

CORRESPONDENCE

Breast-conserving surgery

Sir—Ann Nattinger and colleagues (Sept 30, p 1148)¹ report an increase in the proportion of women undergoing an inappropriate form of breast-conserving surgery (with omission of radiotherapy, axillary dissection, or both) from 10% in 1989 to 19% in 1995. No clear explanation for these findings emerges.

One possibility is that the rise in the omission of appropriate radiotherapy can be accounted for by a progressive rise in the proportion of older patients included from 1989 to 1995. Nattinger and colleagues show in the table that 48 855 (34%) patients were aged 65–79 years and 15 066 (10%) were older than 80, but provide no data or comment on whether the proportion in the age cohort remained constant over time. Ballard-Barbash and colleagues² have shown from the SEER registry that the oldest old and those with two or more comorbid disorders were less likely to receive radiation therapy than younger or healthier patients.

There are randomised and non-randomised data suggesting that the risks of local recurrence after breast-conserving surgery and breast radiotherapy decline with age, and Veronesi and colleagues³ in a randomised trial of quadrantectomy, axillary clearance, and adjuvant systemic therapy with or without breast radiotherapy showed a significant fall in local recurrence in women over 55 years (3.8%) compared with 8.7% in the 46–55 year age-group and 17.5% in women younger than 45 years in whom radiotherapy was omitted. Similarly, the retrospective study of Gruenberger and colleagues⁴ in women aged 60 years and older, treated by quadrantectomy and axillary clearance with or without breast irradiation in low-risk, node-negative, oestrogen-receptor-positive patients showed a 3% local recurrence rate in the group in whom radiotherapy was omitted, similar to 2.6% in the irradiated group at a median follow-up of 60 months.

Few randomised trials that have assessed the role of radiotherapy after breast-conserving surgery and appropriate systemic therapy have included women older than 70 years. Little is known of the trade-off that older patients make between local

control and radiation-induced morbidity. New randomised trials are needed in older patients at low risk of local recurrence to find out whether or not breast radiotherapy is needed for local control after adequate breast-conserving surgery, and to assess its effect on quality of life. In the UK, the PRIME trial (Postoperative Radiotherapy In Minimum-risk Elderly) is currently looking at quality of life. Until such data are available, clinicians will remain uncertain whether, as Richard Sainsbury states in his commentary (Sept 30, p 1124),⁵ “missing radiotherapy . . . probably means undertreatment of the patient”.

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- 1 Nattinger AB, Hoffman RG, Kneusel RT, Schapira MN. Relation between appropriateness of primary therapy for early-stage breast carcinoma and increased use of breast-conserving surgery. *Lancet* 2000; **356**: 1148–53.
- 2 Ballard-Barbash R, Potosky AL, Harlan LC, Nayfield SG, Kessler LG. Factors associated with surgical and radiation therapy for early stage breast cancer in older women. *J Natl Cancer Inst* 1996; **88**: 716–26.
- 3 Veronesi U, Luini A, Del Vecchio M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993; **328**: 1587–91.
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- 5 Sainsbury R. Towards appropriate local surgery for patients with breast cancer. *Lancet* 2000; **356**: 1124–25.

Authors' reply

Sir—It is true that older women are less likely than younger women to undergo radiotherapy for breast cancer.^{1,2} However, a shift in the demographics of women treated for breast cancer did not account for the decline in appropriateness of care that we saw between 1989 and 1995. As we mention in our results section, there was a significant decline in the likelihood of receiving appropriate care in each subgroup of age. The decline in appropriateness was smaller among women aged 80 years and older than

among younger women, probably because the use of breast-conserving surgery between 1989 and 1995 increased the least in the oldest age group.

Ian Kunkler cites studies suggesting a lower risk of local recurrence in older women treated without radiotherapy, compared with younger women treated without radiotherapy. The bulk of the evidence, as synthesised in systematic overviews, however, shows that the protective effect of radiotherapy against local disease recurrence is not affected by age.^{3,4} With the small numbers of women aged 70 and older included in randomised trials to date, such a trial in low-risk elderly women is certainly welcome. Yet in our study, we saw no differential decline in appropriateness among low-risk women; therefore, concerns about late effects of radiotherapy in low-risk patients are unlikely to have accounted for the observed reduction in appropriateness of care.

To clarify the percentages Kunkler cites, 10% of all cohort patients (those undergoing mastectomy or breast-conserving surgery) received an inappropriate form of breast-conserving surgery in 1989, and almost 19% did so in 1995. However, about 35% of the women undergoing breast-conserving surgery received inappropriate care in each year.

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- 1 Mann BA, Samet JM, Hunt WC, Key CR, Goodwin JM, Goodwin JS. Changing treatment of breast cancer in New Mexico from 1969 through 1985. *JAMA* 1988; **259**: 3413–17.
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Acute radiation proctitis

Sir—In their report, P Vernia and colleagues (Oct 7, p 1232)¹ present a compelling case for the use of butyrate in the treatment of acute radiation proctitis (ARP). They detail a methodological approach, including a standard scoring system for severity of ARP.

