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Adrenal insufficiency should be excluded before thyroxine replacement is started

EDITOR,—We strongly agree with C M Brosnan and N F C Gowing's comment that Addison's disease remains the unforgiving master of non-specificity and disguise.¹ We report two cases of Addison's disease in which the finding of a raised thyroid stimulating hormone concentration during investigations of weight loss prompted inappropriate treatment with thyroxine and precipitated an Addisonian crisis.

Case 1—A 58 year old woman presented to her general practitioner with persistent nausea, vomiting, and weight loss. Thyroxine was started when investigations showed a thyroid stimulating hormone concentration of 27 mU/l (normal 0.3-5.0). Her condition deteriorated considerably, with abdominal pain and vomiting necessitating emergency admission. On examination she was dehydrated and shocked. Abdominal examination was unremarkable. Investigations showed a low thyroid stimulating hormone concentration (<0.05 mU/l) and a high total thyroxine concentration of 251 nmol/l (65-150). An abdominal ultrasound scan and results of upper gastrointestinal endoscopy were normal. She was noted to be pigmented. A short tetracosactrin test was performed, and intravenous hydrocortisone was started. Her improvement was dramatic, with resolution of all the symptoms. A positive result of the short tetracosactrin test, raised adrenocorticotrophic hormone concentration, and presence of adrenal antibodies confirmed autoimmune Addison's disease. Results of thyroid function tests remained normal after thyroxine was withdrawn.

Case 2—A 39 year old woman was admitted direct from the outpatient department, having been referred for investigation of weight loss, increasing weakness, and epigastric discomfort. Four weeks before her admission thyroxine replacement had been started because her thyroid stimulating hormone concentration was raised. On examination she was unwell and shocked, but otherwise the examination was unremarkable. Investigations showed a low sodium and a high potassium concentration. Withdrawal of thyroxine and replacement with hydrocortisone resulted in a dramatic resolution of her symptoms, as in case 1. Investigations confirmed autoimmune Addison's disease. Results of thyroid function tests remained normal.

The association of autoimmune thyroid and adrenal disease is well recognised and described.² Addisonian crisis precipitated by thyroxine replacement in patients with hypothyroidism has been documented.³ To avoid precipitating a potentially fatal Addisonian crisis in patients with hypothyroidism it is important to exclude adrenal insufficiency before starting thyroxine replacement treatment. In many patients with adrenal insufficiency abnormal blood thyroid variables return to normal after treatment with corticosteroids.⁴

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Hydrocortisone should be started immediately adrenal insufficiency is considered

EDITOR,—The most important lesson to be learnt from the cases of Addison's disease reported by C M Brosnan and N F C Gowing is not stated.¹ In any patient in whom Addisonian crisis is suspected, serum should be saved for measurement of cortisol and adrenocorticotrophic hormone concentrations and treatment with intravenous hydrocortisone 100 mg should be started immediately. This should then be continued four hourly. The search for the precipitating cause can be concurrent.

Case 1 in Brosnan and Gowing's paper is a fairly classic case, and the biochemical abnormalities are suggestive of adrenal insufficiency. The authors state that the diagnosis of Addison's disease was considered, yet no treatment was started. I would hope that the lesson of the week is that, having considered the possibility of adrenal insufficiency, despite its non-specific presentation, you should treat it. Failure to do so has rapidly lethal results, as the case shows.

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N of 1 trials

Research is needed into why such trials are not more widely used

EDITOR,—Ten years after n of 1 trials were discovered for medicine by clinical epidemiologists from McMaster University,^{1,2} Jeffrey Mahon and colleagues' study on theophylline for irreversible chronic airflow limitation merits several comments.³ The authors cautiously state that further studies are needed before widespread use of n of 1 trials can be advocated in routine clinical practice. In 1986 we also wondered what the relevance of the contributions of this design to patients' care would be.⁴ In view of the progress achieved since then we now hope that greater attention will be given to reasons why these designs are not more widely used despite their suitability to many problems.³

N of 1 trials have much in common with the classic crossover clinical trial.⁴ In particular, both types of trials are subject to two sources of bias, sometimes referred to as treatment-period interaction. These sources of bias are, firstly, carryover effects (pharmacological effects persist in the second period) and, secondly, period effects (responses in the second period differ substantially from those in the first period, possibly owing to saturation of some biological response, fluctuations in the severity of disease, patients responding differently because of the "practice" in the first period, or other changes in environmental circumstances). In classic crossover studies, tests for carryover and period effects should routinely be conducted in the early stages of the analysis.⁴ We thus wonder why tests for treatment-period interaction are not more common in n of 1 trials.

