worsening access to intermediate care.

It's not clear whether those services will be given sufficient priority in the NHS 10 year plan or in local plans for integrated care systems. And it will be at least two years before the green paper on adult social care becomes a white paper or act of parliament.

Ultimately, I suspect that the solutions lie in joined-up local system leadership and a relentless focus on operational detail and sustainable implementation—a view shared by the King's Fund in last week's report on integrated care.

It remains to be seen whether, after the initial push and focus, such turnarounds can be sustained or whether every health system can replicate these successes. Personally, I doubt that central targets and toolkits can achieve the goal.

We need more capacity in out-of-hospital health and care services and more flexibility for local leaders to collaborate and innovate. For the good of all patients needing scarce acute beds and all of those needlessly trapped in them, let's hope that the plan works.

David Oliver is a consultant in geriatrics and acute general medicine, Berkshire davidoliver372@googlemail.com Cite this as: *BMJ* 2018;362:k4006

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BMJ OPINION

Asif Munaf

Medicine: another bastion of the UK's great class divide

Doctors should help pupils and students who lack the necessary support to navigate the tricky road towards medicine

atients come from a range of different backgrounds. Yet, based on my 12 years of studying and working in medicine, I have sadly concluded that the same cannot be said of those who deliver healthcare.

Throughout medical school I felt tremendously out of place, not in terms of the curriculum but because of the class divide that permeated the year groups. There was always an undertone of classism and, although no one talked about it openly, it was evident from the outset and it came



to dictate the friendship groups that eventually formed.

British society is uniquely defined by class, with all its permutations, in a way that can't be said of many other countries. This divide is particularly apparent in medicine. Indeed, the Royal College of Physicians was originally formed in 1518 through royal charter as the King's College of Physicians, and was placed under the custodianship of Henry VIII to preserve the profession's "classical training" from the apothecaries. Furthermore, for more than 300 years

We should aim to bridge the gap through out-of-school mentoring only Oxbridge graduates could be admitted as fellows to the college, which perpetuated class division.

Air of privilege

Have things at the top changed? With the advent of the NHS in 1948 and the influx of overseas doctors, the short answer is yes. But the air of privilege remains. Earlier this year, I became a member of the Royal College of Physicians. Was I filled with a sense of achievement? Yes. But equally, I was filled with a sense of despair that the college's grand halls are simply

BMJ OPINION Maria Kristiansen

The difference that compassionate care makes

Many patients will have stories of seemingly small acts of kindness that unfolded in clinical encounters, and the effect these had on them and their relatives. Losing sight of this is easy in increasingly complex, fragmented, and hurried healthcare systems, but it's vital that healthcare professionals keep it at the heart of how they practise.

I've spent the past 10 years researching healthcare encounters, which has confirmed what firsthand experience had already taught me about the difference



Moments of kindness shaped my experience of my son's illness compassionate care makes. I found out just how much being treated with empathy and understanding helped—not only as those moments played out, but in the time afterwards as I processed what had happened to me.

My firstborn child was diagnosed with a rare genetic disorder. During the seven months he lived, I met incredibly caring doctors. But I also encountered hurried and disengaged doctors who appeared unable to truly see the patient—my son—and myself.

The compassionate doctors listened to my attempts to make sense of the upcoming death of an infant and encouraged me to find ways to maintain some normality, doing what parents would usually do but in a much shorter time period. We celebrated small victories that my son's diagnosis could have made impossible—like the first smile or a coordinated hand movement.

In retrospect, these moments of kind and compassionate care shaped my experience of my son's beyond the reach of many other talented aspiring doctors, who lack the connections and background to break through into medicine.

I recently became a father, and if my son wanted to, of course, I would support him to follow in my footsteps and become a doctor—a profession that remains varied and rewarding. But I am under no illusion that he would have a head start compared to someone born up the road, who attends a different school, and has different parental support at home. Children cannot pick their parents. And parents sometimes cannot select their child's school-that is dependent on the local catchment area. This postcode lottery can dictate a child's future.

It would be a huge challenge to overhaul the UK's archaic two tiered schooling system, although countries like Finland provide successful examples of how this can be done. We should, however, aim to bridge the gap through out-of-school mentoring. There are some brilliant programmes which offer mentoring and coaching aimed at state school applicants to medicine—the Roval Society of Medicine has been especially active on this front—but you need to be in the know. How can we possibly expect teachers, already working in highly demanding jobs, to guide their pupils towards these schemes? This is precisely why outreach mentoring is so important.

I believe that the moral responsibility falls on us as doctors to reach out. Through outreach work we can have an impact, otherwise many hugely talented children will not be able to pursue a career in medicine.

