Letters to the editor

Hyperglycaemia and chorea

Regarding the paper by Degnan et al,[1] I would like to draw attention to the fact that hyperglycaemia was omitted from the list of metabolic/endocrine causes of chorea. One example was that of a 72-year-old man with non-ketotic hyperglycaemia characterised by blood glucose 57.7 mmol/l, corrected serum sodium 141 mmol/l, and normal calcium and magnesium levels.[2] After fluid replacement therapy and correction of hyperglycaemia there was no recurrence of hemichorea-hemiballismus.

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References

1 Degnan AJ, Capek E, Bowman A. Chorea in the older adult: a full blooded answer. *J R Coll Physicians Edinb* 2016; 46: 244–6.
2 Lee PC, Kek PC, Soh AWE. Hyperglycamia-associated hemichorea-hemiballism: The spectrum of clinical presentation. *Intern Med* 2015; 54: 1881–4.

Caleb Parry and 18th century controlled comparisons of Turkish and English rhubarb

I enjoyed reading the paper by Lee et al. on Edinburgh's role in the cultivation and development of rhubarb.[1] They refer to the replacement of expensive imported rhubarb with rhubarb grown in the UK, particularly in Bodicote, near Banbury, and Dewsbury and Wakefield in West Yorkshire.

The replacement of imported rhubarb with 'home grown' rhubarb may have been encouraged by the results of research done in Bath in the 1780s by Caleb Hillier Parry.[2] He compared two locally grown varieties of the plant with 'Turkey' rhubarb in a series of n-of-1 crossover trials in patients in the Pauper Charity. These ranged in age from 5 weeks to 74 years. Parry concluded that:

> So far as these experiments go, we may infer that the specimen of English rhubarb No. I was fully equal in its purgative quality to the Turkey, and that they are both somewhat superior to No. II.[3]

Parry's account of his crossover trials can be viewed in the James Lind Library – www.jameslindlibrary.org

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References

1 Lee MR, Hutcheon J, Dukan E et al. Rhubarb (Rheum species): the role of Edinburgh in its cultivation and development. *J R Coll Physicians Edinb* 2017: 47: 102–9.
2 Rolls R. Caleb Hillier Parry (1755-1822). *JLL Bulletin: Commentaries on the history of treatment evaluation* 2003. http://www.jameslindlibrary.org/articles/caleb-hillier-parry-1755-1822
3 Parry CH. Experiments relative to the medical effects of Turkey Rhubarb, and of the English Rhubarbs, No. I and No. II made on patients of the Pauper Charity. *Letters and Papers of the Bath Society* 1786; 11: 431–53.

Atherothrombotic strokes in NVAF

When evaluating stroke risk in nonvalvular atrial fibrillation (NVAF),[1] we should recognise that, among patients of mean age 69.5 with NVAF-related stroke, up to 29.6% of those strokes may be of atherothrombotic aetiology.[2] The rationale is that in 29.6 % of those patients there may be a coexistence of stenotic (50% or more stenosis) cerebrovascular disease,[2] the latter a risk factor for stroke in its own right. Accordingly, failure of vitamin K antagonists (VKAs) to reduce stroke risk in as many as 38% of NVAF subjects,[3] merely underscores the reality that VKAs are not able to prevent strokes attributable to an atherothrombotic aetiology. Both in the context of NVAF[4] and outside the context of NVAF,[5] the optimum thromboprophylaxis against atherothrombotic strokes might well be co-administration of clopidogrel and aspirin, due to the fact that among patients of median age 62.5 with sinus rhythm, combined treatment is significantly ($p < 0.001$) superior to the sole use of aspirin for secondary prevention of stroke.[5] In the context of NVAF, among patients of mean age 71 with NVAF, combined treatment was significantly ($p < 0.001$) superior to the sole use of aspirin in preventing stroke, even though extracranial embolism occurred with equal frequency (54 out of 3,772 patients vs 56 out of 3,782 patients) in patients on combined treatment vs patients in whom aspirin was the sole antithrombotic agent.[4]

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References

1 Voukalis C, Shantsila E, Lip GYH. Stroke prevention in atrial fibrillation. *J R Coll Physicians Edinb* 2017; 47: 13–23.
2 Kim YD, Cha MJ, Kim J et al. Increases in cerebral atherosclerosis according to CHADS2 score in patients with stroke with nonvalvular atrial fibrillation. *Stroke* 2011; 42: 930–4.
3 Hart RG, Benavente O, McBride R et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1996; 131: 492–501.
4 Connolly J, Pogue J, Hart RG et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009; 360: 2066–78.
5 Wang Y, Wang Y, Zhao X et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013; 369: 11–19.