The first phase of this randomised, crossover trial suggests a real effect of butyrate, with a difference in clinical scores favouring butyrate over placebo. Although Vernia and colleagues state that there were no important differences between groups at the start of the trial, the number of bowel movements in the butyrate group were higher than in the placebo group (3.7 [SE 0.6] vs 2.8 [0.3]). If the butyrate group had worse proctitis before treatment, these patients might have improved strikingly over time. The process of ARP is self-limiting and the duration can vary. A more detailed presentation of pretreatment variables would have been useful.

It is more difficult to draw conclusions about the crossover phase. Vernia and colleagues acknowledge a significant crossover effect, but do not mention an important bias. In our experience, long-term rectal symptoms from radiation proctitis are uncommon at the external-beam doses used in the study. Patients should have entered the trial at a common time after the completion of radiotherapy, instead of having variability of 1–3 weeks. If patients were not equally represented by this variable, an erroneous lead-time bias might exist that would become more important in the crossover phase. We wonder what the natural history of symptom resolution in a similar patient population would have been? A control group of placebo-placebo would have showed the importance of this confounder. We also ask, how variable ARP is from patient to patient and how can the benefits of treatment be confidently established in a sample of 18 patients?

Two prospective trials have assessed treatment for ARP. Australian workers did a double-blind randomised study in 86 patients of sulcrate enemas or placebo, once daily, for 2 weeks after radiation therapy. Toxic effects did not differ significantly between groups. Grade 2 proctitis arose at a median of 33.5 and 36.0 days, respectively, in the sulcrate and placebo groups. The median duration was 9.5 and 15 days.² A second trial was in 16 patients treated for prostate cancer randomly assigned misoprostol suppositories or placebo before daily radiotherapy. A radiation

proctitis score was devised and measurements recorded from 4 to 36 weeks after radiotherapy. Misoprostol was significantly more effective in reducing the severity of proctitis-related symptoms than placebo.³

If patients are to self-administer enemas daily for several weeks, the effect must be real. To assess to what degree butyrate can relieve symptoms over simple supportive measures (antidiarrhoeal agents, antispasmodics, steroid enemas, and topical ointments) requires study of many patients in a randomised control trial setting.

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- 1 Vernia P, Fracasso PL, Casale V, et al. Topical butyrate for acute radiation proctitis: randomised crossover trial. *Lancet* 2000; **356**: 1232–35.
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- 3 Khan A, Bircik J, Anderson J, et al. A prospective randomised placebo-controlled double-blinded pilot study of misoprostol rectal suppositories in the prevention of acute and chronic radiation proctitis symptoms in prostate cancer patients. *Am J Gastroenterol* 2000; **95**: 1961–66.

Sir—P Vernia and colleagues¹ trial shows improvements mainly in symptoms such as bowel frequency after treatment with butyrate enemas.¹ A randomised trial of oral sucralfate has shown similar effects.² Whether parasympatholytic medications (eg, diphenoxylate) were available to patients is unclear. Since ARP resolves spontaneously and infrequently causes major symptoms, daily enemas are not likely to be acceptable to patients.³

The real importance of the report is that reducing acute injury might lower the incidence and severity of chronic radiation proctitis. Although the association between acute and late proctitis is fairly weak and might not be causal (ie, patients might simply be more liable to acute and chronic effects independently), this effect remains an important therapeutic possibility.^{4,5} Vernia and colleagues, however, tested treatment rather than prevention; earlier measures might be more likely to be beneficial.

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- 1 Vernia P, Fracasso PL, Casale V, et al. Topical butyrate for acute radiation proctitis: randomised crossover trial. *Lancet* 2000; **356**: 1232–35.
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- 5 Schultheiss TE, Lee WR, Hunt MA, Hanlon AL, Peter RS, Hanks GE. Late GI and GU complications in the treatment of prostate cancer. *Int J Radiat Oncol Biol Phys* 1997; **37**: 3–11.

Authors' reply

Sir—The treatment of ARP is largely anecdotal¹ and frequently conflicting; thus, no proven effective treatment is, as yet, available. We reported that topical butyrate offers substantial advantages compared with placebo in a crossover protocol. We chose this format since it provided more reliable information in a small pilot study² than open-label or placebo-controlled protocols. The results exceeded the most optimistic expectations.

We are well aware that the small size of the population suggests caution; as well as the existence of an important carryover effect, we first reported the analysis of data related to the first 3 weeks of the study, instead of the formal crossover analysis.

We do not agree with Christopher Leighton and colleagues' observation that the duration of ARP before enrolment, or its overall duration, could have represented an important bias. The time lag between completion of radiotherapy and enrolment varied between 1 and 3 weeks, but was identical in the two treatment groups. Moreover, the efficacy of butyrate was confirmed in the second part of the study despite the carryover effect. Eight of the nine of the previously placebo-treated patients improved on butyrate, whereas three patients on butyrate had a relapse when switched to placebo.