No roadmap

I recently started mentoring three children. One of them will begin studying medicine this year, one is in the process of applying, while the third is taking a gap year and applying thereafter. I managed to arrange work experience for all three and helped two of the students with their applications and personal statements. If it wasn't for circumstance, they would have been left to navigate the tricky road towards medicine without a roadmap.

As yet another application window for medicine approaches, it is time to start encouraging doctors to reach out to more students who lack the necessary parental and teacher support to successfully apply for the increasingly competitive medical degree. Only then can we demonstrate that the domed roof of the royal college is not just another glass ceiling, but an achievable reality for all.

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illness and my bereavement, thereby making it more bearable.

In my research, I continue to witness the struggle that patients, relatives, and often also clinicians have in processing encounters where suffering and loss, but also immense resilience, are at play. I'd argue that unhurried, compassionate care helps us all (doctors included) to make sense of these experiences and to deal with them, even long after the clinical encounters have ended.

Empathetic care can support patients' and relatives' attempts to understand and cope with

the inexplicable—be it the death of a child, the diagnosis of an illness, or one of the many other experiences that bring us into contact with healthcare systems. To value and highlight this, we need to grasp any opportunitypersonally and professionally-to reflect upon the humanity of clinicians, the difference it makes, and what could be done to enhance this approach to care.

Maria Kristiansen is associate professor and research group leader at the Department of Public Health and Center for Healthy Aging, Faculty of Health and Medical Sciences at University of Copenhagen, Denmark

BMJ OPINION Kathryn Harrison

Social prescribing: let's not leap in without the evidence

Health secretary Matt Hancock's vision for creating parity between physical and mental health, outlined in a speech this summer at West Suffolk Hospital, is a welcome step forward. On reading about his plans for social prescribing, however, it seems we're taking two steps back. Hancock promises a £4.5m investment to help set up social prescribing schemes to "improve patients' quality of life and reduce pressure on other NHS services" and "reduce

the overprescription of unsophisticated drugs." The problem is that mental illness is often intricately linked to chronic physical disease as well as social problems: applying a blanket approach belittles the complexity of an individual's case. Working in partnership with patients to form a tailored management plan is what GPs do best. We need to increase GP time

through primary care workforce expansion rather than resorting to diversion tactics. I attended a STOP Suicide workshop recently. Training covered how to assess a patient's risk of suicide and

included identifying red flags that signify increasing

risk. Chronic medical illness, pain, and substance misuse are among them. The process of assessing a patient and formulating a safety plan is inevitably time consuming. GPs strive to achieve person centred

We need to increase GP time, not resort to diversion tactics

care within the limitations of appointment times and an ever increasing workload. I fear that social prescribing in this context is being sold as a way to keep patients out of GP surgeries; to "manage" an unmanageable workload instead of helping doctors to make the time that these patients need.

Voluntary sector services can have a positive impact within patient communities but there is a lack of clear evidence demonstrating the long term benefits of social prescribing for patients, a reduction in GP workload, or a decrease in antidepressant prescribing. As with any intervention in medicine, patient benefit must be at its heart, backed by high quality evidence. Furthermore, it is unhelpful to publicly dismiss antidepressants as overprescribed and unsophisticated. There will be those who need them and this negative press serves to undermine GPs and adds to the stigma many patients fear.

Social prescribing may well be a useful tool but it's only part of the answer. There must be a greater evidence base to inform policy and resource allocation. Patients and GPs need the time and space to build therapeutic relationships. Increasing the primary care workforce and reducing time spent on paperwork would allow GPs to get back to delivering the continuity of care patients need.

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ANALYSIS

Are myocardial infarction, stroke, and cancer recurrence still hard endpoints in clinical trials?

What qualifies as disease may be getting so broad that outcomes are becoming less meaningful and harder to interpret, argue **Go Nishikawa** and **Vinay Prasad**

KEY MESSAGES

- Improved diagnostic technology and expanding definitions may be reducing the relevance of accepted trial endpoints
- Reductions in myocardial infarction, stroke, and cancer metastases may not always translate to improved quality of life or survival
- Trialists must routinely measure and report health related quality of life
- Data sharing and patient involvement in developing trial protocol may ameliorate these concerns

t is intuitive and obvious that no person desires a myocardial infarction, stroke, or recurrence or metastasis of a previously localised cancer. Reducing the risk of these endpoints is therefore used as the evidentiary basis of a wide range of drugs, devices, and surgical procedures.

However, recent trials in cardiovascular and cancer medicine force us to revisit the assumption of their value as endpoints. Several studies have produced discordant results, with interventions that reduce myocardial infarction, stroke, or metastasis having no effect on cardiovascular death, health related quality of life, cancer related death, and overall mortality—four harder clinical endpoints.

Is the avoidance of myocardial infarction, stroke, and cancer recurrence or metastasis less meaningful than it used to be? Or has the severity of these events lessened, partly because of advances in imaging and assay sensitivity?

