AIR POLLUTION AND STROKE – IS A CAUSATIVE ASSOCIATION POSSIBLE?[1]

Sir,

This is a well written piece and I very much enjoyed the anecdotes. However, I would like to make a few points from my perspective as a stroke epidemiologist.

The author states that stroke is a much less common cause of death than heart attack. Not so – in 1990, cerebrovascular disease was the second most common cause of death worldwide (about 4·5 million deaths) after ischaemic heart disease (about 6 million deaths.)[2] There are many, many millions of strokes occurring each year in developed and developing countries – low frequency is not a problem here.

The author is rather selective in his presentation of studies to support his point. He mentions that several studies have shown an association between air pollution and stroke, but quotes the results of only one that was statistically significant.[3] However, what does the totality of the evidence show? Have there been negative studies? How methodologically sound are the positive studies. In other words, is the association real or the result of some sort of bias? What about publication bias? Similarly, is the 4% increase in mortality in the Netherlands study[3] relative or absolute?

As an epidemiologist, I would be interested to see a discussion of possible alternative explanations for the observed association between air pollution and occlusive vascular disease, i.e. chance, publication bias or confounding (e.g. an association between exposure to air pollution and smoking).

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STROKE, AIR POLLUTION AND EPIDEMIOLOGISTS

Sir,

Numbers are better than adjectives. In 1993, in England and Wales, ischaemic heart disease was responsible for 29% of deaths, cerebrovascular disease 8%. Among men, the former was responsible for 79,000 deaths and 135,000 years of working life lost, and in women 67,000 and 31,000 respectively. The corresponding figures for stroke were 23,000, 26,000, 38,000 and 28,000.[1] No-one is trying to say that stroke is unimportant – the point is that power considerations require larger studies to demonstrate weak epidemiological effects for less common diseases.

My short article[2] was an invited commentary on a specific paper and was intended to draw the attention of neurologists and other physicians to an apparently strange and unexpected association and a plausible explanation. The literature is complex – different diagnostic categories (haemorrhagic stroke is unlikely to be related to pollution), many different indices of air pollution and several different study designs. A comprehensive review and meta-analysis of the published time series studies[3] on cardiovascular diseases is currently being undertaken by my friend Professor Ross Anderson in St George's Medical School on behalf of the Department of Health's Committee on the Medical Effects of Air Pollution and a report will be published in the later part of this year. I would certainly anticipate that this will show some evidence of publication bias, and I anticipate the results will indicate the strength of any associations.

I am pleased to have interested a fellow epidemiologist in the issue of air pollution, and I hope that Dr Sudlow, after assessing the literature herself, might next join me in speculating about the apparent link between air pollution episodes and cot death, which I think is a form of vertebro-basilar stroke. It is right for an epidemiologist to be sceptical; my experience suggests that imagination, lateral thinking and the ability to write provocatively are also desirable attributes if hypothesis formulation is part of one's role.

A SEATON

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3 'Time series studies' examine statistical associations in time between putative causative factors and suggested effects.

MEDICAL POSTGRADUATE TRAINING AND PRACTICE IN THE EXPANDED EUROPEAN UNION

Sir,

According to the author, the challenges facing the countries joining the European Union include 'changing demography, from a declining birth rate and ageing population'.[1]

The reality is that the most fundamental failure of both undergraduate and postgraduate teaching in the 'first' world has been the failure of acknowledgement that

older people constitute a sizeable proportion of patients in primary care, as well as in secondary care, being arguably in the majority in the former. The consequence of this 'denial' is that general medicine, general surgery, and, most lamentably of all, orthopaedics, is not taught either at undergraduate or at postgraduate level with special relevance to the following:

- clinical presentation in the elderly;
- principles of clinical problem solving in the young and the old ('Occam's razor' in the young; and 'Saint's triad' in the old);[2]
- risk profiling in the old (especially relevant in the surgical specialties); and
- the evaluation of risk vs benefit in the context of investigative as well as therapeutic interventions in the old.

None of these are mainstream issues in undergraduate medical education. Instead, at undergraduate level, geriatrics is taught as an appendage of general medicine, whilst, at postgraduate level, rotation through geriatrics is regarded as an optional extra even, would you believe it, in training programmes for specialisation in orthopaedic surgery.