As to the question raised by Sean Bydder, the patients enrolled in the study did not use antidiarrhoeal drugs since the number of bowel movements was never excessive.

Bydder and Leighton and colleagues note that ARP is frequently associated with mild symptoms and heals spontaneously. Thus, daily treatment based on enemas may not be acceptable to all patients, but we suggest it helps some by reducing urgency and diarrhoea, which deserves confirmation.

Finally, we agree that the most interesting point emerging from the study is the possibility that butyrate could lower the prevalence of late

radiation damage, if given during the course of radiation therapy. This hypothesis is under assessment in a large Italian multicentre study.

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- 1 Zimmerman FB, Feldmann HJ. Radiation proctitis: clinical and pathological manifestations, therapy and prophylaxis of acute and late injurious effects of radiation on the rectal mucosa. *Strahlenther Onkol* 1998; 174 (suppl 3): 85–89.
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Human herpesvirus 8 as a sexually transmitted agent

Sir—Sabine Plancoulaine and colleagues (Sept 23, p 1062)¹ show that in an endemic population human herpesvirus 8 (HHV-8) is mainly transmitted from mother to child and between siblings during childhood and adolescence, and that there is no significant seroepidemiological correlation between spouses. This conclusion adds to the existing doubts on the accepted notion that the HHV-8 and Kaposi sarcoma (KS) prevalence rates among homosexuals are high exclusively because of their sexual orientation. We would like to review the present evidence against such hypothesis.

HHV-8 has been detected in several body fluids, including nasal secretions and saliva,² but its presence in semen is not decided. In healthy people's semen, only one group has reported HHV-8 DNA, and it is rare even in endemic countries. In KS patients' semen (and from HIV-1-infected men without KS) HHV-8 is very rare. Thus Plancoulaine and colleagues agree that only a few susceptible patients have HHV-8 DNA in their semen. The anal route of infection, which also applies to women, seems, therefore, not an easy one.

The sexual route in general is also doubtful, and Plancoulaine and colleagues' findings add to this uncertainty. In cervicovaginal secretions, HHV-8 is only rarely seen in women positive for HIV-1 and HHV-8,³ and detection in HHV-8 seropositive women (27%) is paradoxically higher than that in semen of HHV-8 and HIV-1 seropositive homosexual men (10–25%).⁴

A prevalent sexual transmission would not explain the high prevalence rate in children living in endemic areas. Children's HHV-8 endemism bears some similarity to that for

syphilis, but the contagion among children with endemic syphilis occurs through skin and mucosal lesion, which is not the case for HHV-8 infection. Children, furthermore, can be infected also in non-endemic areas. 2–8% of North-American children are infected, compared with 18–28% of older individuals,⁵ and an explanation of sexual transmission is unfeasible.

A high number of sexual partners has been suggested as a possible explanation of KS predilection for homosexual men. If the number of sexual partners did matter, however, KS prevalence rate in, for example, female prostitutes should also be high.

Other issues remain unclear. Why, for example, only a small subset of HHV-8 infected subjects develop KS? This finding does not support the hypothesis that HHV-8 alone causes KS, but suggests that a widespread virus like HHV-8 might reactivate in certain patients who have a downregulated immunocompetence or are co-infected with other viruses. The presence of HHV-8 in proliferative benign and malignant angioproliferations, therefore, could simply mean that endothelioid cells represent an ecological niche for the virus and that growth factors such as the angiogenic cytokines expressed in those lesions might favour its replication and, consequently, its detection.

The route of transmission of HHV-8 remains poorly understood and we believe that, since it has occurred with HIV-1 lately, the predilection of KS for homosexuals has been too hastily related to their sexual behaviour.

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- 1 Plancoulaine S, Abel L, van Beveren M, et al. Human herpesvirus 8 transmission from mother to child and between siblings in an endemic population. *Lancet* 2000; 356: 1062–65.
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Use of medication in Zanzibar

Sir—G Birrell and K Birrell (Sept 23, p 1084)¹ report that a teaching programme was effective in improving rational use of medication in Zanzibar. Misuse of medications endanger patients' outcomes, causes unnecessary adverse drug reactions, and wastes precious health-care resources.

Of particular concern is the misuse of injections, which cause large-scale transmission of blood-borne pathogens,² and antibiotics, which contributes to antimicrobial resistance, now recognised as a global issue.³ Thus any intervention that results in the sustained reduction in inappropriate use of injections and antibiotics would be of interest to the international public-health community.

Birrell and Birrell report that their teaching programme achieved a significant, sustained, improvement in the treatment of upper-respiratory infection, scabies, and anaemia, and a small, though significant, reduction in the proportion of prescriptions containing at least one injection or an antibiotic. In assessment of the effectiveness and applicability of any intervention to change prescribing practices, however, it is important to know several factors, which remain unanswered in this report.

First, the training programme is not described or costed, and any judgment on cost effectiveness is, therefore, impossible. Although Birrell and Birrell claim that there was no further training or supportive interventions after the initial training, each student was supervised and monitored by continuous assessment and appropriate feedback. Thus the intervention consisted of more than a training programme.