As technology advances and diagnostic categories broaden we need to consider whether there comes a point when endpoints that are widely believed to be measures of patient centred outcomes become test based, non-clinical endpoints. We have selected four recent randomised trials that highlight how benefits hinge on the nature of events averted.

Trials with discordant results

The FOURIER trial compared the effect of evolocumab, a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9), with placebo in patients with cardiovascular disease. The trial used a primary composite endpoint of cardiovascular death, myocardial infarction, stroke, hospital admission for unstable angina, or coronary revascularisation and found a benefit for the drug. However, the drug had no favourable effect on cardiovascular death.

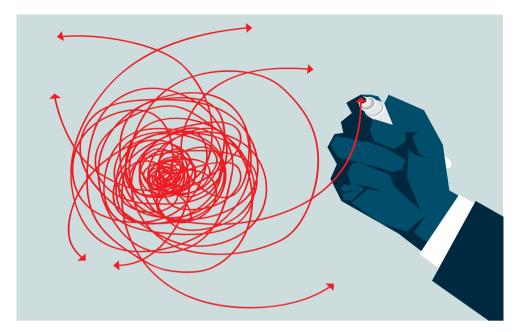
The findings contrast with those of older secondary prevention trials in which cardiovascular endpoints and mortality improved in parallel. A decade earlier, for example, the PROVE IT—TIMI 22 trial randomised patients admitted to hospital with an

acute coronary syndrome to standard dose pravastatin or high intensity atorvastatin.² At two year follow-up, the trial found significant improvement in the composite primary endpoint of stroke, death from any cause, myocardial infarction, unstable angina requiring hospital admission, or, the most common event contributing to the composite, revascularisation. This occurred alongside non-significant improvements in death from all causes, and death from coronary heart disease (1.4% ν 1.1%).

Patients in FOURIER and PROVE IT-TIMI 22 were evaluated at comparable time points (average follow-up 26.4 months and 24 months, respectively). In other words, the 15% relative risk reduction in the primary composite endpoint in FOURIER was associated with no perceivable difference in harder endpoints, whereas the 16% reduction in the primary endpoint of PROVE IT-TIMI-22 occurred alongside suggestion of improvement in harder outcomes.

Cancer medicine provides three further examples, with the endpoint of recurrence or metastasis after potentially curative therapy not translating into survival benefits. For prostate cancer, the ProtecT investigators found no difference between active surveillance, radical prostatectomy, and radical radiotherapy with hormones on cancer specific mortality among men with localised prostate cancer.³ Among the arms, prostatectomy had the greatest negative effect on sexual function and urinary continence, while radiotherapy had significant negative effects on sexual function and bowel function. Higher rates of metastases were observed in the active monitoring group.

There was no difference in health related quality of life between the arms, but, because of the increased rate of metastases, some experts argue that active surveillance is inferior. In a defence of this view, D'Amico writes, "Developing metastatic PC is a life-changing event ... which brings the fear of dying of PC" into patients' lives, and, "Is it really considered a success if a man suffers recurrence with metastatic disease, which often means a painful bone fracture along with castration and all of its toxicities"?



Another example is sunitinib, which the US Food and Drug Administration approved for the adjuvant treatment of resected kidney cancer in 2017.5 This approval was granted on the basis of one randomised trial (S-TRAC) that showed sunitinib, when compared against observation, delayed the time until the composite endpoint of recurrence or death (hazard ratio=0.76, 95% CI 0.59 to 0.98; P=0.03), though it did so without any improvement in overall survival (1.01, 0.72 to 1.44; P=0.94). Overall survival curves, presented in the paper's supplement, are superimposable over the first eight years of follow-up, suggesting that the lowered rate of recurrence has shown no evidence of translating into improved survival.

Finally, consider gefitinib, a small molecular inhibitor of the epidermal growth factor receptor. In a randomised trial of patients with lung cancer who had their tumours resected (ADJUVANT), the drug improved the time till disease recurrence or death (hazard ratio=0.60; 95% CI 0.42 to 0.87; P=0.005). Overall survival was virtually identical between the arms, with 34.2% of patients in the trial dying, whereas in previous studies of non-small cell lung cancer, improvements in disease recurrence strongly predicted improvements in overall survival.8

If the events averted are mild then net benefit becomes questionable

Weighing the benefits and harms

Together these examples show a new challenge facing patients and providers. If the myocardial infarctions, strokes, and metastases averted in these studies are severe, then the interventions probably offer net benefit. At the same time, if the events averted are mild—for instance, if most metastases are asymptomatic or indolent—then net benefit becomes questionable, particularly when weighed against side effects and therapeutic and financial burden.