Reply

The role of adding antiplatelets in the prevention of vascular events, especially for patients with atrial fibrillation (AF) after percutaneous coronary angioplasty is generally recommended, but there is a fine balance between the risk of bleeding and prevention of vascular events especially given

that combination therapy with oral anticoagulation (OAC) and antiplatelets confers an increased risk of serious bleeding.[1] Apart from the setting of percutaneous coronary stenting, there is inadequate evidence from prospective randomised controlled trials (RCT) to support a positive net clinical benefit of the combination OAC plus antiplatelets against OAC monotherapy.[1]

Posthoc analyses of large randomised trials and large observational cohorts do not show any convincing reduction in stroke, death or cardiac events with combination OAC plus antiplatelet therapy – but instead show a significant increase in major bleeding and intracranial haemorrhage.[1,2]

Of note, the combination of aspirin plus clopidogrel is inferior to OAC for stroke prevention, with a similar rate of major bleeding.[3] Especially in the elderly, aspirin is not associated with lower risk of major haemorrhage or intracranial bleeding compared with OAC.[4,5] In short, there is no robust evidence for the efficacy combination OAC plus antiplatelet therapy in AF patients with stable vascular disease, but serious bleeding risk may occur.

Nevertheless, we would agree that all patients (including those with AF) with confirmed cardio-embolic aetiology of a cerebrovascular event require further non-invasive investigations for bystander atherosclerotic disease as they might benefit from secondary prevention measures (statins, angiotensin converting enzyme inhibitors, etc), as well as control of amenable risk factors (e.g. blood pressure) and lifestyle changes.[6]

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References

1 Lip GYH, Windecker S, Huber K et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on. *Eur Heart J* 2014; 35: 3155–79.
2 Lamberts M, Gislason GH, Lip GYH et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. *Circulation* 2014; 129: 1577–85.
3 Connolly SJ, Pogue J, Hart RG et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med* 2009; 360: 2066–78.
4 Lip GY. The role of aspirin for stroke prevention in atrial fibrillation. *Nat Rev Cardiol* 2011; 8: 602–6.
5 Marinigh R, Lip GYH, Fiotti N et al. Age as a risk factor for stroke in atrial fibrillation patients: implications for thromboprophylaxis. *J Am Coll Cardiol* 2010; 56: 827–37.
6 RCP London. National clinical guideline for stroke. 2016. https://www.strokeaudit.org/Guideline/Full-Guideline.aspx

HIV infection in Muirhouse

I read with interest Roy Robertson's account of HIV infection in the Muirhouse area of Edinburgh.[1] I was a Consultant in Infectious Diseases at the time of the outbreak and my personal reflections might be of additional interest.

The first intimation of the Edinburgh problem was a worrying positivity rate when the original HIV tests were introduced.[2] This prompted a clinically-based study that revealed 83 out of 164 intravenous drug abusers (IVDUs) in Muirhouse were seropositive in 1985, with the first positive being in late 1983.[3] I doubt if this research would now gain ethical approval.[4] The epidemic curve was not that of the one-person to one-person spread of a longish incubation illness but rather suggested that multiple needle sharing in 'shooting galleries' had occurred, such that one person could infect several others simultaneously. Shooting galleries were common because heroin was available, whereas needles and syringes were in short supply. Generally, each user realised their share should include the 1 ml in the syringe hub and needle, so they would draw back about 1ml of their blood and then inject the same volume and pass the needle and syringe to the next user who received a diluted 1 ml of the previous user's blood. An HIV positive user could infect many others.

Epidemics with similar 'explosive' growth due to multiple, transitory, sexual contacts were observed among men who have sex with men on the west coast of the USA, and heterosexual communities in sub-Saharan Africa. The pattern of sequential monogamy slowed down the spread of HIV in the general population in the UK.

Some previous observations made in the Infectious Diseases unit about (mostly) hepatitis B in 1984[5] yielded quotes which later emerged as highly relevant to HIV. 'Heroin was fashionable but things have moved on, it's now marijuana.' Drug abuse has its fashions! 'I only had heroin once', with the supplementary question 'Did you share needles?', and the obvious reply 'Of course, the first time you are offered it you never have your own needle and syringe.'