Second, the magnitude of the effect of the intervention is unknown. Birrell and Birrell do not specify the proportion of patients who presented with upper-respiratory tract infections, scabies, and anaemia, do not report how serious the drug misuse associated with these diseases was, and do not quantify preintervention injection and antibiotic misuse. Information transfer alone through teaching is generally not sufficient to change the behaviour of most people,⁴ especially for overuse of injection and antibiotics. For such difficulties with prescriptions, interventions that incorporate more than just teaching are needed to change behaviour.⁵

Third, the report has several limitations in the design that make

interpretation of the effect of the intervention difficult. In the absence of a control group, the improved prescribing cannot be definitely attributed to the intervention rather than some other factors, such as changes in drug availability. The analysis seems to have been done at the level of the patient, rather than at the prescriber or the health-facility level. However, the area of interest is the prescriber-patient interaction, and analysis should, therefore, be at least at the level of the prescriber. Since prescribers within facilities behave similarly, the analysis would be better done at the level of the facility, if conclusions concerning the external validity of the study are to be drawn.

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Authors' reply

Sir—Kathleen Holloway and Yvan Hutin raise some useful points. Supervision of primary-health-care workers should be an integral part of managing a primary-health-care team.¹ Our training programme consisted of 12 workshops and a single training or supervision visit to every health-care unit after each workshop. The programme² was spread over 12 months. There was no further training or supportive intervention after this time.

We analysed 6800 patients' records from each year of the study. At the end of the programme, 458 of 6800 patients were diagnosed as having an upper-respiratory infection (see table 2 in our report). 7% of patients in this cross section were diagnosed as having upper-respiratory infections, 3% as having scabies and 6% as having anaemia. 22% of these disorders were treated appropriately before the training programme, compared with 58% immediately after the programme.

In our series 15% of patients were given injections and 34% of patients were given antibiotics before the intervention. These percentages came down to 12%

and 27%, respectively, immediately after the intervention. Other disorders, although not objectively measured were also diagnosed and treated more appropriately after the training programme.

To change established behaviour is an enormous challenge. Many trained medical assistants had entrenched poor prescribing habits. Orderlies and untrained nurse prescribers, however, quickly adopted good prescribing habits and their use of inappropriate injections and antibiotics decreased. Our detailed notes from health-unit visits attest to this. One of the main determinants of treatment given was the availability of medicines. The monthly supplies of medicines to each health-care unit were generally inadequate. Hence, towards the end of the month, injections not used earlier in the month were frequently the only antibiotics and malaria treatments available. These potentially misusable medicines were made available to health-care units through a donor-funded essential drug programme that was not responsive to changes in demand or improvements in prescribing habits.

We have discussed the desirability of a true control for our study. Health-care workers not trained in our programme continued to prescribe poorly according to our quality indicators. Since we collected data retrospectively from attendance ledgers, at the level of the health facility, control data continue to be available in other Zanzibari health-care units. We would be delighted to collect this data if sponsored.

We agree that interventions incorporating more than teaching are needed to change behaviour. Our determination that others should benefit from such an approach resulted in the publication of a training manual,² which is designed to be a course guide for local trainers and supervisors, and a self-study guide. Initially, experienced trainers in primary health care will be required to set up the training courses and to train trainers, although the original programme was run by visiting doctors from the UK.

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- 1 Comolet TM, Raktomalala RA, Rasolomahefa D. Evaluation of a supervision program of health centres at the district level in Madagascar. *Sante* 1997; **7**: 103-08.
- 2 Birrell KG, Birrell G. Diagnosis and treatment: a training manual for primary health care workers. London: VSO books/Macmillan, 2000.

Adult growth-hormone deficiency

Sir—V Popovic and colleagues (Sept 30, p 1137)¹ claim to show a reliable test for adult growth-hormone (GH) deficiency and underscore inconsistencies in measuring insulin-like growth factor (IGF)-1, IGF binding protein 3 (IGFBP3), and a 24 h GH measurement in these patients.²

The study involved seven different GH measurement methods, done at several different centres, which will have generated imprecision when compared with the other variables such as the IGF-1 concentration. The excellent agreement for GH claimed between the methods used was surprising, since for at least the past 2 years the UK National External Quality Assessment Scheme (NEQAS) data have shown that the Wallac DELFIA method has a median negative bias of -28%, whereas the DPC immulite method has a median positive bias of 2.5% (personal communication).

J H Barth and colleagues showed that the various assays measure different isoforms of GH and that there was poor agreement in the measurement of GH between commercial immunoassays when measurements were made on stimulated cycles in short children.³ Popovic and colleagues did not record the numbers of tests assayed by each kit method. Reanalysis would be appropriate by constructing a receiver operating curve for each method of GH measurement. Since the study compared adults with severe GH deficiency and normal controls, this would be more acceptable than grouping the peak GH concentrations in the stimulation tests.