At some point, if observed endpoints do not directly affect patients' perceived health or health related quality of life, they may be thought of as a risk factor for a future clinical event, and not an event themselves. An easy way to adjudicate these concerns is appealing to health related quality of life-did it improve? However, in the trials described above this was not reported for evolocumab, showed no difference in ProtecT, was worse in S-TRAC, and modestly improved when comparing gefitinib with chemotherapy in the ADJUVANT trial.

Evidence exists of a progressive expansion of all these disease categories over time. Diagnoses of myocardial infarctions have changed substantially since the introduction of more sensitive cardiac markers, including creatinine phosphokinase (CK), myocardial band fraction of CK, and high sensitivity cardiac

troponin. ^{9 10} This expansion requires that we consider two new aspects when interpreting the biomarkers: a gradient risk in biomarker levels, as suggested by the prognostic value of different troponin levels, ¹¹ and increased sensitivity of the disease. ¹² Professional cardiology societies have cautioned about the importance of applying constant definitions when tracking time trends in the rate of myocardial infarction when diagnostic criteria are altered. ¹³

In the case of stroke, improvements in the availability and quality of imaging techniques may have resulted in more silent infarcts being identified, leading to a lower diagnostic threshold.14 Asymptomatic ischaemic lesions occur in 7-28% of elderly people, more than fivefold higher than the prevalence of symptomatic stroke. 14 15 These infarcts have been reported to be associated with subtle deficits in physical and cognitive function and increased risk of subsequent stroke or dementia,14 but it is not clear whether these events compromise health related quality of life and, most importantly, whether their avoidance is worth the side effects and burden of intervention.

In the evolocumab study, the drug's massive effect on low density lipoprotein cholesterol level—reducing it from a mean of 2.3 mmol/L in the control arm to 0.8 mmol/L in the intervention arm—is likely to have effectively unblinded the study. ¹⁶ Knowledge of LDL may have influenced decision making and coding of subsequent events.

Cardiologists may be more likely to recommend percutaneous coronary angioplasty in a patient with LDL over 2.6 mmol/L than below 1.3 mmol/L at similar levels of chest pain or discomfort. And, though the FOURIER authors report there was no increase in type 4 (or percutaneous angioplasty related) myocardial infarctions between the arms, they fail to report what percentage of infarctions were ST elevated, leaving open the question of the clinical severity of the events. ¹⁷

Moreover, although the trial met its primary composite endpoint, cardiovascular death and overall

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mortality were not improved. Beyond type 4 myocardial infarctions, knowledge of LDL may influence the coding of other cardiac events that require provider discretion. For instance, in a case of suspected unstable angina in someone with an ambiguous clinical history, a clinician may rely on a low but detectable troponin level, and knowledge of a patient's most recent LDL measurement may affect such decisions. ^{16 18}

Interpretation of the FOURIER trial requires knowledge of the rates of ST elevated infarction (an echocardiography driven endpoint) and infarction leading to cardiogenic shock requiring pressors, another more objective endpoint. Additionally, further data, including the presence of new ST-T changes or Q waves, new left bundle branch block, imaging evidence of loss of viable myocardium, or new regional wall motion abnormality should be reported. 19

In the case of ProtecT, the higher incidence in metastasis did not worsen a true patient centred endpoint: health related quality of life. The trial defined metastasis broadly as the spread of prostate cancer to bone, viscera, or lymph nodes or a PSA level >100 ng/mL, and it does not report how often metastasis led to fracture. Earlier trials used narrower definitions. For example, compared with the Scandinavian Prostate Cancer Group 4 study, 20 21 ProtecT added PSA rise over 100 ng/mL and regional lymph node disease to the definition of metastasis.

This disease expansion matters because metastatic disease becomes a composite outcome of several discrete events, not unlike composite outcomes in cardiology. And while there is clear evidence that skeletal related events do confer a poor prognosis, ²² there is not comparable evidence for each of the other events included in the composite.

Making endpoints more meaningful

An important step towards untangling these endpoints is further details on trial outcomes. The evolocumab investigators could



break down myocardial infarction into ST elevation, non-ST elevation, those that occurred immediately after revascularisation and those that occurred spontaneously, and those that resulted in shock or long term diminished ejection fraction and those that did not. Among infarctions without ST elevation, the investigators could provide breakdown by TIMI risk score to further gauge severity and, again, those leading to shock or systolic dysfunction. Authors should report events based on the third universal definition of myocardial infarction.¹⁹ The ultimate solution to interpreting endpoints would be the reporting of outcomes with individual endpoint biomarker or quantitative imaging data for independent review.

In the case of ProtecT, given concern about metastasis leading to fracture, this outcome could be explicitly reported. There seems little value in having experts speculate about the consequences of metastasis⁴ when these are known. Data sharing has potential to lead to greater clarity and transparency, as other investigators may further refine the breakdown and transparency of endpoints, particularly in trials over time.