Why was Edinburgh the harbinger of HIV? It was the first to highlight a clinical problem[3] and people assume that 'first means worst.' The vigorous police anti-IVDU policy of heroin and needle plus syringe seizure seemed sensible but in retrospect encouraged needle sharing as heroin is easily concealed; needles and syringes are more difficult to conceal and thus likely to be in relatively short supply. The epidemic of Edinburgh needle sharing occurred when infectivity was high because viral loads are highest around the time of seroconversion. Edinburgh was gifted the accolade of AIDS Capital of Europe by the *Sunday Telegraph* on 13 April 1986, although a subsequent analysis, particularly of pregnant women, revealed that Edinburgh was only fifth. Barcelona, not even a capital city, came first.[6]

Once the prevalence of HIV in the Muirhouse IVDUs was known, planning had to take place. The police restrained their confiscation policy, and harm reduction including methadone was introduced. This gave IVDUs some stability, reduced the necessary crime to fund their habit, reduced their need for IVDU and encouraged medical contact as drug users and ex-drug abusers had to attend clinics to obtain methadone. The clinicians involved in patient care had to develop expertise in all management aspects of this difficult patient group.

In retrospect there were several epidemics which followed the epidemic of intravenous drug abuse. Focal sepsis, endocarditis, hepatitis B, hepatitis C (known as non-A, non-B hepatitis at the time) and then HIV. The tragedy of HIV was that the IVDU community had experience of hepatitis B and knew that most of them would recover. When it became known that there was a risk of HIV and AIDS, most HIV positive IVDUs were asymptomatic, as were their fellow users, and I suspect they thought the medical profession was overemphasising risks. Certainly I found that IVDU behaviour improved once their fellow IVDUs became unwell.

It may be decades before we have drugs that can penetrate every HIV-infected human cell and selectively remove HIV-directed nucleic acid sequences from the host cell genome. It is likely to be even longer before a useful vaccine is widely available. Vaccination before infection would have to invoke a greater response than that to the natural infection and a live attenuated vaccine of a virus known to mutate rapidly would be too dangerous. Questions arise. Would the vaccine protect against all strains of HIV arriving by all of the possible routes? How long would immunity last? Would a vaccine, if not preventative, increase the incubation period and/or reduce infectivity? Would vaccination encourage more at-risk behaviour in at-risk groups? How could the vaccine be shown to be safe and effective? To whom should it be given – to all children, as it would not be predictable who would later indulge in at risk behaviour? Could the whole of Africa be vaccinated?

Curiously HIV was predicted. In 1933 HG Wells wrote *The Shape of Things to Come* in which he described 'the maculated fever' (anticipating Kaposi's sarcoma) which was 'hitherto known only as a disease of captive baboons,' (it was wild sooty mangabey monkeys who harboured HIV-2 and chimpanzees who harboured HIV-1) 'all who took it died' (without treatment HIV is ultimately fatal) and that 'the real disease…may not have been the maculated fever at all, but the state of vulnerability that had spread unsuspected throughout the world' (the asymptomatic phase of HIV before AIDS develops is about 10 years in the untreated). I hesitate to emulate HG Wells but I wonder whether there are additional ultra-long incubation viruses lurking in the IVDU population which will manifest in years to come.

I was a generalist by nature and although active in writing about HIV, I was not as proactive as other colleagues, notably Ray Brettle in the Infectious Diseases unit and Roy Robertson in General Practice. Edinburgh ought to be proud of these and others who worked both independently and together to tackle this problem.

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References

1 Robertson R. Misadventure in Muirhouse. HIV infection :a modern plague and persisting public health problem. *J R Coll Physicians Edinb* 2017; 47: 88–93.
2 Peutherer JF, Edmond E, Simmonds P et al. HTLV-III antibody in Edinburgh drug addicts. *Lancet* 1985; 2: 1129–30.
3 Robertson JR, Bucknall ABV, Welsby PD et al. Epidemic of AIDS-related virus (HTLV-III/LAV) infection among intravenous drug abusers. *BMJ* 1986; 292: 527–9.
4 Welsby PD. Personal View. *BMJ* 1986; 292: 954
5 Leen CLS, Welsby PD. Differentiation between medical and surgical jaundice. *Practitioner* 1985; 229: 183–5.
6 McCarthy C, Welsby PD. Edinburgh – the AIDS Capital of Europe? *Scot Med J* 2003: 48: 3–5.

In memoriam

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