At least three patients in figure 2 seem to have high IGF1 concentrations with low GH peaks. We would like to know how Popovic and colleagues explain these data and whether they can account for the age-adjusted ranges for IGF-1 concentrations in these patients before calculating the correlation of GH peak and IGF-1 concentrations. The coefficient of 0.204 for the correlation might become significant on log transformation of IGF-1; however this change does not confirm a trend, it merely confirms that the correlation is weak, with the GH response accounting for less than 5% of the variance in IGF-1. Significance is a measure of certainty, not of correlation.

The commentary by Ken Ho (Sept 30, p 1125)⁴ disagrees with Popovic and colleagues' statement that the combined GH-releasing hormone/GH-releasing peptide-6 test assesses the whole

hypothalamopituitary unit. Ho suggests that this test can safely establish GH deficiency only in patients with organic pituitary disease. Popovic and colleagues should, therefore, reanalyse their data after dividing their patients into those with known hypothalamic disease and those with organic disease.

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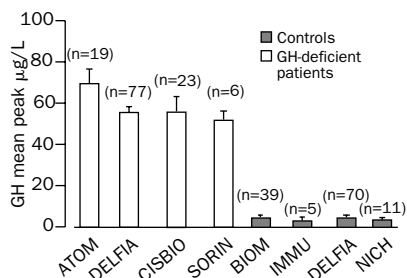
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- 4 Ho KY. Diagnosis of adult GH deficiency. *Lancet* 2000; **356**: 1125–26.

Authors' reply

Sir—We agree with D Devendra and colleagues that the diagnosis of GH deficiency in adults is complex, since several variables affect the outcome of GH-provocative tests.

The advantage of the combined administration of GHRH-GHRP-6, which we propose as the new gold standard test for GH reserve in adults, is that in addition to its being devoid of side-effects, it is not affected by age, sex, adiposity, thyroid status, glucocorticoid status, diabetes mellitus, time of day, previous food intake, pre-treatment with GH, or the previous GH basal concentrations.¹ Moreover, to have a test not affected by the assay used would be a bonus, since the assay is a powerful factor that confuses the diagnosis of GH deficiency.

As proof of absence of interaction, the ITT cut-off of 3 ng/mL is valid



GH mean peak in controls and GH-deficient patients with different assays

BIOM=BioMérieux, IMMU=Immunitel, NICH=Nichols.

only for polyclonal antibody-based assays,¹ which have almost disappeared from current laboratory use. For the most commonly used test, therefore, there is no widely accepted valid cut-off value.² We are aware of the systematic bias introduced in the GH determination by the assay used, and we agree that we have not done a rigorous analysis of how the GH peaks produced by the combined test are altered by different assays, since this analysis was out of the scope of the study. However, in our preliminary data, not included in the report because of space constraints, we found that mean GH peaks in the different assays were similar (figure), although the number of patients in each group was too different to be sure. Second, when we took into account only the values provided by Delfia (time-resolved monoclonal-antibody-based fluoroimmunoassay), the result was identical. These data suggest that the noise introduced by use of seven different assays in the same study was not intense enough to alter the identification of healthy patients and those with GH deficiency.

GHRH-GHRP-6 test does not act at the pituitary level. Although GH secretagogues were developed by their in-vitro GH-releasing capabilities, overwhelming evidence shows that compounds such as GHRP-6 and the combined GHRH-GHRP-6 act mainly at the hypothalamus.¹ We, along with other groups, have reported that any organic alteration in the hypothalamus, the pituitary stalk, or the pituitary, blunts GHRH-GHRP-6-mediated GH release.³ Therefore, the test explores the whole hypothalamopituitary unit, as does the ITT, identifying any organic or structural alteration. The efficacy of the test in the so-called functional, non-organic or idiopathic GH deficiencies has not yet been assessed. However, several groups agree that this syndrome, which is fairly rare in adults, is debatable or at least poorly defined.

The GHRH-GHRP-6 test is scarcely affected by the GH assay used and detects organic lesions located at any level of the hypothalamopituitary somatotrope axis. We eagerly await the experience of other groups with this test in the clinical setting.

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Rats and risk

Sir—Research has shown that the so-called natural pesticide, rotenone, might be associated with Parkinson's disease.^{1,2} As the news began to slowly circulate, the saying by Victor Cohn (a once senior columnist with the Washington Post) that "Scientists are to journalists what rats are to scientists" came to mind. The research in question showed that rotenone can produce Parkinson's disease in rats when it is administered via injection in low doses. Most rats, and human beings, however, do not willingly undertake direct injections of any sort of pesticide, natural or not. So the results and their applicability to human health remain controversial. But, rates are one of the, albeit blurry, windows on long-term human health effects. So the risk question that arises is, are natural pesticides potentially dangerous?

In the autumn of 1998, Arpad Pusztai from the UK told television interviewers that a handful of rats fed genetically engineered compared with those fed conventional potatoes displayed some differences—differences that soon became a mantra for many around the globe, including journalists, as evidence of hypothetical danger associated with genetically engineered crops.