Finally, validity of outcomes may also be improved by greater patient involvement, at the outset of clinical trials, in their design and conduct. Patients can help to develop

An important step towards untangling these endpoints is further details on trial outcomes instruments that best capture their burden of symptoms or sequelae of disease. Promising efforts are already being made, including the collaborative group OMERACT in rheumatoid arthritis outcomes. We suggest that this process is iterative, performed before, during, and after trials. This way, patient experiences during the clinical trial process may improve capture of outcomes in subsequent investigations.

What next?

It is understandable that investigators would be tempted to declare reductions in cancer metastasis, myocardial infarction, or stroke as proof of therapeutic efficacy. However, because diagnostic drift now includes illness of lesser severity, it is no longer clear that any of these events implies loss in health related quality of life. Direct consideration of health related quality of life has the added advantage of balancing benefit against the harm of interventions, such as side effects, toxicity, treatment burden, time commitment, and financial costs. We believe greater detail in outcomes reporting and data sharing can overcome this challenge, which, to a large degree, represents our success in the technological advancement of diagnostic testing.

Cite this as: *BMJ* 2018;362:k3783

Go Nishikawa, instructor

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STOPPING OF VIAGRA TRIAL

Animal studies omitted from STRIDER trial

The recent announcement that the STRIDER trial intervention resulted in 11 infant deaths due to lung related problems raises serious questions (This Week, 4-11 August).

The STRIDER summary cites only five animal studies that were considered supportive. None examined pulmonary effects or postnatal consequences.

At least one relevant study showed adverse effects of sildenafil and concluded that it should be used with caution. Why this study was omitted is unclear.

Critically, no physiological measures of the fetus were reported, and the study was funded by Pfizer, the manufacturer of Viagra. These are important omissions. To avoid such oversight in trial planning, especially during pregnancy, a thorough literature search of animal studies and meta-analyses should be undertaken. The advisory panel must ensure that all relevant publications are included and appropriately considered.

A more comprehensive approach may have prevented the STRIDER trial.

Michael E Symonds, professor, Helen Budge, professor, Nottingham Cite this as: *BMJ* 2018;362:k4007

Including pregnant women in clinical research

Media reporting of STRIDER failed to mention the importance of conducting clinical research in pregnant women.

Wanting to protect women and fetuses from harm, physicians, midwives, and researchers are reluctant to include them in clinical research, but it is the only way to increase the evidence base about safety and efficacy of drugs in pregnancy. We must consider the risks of not conducting



LETTER OF THE WEEK

Brexit affects our ability to tackle drugs trade

Though much attention has been given to the European Medicines Agency leaving London because of Brexit, the consequences of potential exclusion from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) have been overlooked (Editorial, 26 May).

The EMCDDA is responsible for conducting surveillance, establishing best practice, facilitating data exchange, providing leadership on new psychoactive substances, and assisting policy makers. The intelligence assembled by the EMCDDA and Europol has been crucial in the UK's response to organised crime and illicit trade in drugs. The UK risks exclusion from the EU Drugs Action Plan, an initiative that will strengthen surveillance of drug markets, drug related crime, and drug supply reduction.

The EMCDDA has had an important role in supporting drug and health policy in EU member states, including the UK. It has developed a strategic, situational, and holistic understanding of the European drug situation; identified new threats to public health and security; and established best practice for effective interventions and informed policy making. The challenges of Brexit arrive when the UK relies most heavily on the EMCDDA to tackle the trade of illicit substances, especially involving organised crime, the consequences of which are seen on the streets and in emergency departments every week.

Ministers have committed to ensuring Brexit will not undermine public health. This is an opportunity to show that commitment.

Andres Roman-Urrestarazu, Gillings fellow in global public health, Cambridge;
Roy Robertson, professor of addiction medicine. Edinburgh: Justin Yang, PhD

Andres Roman-Urrestarazu, Gillings Fellow in global public health, Cambridge Roy Robertson, professor of addiction medicine, Edinburgh; Justin Yang, PhD student, Cambridge; Alison McCallum, director of public health and health policy, NHS Lothian; Christina Gray, chair, Faculty of Public Health Mental Health Special Interest Group; Martin McKee, professor of European public health, London; John Middleton, president, Faculty of Public Health

Cite this as: *BMJ* 2018;362:k4003

research in pregnant women.
Sildenafil has been prescribed
by doctors around the world for
women pregnant with severely
growth restricted fetuses. It is only
because of this study that the
potential adverse outcomes are
now flagged.

Clinical research with pregnant women should not be prevented but encouraged. All stakeholders must encourage carefully designed and executed research. Ultimately, we need research like this to increase the evidence base and improve maternal and fetal health.