Denial is, of course, a mindset almost inherent in medical practice. Errors of omission logically flow from denial, and the two most profound errors of omission in the era of evidence-based medicine include the one which flowed from the denial that left ventricular failure attributable to diastolic dysfunction (arguably, again, an age-related issue) can exist in the presence of a normal left ventricular ejection fraction,[3] and the error of omission attributable to the denial that there is an opportunity for thrombolytic therapy even when myocardial infarction presents without chest pain,[4] also an age-related issue.[5] In the former instance, there was, until very recently, a missed opportunity to evaluate therapeutic opportunities in left ventricular diastolic dysfunction. In the latter instance there was an omission to validate the reliability of symptoms and signs that could be a surrogate for chest pain in the timing of onset of myocardial infarction, and opportunities were missed to modify the subsequent natural history of myocardial infarction in the most decisive manner possible.

The old/young dichotomy is, of course, superficial. Far better to rely on a characterisation predominantly based on parameters such as that individual's mental, physical and physiological function. Only that way can we optimise the cost:benefit ratio of healthcare, and square the circle of rationalisation and rationing of resources.

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EDITOR'S NOTE

William of Occam stated in the fourteenth century that 'plurality must not be posited without necessity', or expressed differently, 'among competing hypotheses, favour the simplest one'. This injunction to find a single diagnosis for a patient's complaint has dominated for 500 years. By contrast, Saint's Triad states that multiple diagnoses should be considered where features are atypical, or as the pithy Hickam's dictum from North America says 'A patient can have as many diagnoses as he darns well pleases'![2]

ALLOPURINOL INDUCED DIABETES

Sir,

I am indebted to Drs Jawad and Dunkley for their suggestion, in reply to my letter to *The Journal*,[1] that allopurinol might induce diabetes by potentiating a thiazide diuretic.[2] It is an interesting and important suggestion that merits further study.

On the face of it, their revelation of two studies, the Boston Collaborative Drug Surveillance Program of 1,835 patients[3] and the report of McInnes *et al*., involving 1,748 patients,[4] all taking allopurinol and none having diabetes, would seem to deal a body blow to the view that hyperglycaemia could be attributed to allopurinol. But all is not as it seems.

The Boston study was concerned with an excess of rashes caused by the combination of ampicillin and allopurinol. It was based on examination of hospital records, the information sought being the 'age, sex, race, admission blood urea nitrogen, discharge diagnosis and details of all drug administrations and adverse events attributed to them'. There is no mention of other investigations being performed, and if the words diabetes, hyperglycaemia or glycosuria occur in the article, I could not find them. The McInnes study was not an out-patient population, as stated, but was based on observations on in-patients made by nursing staff working in 22 hospitals, and includes patients from the previous study. The method used was

> . . . trained nurse monitors use standardised self-coding sheets to record information on consecutive patients admitted to participating medical wards. The information collected includes patients' characteristics, diagnosis, drug administration, and

outcome of hospitalisation.[4]

The search for side-effects discovered fever, blood disorders, renal disease, mental confusion and gastrointestinal disturbance. There is no mention of diabetes, and no reason to suppose that anyone looked for it. The Jick *et al.* reference[5] relates to a letter identifying renal failure, liver disease and thrombocytopoenia as rare complications of using allopurinol, but there is no mention of diabetes: nor is there any mention as to how the cases were investigated.

Baird, contributing to *Davidson's Principles and Practice of Medicine* (1981),[6] estimated the prevalence of diabetes to be over 1% in Britain, and, as by that date, obesity had become a problem in North America, there is no reason to suppose that the incidence there was any less. The mean age of McInnes's patients was 60 years, so youth would offer them no protection from diabetes. So Hicks's 1,748 patients plus McInnes's 1,835 patients could be expected to unearth 36 diabetics, whatever role allopurinol played in the matter. Yet, apparently, they did not find a single case. This, clearly, is not credible. Either, as I suspect, they were not looking for hyperglycaemia, or they have shown that allopurinol confers protection against developing diabetes. If that is the case, it should be shouted from the rooftops.

I can understand that many people would find it unbelievable that, after 40 years of use, a common disorder could be proposed as a possible side-effect of allopurinol. But I can only report my own experience, and what literature there is on the subject, in the hope that it might stimulate further research.

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ERRATUM

Re: Delivering the National Service Framework for coronary diseases (*J R Coll Physicians Edinb* 2004; 34:162)

It has been brought to the Editor's attention that a typographical error occured in the first paragraph of this letter. The opening sentence should read:

> The statistics showing a progressive improvement in door to needle time would be highly commendable were it not for the fact that they take no recognition of the fact that the National Service Framework (NSF) guidelines do not even attempt to 'capture' the 'lost tribe' of myocardial infarct (MI) patients who have, by default, lost their entitlement to thrombolytic therapy solely by virtue of a pain-free clinical presentation, notwithstanding its association with electrocardiographic (ECG) as well as 'time frame' criteria for thrombolysis.[2]