A given set of n of 1 trials will also share several intriguing features with another design,

the recently developed case crossover study, which seems particularly appropriate for studying transient effects on the risk of acute events.⁵ Might some of the analytical strategies proposed for the case crossover design be applicable to a study of n of 1 trials such as the one by Mahon and colleagues? We believe that most such studies of trials could benefit from methodological cross fertilisation—that is, from developments achieved both before and after the advent of n of 1 trials.

Beyond methodological matters, several issues that are clinically relevant warrant further scrutiny. One concerns the nature of the inferences made possible by the three types of studies (for example, on the therapeutic effectiveness of a given drug in groups of patients versus the clinical value of the drug in an individual patient). Surely other issues lie ahead.

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Placebos should be abandoned

EDITOR,—Jeffrey Mahon and colleagues report that n of 1 trials led to less use of theophylline without adverse effects on exercise capacity or quality of life in patients with irreversible chronic airflow limitation in a tertiary centre.¹ This finding is valuable but highly specific and does not justify the larger trial that the authors advocate to confirm the result. As the authors go some way to acknowledging, there are many other diseases, settings, groups of doctors and patients, forms of treatment, periods of follow up, and outcome measures that could be studied, and the results are not generalisable. Moreover, although the authors claim that "the decision about theophylline in the n of 1 trial group was usually governed by an objective, statistical result," among 18 paired treatment periods the difference in symptom scores was conclusive in only eight, and among four subjects in whom theophylline was continued the 95% confidence interval for the difference in diary scores excluded zero in only one.

A more useful approach would be to improve the ways in which we influence and assess response to treatment. There are good arguments for discarding the placebo since its effect cannot be clearly distinguished from that of either specific treatments² or a range of therapeutic skills.³ Discarding the placebo would make it possible to increase patients' involvement in medical decision making, which itself can lead to improved outcomes.⁴ At the very

least, more than one symptom could be scored and perhaps more attention could be paid to the patients' experience of their illness,³ including how they explain their illness and its course, what effect it has, how they feel about it, and what they expect of treatment (this is relatively easily done in an n of 1 trial). The n of 1 trial could indeed be used more in everyday clinical practice with good instruments, generic diaries, and a patient centred approach.

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Blood donation

Britain's blood service is committed to spirit of altruism among donors

EDITOR,—Ann Oakley raises a moot academic point in her editorial about whether Titmuss's survey of people's reasons for donating blood needs to be repeated.¹ Unfortunately, her superficially interesting hypothesis is undermined by its construction around a series of allegations that do not stand up to even minimal analysis.

Not all blood services are "in a mess." The National Blood Service in Britain, which is recognised as among the finest and the safest in the world, goes from strength to strength, meeting hospitals' ever increasing demand for its products and services thanks to the increasing number of volunteer unpaid donors. Blood services worldwide have had to face the challenges of HIV infection and hepatitis C, and in Britain this has resulted in increasingly safe products. In common with most medical interventions, however, a blood transfusion is not free of risk. The decision to transfuse blood will remain what it has always been: a balanced judgment about the clinical risk of the alternatives to the patient.

The National Blood Authority has not recommended replacing the 14 blood centres with three zonal management teams. The document issued by the secretary of state, Stephen Dorrell, when he approved our proposals makes it clear that all blood centres are to remain open. The proposals are not a cost cutting exercise but rather a cohesive plan for the future that will improve quality, efficiency, and effectiveness to the benefit of patients and donors. There is no profit motive in the British blood supply; the amount of blood collected is determined by hospitals' need for red cells. Plasma based products for use in the NHS are made from the plasma separated from the red cells. Only if a surplus of such products remains after NHS demand has been satisfied is this surplus offered for sale abroad, at prices that only cover the cost of production. This has been practice for many years.

We are fortunate in Britain that the spirit of altruism that underpins our unpaid, volunteer donor base continues to prevail. It is a spirit to which the National Blood Service is committed. If Oakley is arguing for the increased input of donors' views in a service that depends on their gift, I do not necessarily disagree. She may wish to know that the service has already started such a process with, for example, the publication of a donors' charter and a range of other initiatives. It

is a pity that she bases her contention on such a catalogue of false premises.