Joyce Browne, physician and clinical epidemiologist, Utrecht; Indira van der Zande, ethicist, Fryslân; Maarten van Smeden, statistician, Leiden; Rieke van der Graaf, ethicist, Utrecht

Cite this as: BMJ 2018;362:k4013

COW'S MILK ALLERGY

Allergy UK comments on corporate sponsorship

McCartney makes some comments that misrepresent Allergy UK and its activities (No Holds Barred, 4-11 August). The statement in our leaflet, "Your GP will need to switch your infant to a prescribed formula," has been

taken out of context. Inferring that this is followed by the name of a specific formula company is misleading as we do not recommend brands or companies.

Our masterclasses cover several topics, but McCartney infers that we are only covering cow's milk allergy. Nutricia is one of several sponsors, all of which are clearly acknowledged for full transparency.

All our activities are undertaken within relevant codes of practice that include full transparency about funding and clarity around the declaration of financial support.

McCartney says that "adverse consequences" can result from sponsored education. The parents of more than 600 infants who have called our helpline reporting persistent and severe symptoms would probably disagree.

Lynne Pritchard, chair, Allergy UK Cite this as: *BMJ* 2018;362:k4000

GOUT

Alternatives to uric acid lowering in heart disease

As a GPI frequently see patients with gout who have cardiovascular risk factors (*Drug and Therapeutics Bulletin*, 4-11 August). Some drugs increase the risk of gout, the commonest being low dose aspirin and diuretics. Often these can be reduced, stopped, or changed to alternatives that do not increase urate levels, such as clopidogrel (instead of aspirin), or are known to be uricosuric, such as amlodipine or losartan (typically instead of thiazide diuretics).

Also, atorvastatin 40 mg has been shown to lower uric acid levels by 12.5%, whereas simvastatin 40 mg did not.

I think that we should offer these simple teatment options to our patients rather than adding specific uric acid lowering treatment. John A Ashcroft, GP, Ilkeston

Cite this as: BMJ 2018;362:k3895

OBITUARIES

Asok Ranjan Das Gupta

Ear, nose, and throat surgeon Birmingham and Walsall (b 1936; q Nil Ratan Sircar Medical College 1959; DLO, FRCS Eng), died from metastatic carcinoma on 19 May 2018



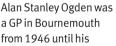
Asok Ranian Das Gupta was born into a highly educated Hindu family in East Bengal. In 1947 he and his family were forced to migrate to Calcutta (now Kolkata) because of the partition of India. After early appointments in ear, nose, and throat medicine in Calcutta, he came to England and began his career at various hospitals in London and the south east between 1961 and 1965. In 1968 he was appointed consultant ear, nose, and throat surgeon in Birmingham and Walsall. He retired from clinical work in 2004 but continued with some outpatient clinics and undergraduate teaching for several years. Beyond medicine and his family, the great love of his life was cricket. He leaves his wife, Anne, and two daughters.

John Temple

Cite this as: BMJ 2018;362:k3526

Alan Stanley Ogden

General practitioner Bournemouth, Dorset (b 1915; q Manchester 1939), died from old age on 26 July 2018





retirement in 1985. In 1946 he and his practice partner started an appointments system and employed a practice nurse. He helped found a very happy group practice in a purpose built surgery. A past chairman of the East Dorset division of the BMA, president of the Bournemouth and Poole Medical Society, and honorary member of BUPA, he was, for 35 years, club doctor to AFC Bournemouth. He personally collected samples of sea water from the bay, which, when cultured in the laboratory, grew salmonella and other noxious agents. He presented the results to the local council, which approved the construction of an inland water purification plant. Predeceased by his wife, he leaves two children, four grandchildren, and four great grandchildren. Alan Stanley Ogden, Judith Hallpike

Cite this as: BMJ 2018;362:k3524

Katherine Mary Donnelly

Community paediatrician Newry (b 1945; q Queen's University Belfast 1970), died from complications related to chronic obstructive pulmonary disease on 7 October 2017



Katherine Mary McLoughlin ("Maura") met her future husband, Brian Donnelly, as a fourth year medical student on an anaesthetics placement at Daisy Hill Hospital, Newry, She completed her house job in the Mater Hospital in Belfast, and after working for a short time in casualty, she took time off to be a full time mother to their growing family. Maura returned to medical practice in the early 1980s, working temporarily in general practice and then as a staff grade in community paediatrics. After Brian's sudden death in 1990, she worked full time to support their four sons through school and university. She retired in 2008. Predeceased by one of her sons, she leaves three sons (including the author of this obituary) and eight grandchildren.