The Lancet also published Putztai's experiments³ with the aim of "making constructive progress in the debate between scientists, the media, and the general public about the safety of GM foods".⁴ On the other hand, the experiments flagging the possible dangers of rotenone, which has been marketed and used in the public domain for many decades as a so-called natural pesticide (sometimes used and marketed by the organic movement) and in various commercial garden care and animal-care products, barely stirred the interest of journalists.

Why was it that one story received so much more attention than the other? Was it that opponents of so-called genetically modified food (of who the loudest are frequently connected to the organic food movement) pushed and promoted the story for their own cause? After all, if conventional foods are deemed safe for people and the environment, then in the absence of a media flurry, why would consumers pay more for hypothetical benefits?

The same media forces that propelled Pusztai's rats to mainstream conversation have been largely silent when it comes to the rotenone rats. Since the organic movement uses rotenone itself, maybe they are choosing to remain quiet on this issue. Surely this action (or lack thereof) brings to light a severe case of double standards. For example, we have yet to see the Greenpeace press release condemning organic farmers for using rotenone and demanding the immediate removal of the roughly 680 rotenone-containing products from the supermarket shelves.

The latest findings about rotenone, which like Pusztai's results draw attention to the need for "further scientific attention", underscores a fundamental approach that North American regulators have taken to various products, including genetically-engineered foods: that is, that nature is not benign, and irrespective of the process used to create new foods—be it genetic engineering, conventional breeding, and a whole host of powerful techniques in between, the end product needs to undergo scientifically valid safety assessments.

The natural does not automatically mean safe. This premise proves the point made by Richard Horton that "What matters is what people believe about (these) risks and why the hold those beliefs".⁵

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Prenatal identification of fetal genetic traits

Sir—Hiroshi Saito and colleagues (Sept 30, p 1170)¹ describe the prenatal diagnosis of a single-gene disorder without clinical consequences, in late pregnancy (fetal achondroplasia) by measurement of extracellular fetal DNA in maternal plasma. This report has once again raised hopes that reliable non-invasive prenatal investigation for fetal genetic loci has made the transition from the laboratory to the clinical arena. We caution, however, the premature introduction of this method into practice.

The basis for the approach originates from the observation made by Lo and colleagues² that free fetal DNA can be detected by PCR in maternal plasma or serum samples. Since fetal and maternal free DNA are present in the maternal circulation, previous studies have focused on the detection of fetal loci not present in the maternal genome, such as the Y chromosome or the rhesus D gene in rhesus d pregnant women.^{3,4} Fetal DNA sequences are more readily detected in second and third trimester maternal blood samples than in those obtained early in pregnancy.³ Diagnosis should, however, be confirmed by an independent test, such as ultrasonography, as Saito and colleagues used, because serious consequences, including termination, might depend on the in-utero findings.

To test the diagnostic accuracy and feasibility of Saito and colleagues' approach, we did a large-scale study of more than 200 samples. We used a highly sensitive real-time PCR technique, which proved suitable for the detection of free fetal loci.³ Furthermore, since this technology is more amenable to automation and not as prone to contamination as is conventional PCR, it is therefore better suited for routine applications.

We have chosen to focus on the fetal rhesus D gene, which would be useful for diagnosis in pregnancies with a rhesus constellation, and on fetal sex, which is important to know in pregnancies at risk for X-linked disorders. In our experimental validation, done on plasma samples obtained from 22 normal healthy men and 48 non-pregnant women, no false results were recorded. The PCR assay for the rhesus D gene detected no anomalous results on plasma samples obtained from 24 rhesus d or 27 rhesus D individuals.

In 11 (6%) of 185 instances, however, in which the fetus was male,

no male free fetal DNA was detectable by the real-time PCR assay specific for the Y chromosome. All 52 samples obtained from pregnancies with female fetuses were identified correctly. The assay for the rhesus D gene could detect fetal rhesus D genotype correctly in 24 (96%) of 25 instances. In two (22%) of the nine pregnancies with a rhesus d fetus the fetus was incorrectly genotyped as being rhesus D.

The frequency of false-negative results for the two assays was close to 5%. Although free fetal DNA is less prevalent early in pregnancy than in the late second or third trimesters, our result cannot be attributed to this factor, since we took samples at 11.5–34.6 weeks' gestation (median of 16.5). In addition, some samples with no detectable concentrations of free fetal DNA had abundant quantities of free maternal DNA on PCR for the ubiquitous glyceraldehyde-3-phospho-dehydrogenase (GAPDH) gene. Therefore, false-negative results probably arose because of a technical deficit such as the inability to extract free DNA from the sample in question.

The two false-positive results for the rhesus D gene are probably attributable to contamination of the initial PCR template material, despite rigorous precautions.⁵ Appropriate strategies are needed to ensure that no false-negative results arise in this way.

Our data suggest that, even though the assay is specific, because of the poor sensitivity (95%), the use of free fetal DNA from maternal plasma is currently not suitable for routine prenatal diagnosis of fetal genetic traits in a clinical setting, even with use of the most advanced methods currently available.