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- 1 Oakley A. Blood donation—altruism or profit? *BMJ* 1996;312:1114. (4 May.)

Age limit should be reviewed

EDITOR,—In her editorial on blood donation Ann Oakley mentions that New Zealand is experiencing a fall in blood donation in the face of increasing demand.¹ As I have family in New Zealand, this gave me cause for thought. It also reminded me that, along with countless other pensioners, I am no longer a blood donor, although this is not of my choice. With the number of pensioners increasing annually, I wonder whether it is possible, with due regard to safety, to review the age limits up to which it is permissible to donate blood. I, like many others, would continue to donate if given the chance.

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Relation of C reactive protein to cardiovascular risk factors

Assays would have to be developed to measure C reactive protein

EDITOR,—M A Mendall and colleagues' paper raises the question of the role of the inflammatory response in cardiovascular disease.¹ To avoid immunology and other laboratories being swamped with inappropriate requests for measurements of C reactive protein concentrations it is important to emphasise that the authors' study looked at measurements that are within the conventional normal range. Many laboratories use nephelometric methods designed to measure abnormally raised C reactive protein concentrations and do not detect differences within the normal range—that is, <10 mg/l. Mendall and colleagues used a specially designed, in house enzyme linked immunosorbent assay (ELISA) with a quoted coefficient of variation of 14%. This is a large coefficient of variation for an assay attempting to distinguish between two groups of patients on the basis of a small absolute difference in a measurement.

Fig 1—Shewhart plot showing variation in possible values of C reactive protein when one specimen of known concentration (12.5 mg/l) is analysed with routine automated nephelometer several times a day for several days

Measurements of C reactive protein are currently used to quantify the scale of an inflammatory response associated with infection and other inflammatory disorders. The technique is therefore calibrated to distinguish a wide range of values between 1 mg/l and 500 mg/l. It is not, however, sensitive enough to reliably differentiate small differences in the low concentrations described in this paper. Figure 1 shows the daily variation and the variation over time in results obtained from repeatedly analysing a single quality control specimen of known C reactive protein concentration with our routine nephelometer.

If further studies show the C reactive protein concentration to be useful in the acute management of cardiovascular disease then appropriate assays will have to be made available that do not use techniques currently used in routine laboratories.

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H pylori and C pneumoniae infections may account for most acute coronary syndromes

EDITOR,—M A Mendall and colleagues provide data showing a strong association between C reactive protein concentration (a sensitive marker of systemic inflammation) and coronary heart disease.¹ This finding draws attention to the inflammation as a mechanism underlying the progression of ischaemic heart disease. The same authors have previously shown a greatly increased cardiovascular risk in subjects with *Helicobacter pylori* and *Chlamydia pneumoniae* infections.²

Recently we measured serum levels of antibody to *H pylori* and *C pneumoniae* in patients admitted to an intensive care unit with clinical, electrocardiographic, and biochemical evidence of acute myocardial infarction. We collected serum samples from 37 subjects (28 men, 9 women; mean (SD) age 63 (8) years (range 44-77)). Serum samples from 60 healthy subjects matched for sex and age served as controls. Titres of IgG antibody to *H pylori* were measured with an enzyme linked immunosorbent assay (ELISA; Bio-Rad, Hercules, California) and titres of IgG antibody to *C pneumoniae* were measured with an indirect immunofluorescence test (MRL, California). Cross reactions with *C trachomatis* and *C psittaci* were assessed. IgG titres of ≥ 64 were regarded as positive.

Table 1 shows that a high prevalence of *H pylori* and *C pneumoniae* infections was present in patients with acute myocardial infarction. Thirty two of the 37 patients had antibodies to *H pylori*, 31 had antibodies to *C pneumoniae*, and 28 had antibodies to both; these proportions were significantly higher than those in the control subjects (Mantel-Haenszel χ^2 test: $df=1$, $P<0.001$; odds ratio 5.24 (95% confidence interval 1.97 to 13.90)).

Our data suggest that infection by these two bacteria may have an important role in inducing and sustaining inflammation. The production of C reactive protein is regulated by cytokines, principally interleukin 6. Fibroblasts, T cells, endothelial cells, and monocytes produce interleukin 6; mast cells also synthesise and release this cytokine. We have previously shown that *H pylori* can elicit an IgE specific response.³ Recently it has been found that *C pneumoniae* infection triggers production of IgE specific to *C pneumoniae*.⁴ Thus mast cell activation by these