Brian Donnelly

Cite this as: BMJ 2018;362:k3523

Alan Rhodes

Consultant surgeon Coventry University Hospitals (b 1936; q Birmingham 1959; FRCS Eng), died from Alzheimer's disease on 19 June 2018 Early in his career Alan Rhodes was an anatomy



demonstrator in Birmingham and then spent two years in New York. He returned to the UK in 1963, and after completing surgical training he became a consultant in general and paediatric surgery in Coventry at the young age of 32. Any of his colleagues would tell you that life was rarely dull when he was around. Surgery was where he felt in command, he was deft and meticulous in his surgical approach, and his accompanying commentary made the anatomy come to life for those he was teaching. In retirement he returned to teaching anatomy, this time to mature medical students at Warwick University. Predeceased by his son David in 2001, Alan leaves his wife, Caroline; three sons; and a grandchild.

Clare Marx

Cite this as: *BMJ* 2018;362:k3525

Charles Louis Joiner

Senior consultant physician (b 1923; q 1946; MD FRCP), died from old age on 20 July 2018 Charles Louis Joiner trained at Guy's and won the Beaney prize for pathology. A diabetes



scholarship enabled him to live and research in Pennsylvania, USA. During his years as a medical registrar he contributed to research into insulin and isoniazid. In 1959 he was appointed consultant physician to Guy's Hospital, and latterly to the Bromley Group of Hospitals. During the 1970s he was visiting professor of medicine to Cornell University, honorary physician to the British Army, and fellow of the Royal Society of Medicine. In 1993 Charles finally retired at the age of 70 to enjoy his family and pursue his lifelong interest in military history. Helen, a Guy's nurse whom he had married in 1949, predeceased him by 10 years. He leaves two children, three grandchildren, and one great grandson.

Sarah Fish

Cite this as: BMJ 2018;362:k3602

Noel Stephen Cracroft Rice

Consultant ophthalmologist (b 1931; q Cambridge/ St Bartholomew's Hospital 1956; MD, FRCS, FRCOphth), died from motor neurone disease on 5 November 2017



Noel Stephen Cracroft Rice was appointed consultant ophthalmologist at Moorfields Eye Hospital in 1969. He became one of the first corneal specialists in Europe and pioneered microscope assisted surgery. He specialised in the care of children with congenital glaucoma and introduced the use of anti-scarring therapy in the form of a focal dose of β radiation. As medical director at Moorfields and dean of the Institute of Ophthalmology he presided over a time of growth that helped lead to the joint site becoming the most productive ophthalmology research site in the world. In his retirement he remained active in helping to develop ophthalmology in several parts of the globe. Predeceased by his first wife, Brita, in 1992; he leaves his second wife, Ulla; three children; and seven grandchildren.

Peng Tee Khaw

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William McBride

Alerted the world to the dangers of thalidomide in fetal development

William McBride (b 1927; q University of Sydney, Australia, 1949; CBE, AO, FRCOG), died peacefully on 27 June 2018

In December 1961, the Australian obstetrician William McBride warned in a letter to the *Lancet* that he had observed "multiple severe abnormalities" in babies delivered from women who had taken the drug thalidomide during pregnancy. His concerns were subsequently confirmed by researchers in Europe, and the drug was banned around the world, saving countless infants from being born with birth defects.

William Griffith McBride was born in Sydney. He trained in obstetrics and gynaecology at the University of London. After returning from London to Australia, he worked in Tasmania and then moved to Sydney's Crown Street Women's Hospital, where he was medical superintendent by the age of 28 and remained for 31 years.

Thalidomide

In May 1961, McBride delivered a baby with malformed arms and severe internal damage. The baby died shortly after birth. A few weeks later he delivered two more babies with similar problems. After investigation, he found that the mothers of all three had taken thalidomide during pregnancy to alleviate morning sickness.

McBride stopped prescribing thalidomide, which was developed in the 1950s by the West German pharmaceuticals company Chemie Grünenthal. The drug was marketed in Australia and the UK under the trade name Distaval by UK based Distillers Company.

Even before McBride's letter to the *Lancet*, some doctors were becoming concerned about potential toxic effects of thalidomide. One letter, published on 2 December 1961—two weeks before McBride's *Lancet* letter—came from DJ Hayman, managing director of Distillers Company. In addition to reports of links of peripheral neuritis



McBride set up Foundation 41 to investigate fetal development and drug induced deformities in the first 41 weeks of life to thalidomide, Hayman wrote that "reports have been received from two overseas sources possibly associating thalidomide with harmful effects on the fetus in early pregnancy."

In the months after McBride's *Lancet* letter, doctors from around the world reported observing severe abnormalities in babies delivered to women who had taken thalidomide. Scientific papers describing the drug's link to birth defects began appearing by the middle of 1962.

Thalidomide is estimated to have led to 2000 deaths globally and to 10 000 children being born with birth defects, mainly in Australasia, Canada, and Europe. No cases occurred in the US, where the drug was not approved. The drug is still in limited use today, mainly to treat certain cancers.