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Authors' reply

Sir—Xiao Yan Zhong and colleagues point out some pitfalls in the clinical applications for non-invasive prenatal diagnosis of single-gene disorders by maternal plasma. We essentially agree with their comments.

Many investigators report the detection of free fetal DNA sequences by real-time PCR not present in the maternal blood, such as Y chromosome from male fetus and rhesus D gene in rhesus d pregnant women. We established a highly sensitive quantitative PCR with use of the LightCycler system (Roche Diagnostics, Mannheim, Germany) and analysed the sensitivity of sex determination from maternal plasma through *DYS-14* gene amplification. At 15–20 weeks' gestation, sex could be accurately identified from maternal plasma (20 of 20). In early gestation, however, 8% of results were false negative.

We agree that the procedure is required to prevent DNA contamination or allele dropout. We have previously reported that the detection of fetal nucleated erythrocytes (NRBCs) in maternal circulation by use of HLA *DQα* genotyping without fetal sex determination.¹ In five of 45 cells, the foreign source DNA contamination, except for parental alleles or allele dropout, was seen when whole genome was amplified from single fetal cells by conventional PCR. Another difficulty is the low recovery rate of DNA from maternal plasma. The amount of free fetal DNA in maternal plasma is small—only about 25 copies/mL maternal plasma.² Although we extracted fetal DNA from maternal plasma by QIAamp DNA Blood Mini kit (Qiagen, Hilden), the recovery of fetal DNA from maternal plasma was around 55%. Therefore, we are trying to improve the DNA extraction efficiency to achieve the sufficient sensitivity and accuracy for prenatal DNA diagnosis from maternal plasma.

Non-invasive prenatal DNA diagnosis of single-gene disorders from maternal blood has possibilities, although, according to the previous reports and our data, at the present time, clinical application for prenatal diagnosis from maternal plasma is not suitable for fetal DNA screening.

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Cause of otitis media

Sir—Stephen Pelton's Oct 21 commentary¹ and Pentti Ukkonen and colleagues' report (Oct 21, p 1398)² on the prevention of acute and recurrent otitis media are instructive to doctors who are confronted with patients consulting for pain in the ear associated with various inflammatory signs and symptoms. They discuss the role of oligosaccharides as competitive inhibitors of membrane receptors impairing the adherence of bacteriae and, thereby, reducing the frequency of acute otitis media.

The continued attempt by researchers from specialist units to deal with infective mechanisms and agents as if they were the primary cause of acute otitis media is at odds with our well established knowledge about the pathogenesis of acute otitis media with and without effusion. Upper respiratory tract infections lead to congestion of the mucosa throughout the respiratory tract, including the nasopharynx, eustachian tube, and middle ear. Secretions of the mucosa cannot escape and accumulate in the middle ear because of the obstruction. The proliferation of microbial pathogens in the secretions is secondary to the congestion.³ The inflammatory process is closely linked to the congestion of the mucosa in the eustachian tube, which self-heals well, and the susceptibility of the mucosa to the colonisation of pathogens varies individually. Antimicrobial treatment provides little long-term benefit in improving hearing or in preventing further infections.⁴

There is compelling evidence from practice that to fight infections in the upper respiratory system with antibiotics is unnecessary. Worse, antibiotics might be harmful because of their side-effects and the growing emergence of resistance among respiratory pathogens.

Earache and impaired hearing are the presenting symptoms of acute otitis media with and without effusion. Analgesics and supportive measures for the decongestion of the eustachian tube help to relieve symptoms. Antibiotics are not needed in the first instance.

The reliance on randomised double-

blind controlled trials from tertiary health care and meta-analyses of these trials as the sole means of proof automatically eliminates the contribution to evidence-based, practical, and practicable medicine through properly done prospective observational, controlled, and replicated studies.⁵

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Choroidal abnormalities and mental retardation in neurofibromatosis type 1

Sir—The findings of Takaharu Yasunari and colleagues (Sept 16, p 988)¹ are of utmost clinical importance for the neurofibromatoses, since they highlight the potential importance of choroidal involvement as a new diagnostic criterion for neurofibromatosis type 1 (NF1).

However, their conclusion that infrared light examination might be useful for diagnosis in patients with mental retardation and in infants could lend itself to misinterpretation. Such examination could allow diagnosis of NF1 in younger patients who meet only one of the existing NF1 diagnostic criteria,² but it is unclear whether Yasunari and colleagues propose its use as a screening technique for NF1 in mentally retarded individuals in the general population or just as a (easy and non-invasive) useful diagnostic tool in mentally retarded patients suspected of having NF1 who do not meet the NF1 criteria.³ The former notion could be misleading in that it apparently stands on the old assumption that NF1 is a mental retardation disorder.