In 1971 McBride was awarded a prize from L'Institut de la Vie in France "for his services to mankind," which carried a cash award of 250 000 francs. He used the money to establish Foundation 41, a privately funded charitable foundation to investigate fetal development and drug induced deformities in the first 41 weeks of life.

Controversies

In 1972 McBride published a paper linking imipramine, an antidepressant, with limb deformities, but no further evidence was subsequently found to support his theory. He later linked Debendox (dicyclomine-doxylamine-pyridoxine), an antinausea drug that was used by pregnant women, to birth defects. He testified in court cases in the US as

an expert witness in lawsuits filed by families claiming Debendox (also sold as Bendectin) had caused birth defects. Merrell Dow, the producer of the drug, pulled the drug off the market in 1983 because of lawsuits, the company said, not because it was unsafe.

In 1987 Norbert Swan, a Scottish paediatrician who turned to journalism, alleged on the Australian Broadcasting Corporation's *Science Show* that McBride had falsified research data for a research paper published in 1982. The paper described a study of the effects of scopolamine hydrobromide on the development of chick and rabbit embryones.

McBride denied the fraud allegation, but public pressure mounted and Foundation 41 conducted an internal investigation. The investigation's findings included that "deliberate falsification did occur" and that research "was not conducted in accordance with proper scientific method and was not honestly reported." After a four year inquiry that reportedly cost millions, a medical tribunal found him guilty of 24 of the allegations of medical research fraud, and McBride was struck off in 1993. In 1996 he lost an attempt to be reinstated to the medical register, but in 1998 he succeeded after a judge deemed he had shown sufficient remorse.

McBride leaves his wife, Patricia Glover; four children; and seven grandchildren.

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TWEET OF THE MONTH

Margaret McCartney's swansong

"Many people seek to make money from those who don't understand science. Doctors should call out bollocksology when they see it"

This maxim from Margaret McCartney, one of the 36 she shared in her final BMJ column, was our most popular tweet in September. Many readers tweeted us to share their favourite piece of Margaret's "McWisdom," as one reader put it, and to thank her for her columns over the past four and a half years. As one reader, Graham Kramer @KramerGraham, said: "Thanks

@mgtmccartney for helping us all to ethically navigate through the choppy seas of commercialisation, austerity, political zeal, and dodgy evidence."



MOST READ ONLINE

More than 1200 NHS staff have been disciplined for social media use

▶ BMJ 2018;362:k3947

Cochrane director's expulsion results in four board members resigning

▶ *BMJ* 2018;362:k3945

Pandemrix vaccine: why was the public not told of early warning signs?

▶ BMJ 2018;362:k3948

Medical associate professions: how physician associate and similar roles are developing, and what that means for doctors

▶ BMJ 2018:362:k3897

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LATEST PODCAST

Time to defend policy making based on evidence from ideological attack

In this podcast Chris Bonell, professor of public health sociology, discusses the rise of populism and worries that it is pushing evidence further out of policy making.

"Evidence based practice and evidence based policy hasn't existed for very long. It rose to prominence in the course of the 1980s and 1990s, and we can't assume that it's always going to be sacrosanct...People learning about research and evidence based policy need to understand that it's dependent on politics and it arose from political debate. If we're all more aware of that, then it would encourage a culture among researchers of defending evidence more assertively."



Listen to the podcast and read the essay at http://bit.ly/defending_evidence_policy

WHEN I USE A WORD

Saintly medical specialties



Gods and saints have long and often been invoked for medical reasons and there is no shortage of patron saints of medical conditions and specialties.

St Blaise, or Blasius, who was martyred in AD 316 for failing to renounce his Christian faith, started his career in Armenia as a general practitioner. He specialised in treating diseases of the throat, coughs, quinsy, goitre, whooping cough, and children's diseases. As he died, he prayed that he might be allowed to help all those with diseases of the throat. He is therefore the patron saint of laryngology. Then there is St Lucy (left), the patron saint of ophthalmology, and René Goupil, the patron saint of anaesthesia.

Who is the patron saint of pharmacology and clinical pharmacology? Drug actions are mediated by chemical signalling, and chemical recognition is served by receptors, which are major targets of many important drugs. The mechanisms whereby drug-receptor interactions are translated into therapeutic outcomes involve chemical transmission by substances generally known as second messengers. So, no saint is better qualified to be the patron saint of pharmacology than God's messenger himself, the archangel Gabriel.

So we should celebrate Pharmacology Day on St Gabriel's Day, 29 September. It will be followed this year by Clinical Pharmacology Month in October, with a range of activities.

Jeffrey Aronson is a clinical pharmacologist, working in the Centre for Evidence Based Medicine in Oxford's Nuffield Department of Primary Care Health Sciences. He is also president emeritus of the British Pharmacological Society

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