In the past, rates of NF1 severe neurological impairment have been

reported as high. This assumption generated the idea that every neurological occurrence in a patient with NF1, including mental retardation, was part of the NF1 phenotype. Those rates, however, probably arose because of a bias in ascertaining severely affected patients in old hospital-based series.³ Later population-based studies have shown that the incidence of true mental retardation in NF1 is lower than expected—3.2% in the study of S Huson and colleagues³ (based on retrospective analysis of educational needs) compared with the prevalence of mental retardation (defined as an IQ<70) in the general population (5%).⁴

Research on the cognitive phenotype of NF1^{3,5} have established that most NF1 patients have a mean full-scale intelligence quotient (IQ) in the low to average range (around 90) compared with age-matched or sibling controls, but that their risk of frank mental retardation is low. Intellectual impairment in NF1 presents as learning difficulties and is relatively mild and non-progressive. The situation is compounded in around 40% of patients by impairment of gross and fine coordination.

The recorded prevalence of mental retardation (by means of neuropsychological testing) in our paediatric NF1 population (338 children, aged 2–17 years, studied at our institution in 1990–99) was similar (3.2%) to that in the general paediatric population. None had profound mental retardation (IQ 20–35). 70% of these mentally retarded NF1 children had a more severe NF1 phenotype, including earlier appearance of an unusually large number of discrete dermal neurofibromas, dysmorphic features, seizures, autism, and central nervous system malformations, and carried large deletions of the NF1 gene (unreported data).

Whatever rates we take to be the true incidence of mental retardation in NF1, evidence shows that such developmental disability is not part of the NF1 phenotype. When it occurs in this way, a distinctive and more complex phenotype is recognisable.

To claim that there is a potential simple relation between NF1 and mental retardation without further substantiation would be erroneous.

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Authors' reply

Sir—We agree with Martino Ruggieri and Agata Polizzi that the proportion of patients with NF1 who also have mental retardation is low. The point we wish to make is that infrared light examination is useful even in NF1 patients with mental retardation. Of course, this technique is also useful in patients without mental retardation.

When a patient does not meet the NF1 criteria proposed by National Institutes for Health Consensus Conference in 1988,¹ doctors can use T2-weighted magnetic resonance imaging to detect unidentified bright objects² or optic glioma; computed tomography for osseous lesions such as dysplasia of the greater wing of the sphenoid or pseudoarthrosis,³ or ophthalmological examination for Lish iris nodules. When a patient has difficulty staying still long enough to do these assessments, sedation or anaesthesia might be required.^{2,4} A steady head position is preferable in our infrared light examination, but holding the position can be very temporary.

To detect a fundus, patients assessed by infrared light are less likely to require general anaesthesia than are patients assessed with a slit lamp, since an infrared light is not so bright as a slit-lamp, which is used for a Lish nodule examination.

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Pre-eclampsia

Sir—James Walker (Oct 7, p 1260)¹ discusses the use of magnesium sulphate for eclampsia and pre-eclampsia. We agree that magnesium sulphate is the drug of choice for eclampsia, but would like to correct the details of the dose regimens used in the Collaborative Eclampsia Trial.² Two separate magnesium sulphate regimens were used. For one, the loading dose was 4 g magnesium sulphate intravenously plus 10 g intramuscularly, and maintenance therapy was 5 g intramuscularly every 4 h for 24 h. For the other regimen, the loading dose was 4 g intravenously and maintenance was an infusion of 1 g per hour for 24 h.

For women with severe pre-eclampsia, Walker suggests that magnesium sulphate should be considered. As he mentions, however, the evidence to support this use is not strong and whether, overall, magnesium sulphate does more good than harm is unclear.³ We are currently coordinating a large multicentre trial to compare magnesium sulphate with placebo for women with pre-eclampsia.⁴ More than 6000 women have been recruited, and additional collaborators would be welcome.

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Sir—A little more discussion on prevention and precise diagnosis of pre-eclampsia would probably add to the completeness of James Walker's review (Oct 7, p 1261).¹

There are doubts surrounding the

use of aspirin and supplemental calcium for prevention of pre-eclampsia that are yet to be dispelled. In some studies the benefit of these agents could not be confirmed.^{2,3} Pre-eclampsia is a vascular endothelial disorder, and, maternal inflammatory response being a feature, aspirin might have a role.

Ambulatory blood pressure monitoring would certainly help in the precise diagnosis of pre-eclampsia. White coat hypertension has been reported in as many as 30% of pregnant women.⁴ Women diagnosed as having hypertension by ambulatory blood pressure monitoring have babies with lower birthweights, and this association has not been found in women whose blood pressure is measured conventionally.⁵ This fact has implications for management. Some caesarean deliveries could be avoided if ambulatory measurements are used rather than conventional measurements for the blood pressure.⁴

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Care after cure in leprosy

Sir—Aki Hietaharju and colleagues (Sept 23, p 1080)¹ have identified the need for programmes for care after cure for people treated for leprosy. We agree, but ask for the definition of cure in leprosy.

The current WHO definition seems to be the completion of chemotherapy, which is 6 months of rifampicin and dapsone for paucibacillary disease, and 1 year of these two drugs plus clofazimine for multibacillary disease.^{1,2} Previously, the recommendation was for 2 years of chemotherapy in multibacillary disease, as Hietaharju and colleagues cite,^{1,3} but WHO had the duration reduced to 1 year.² These drugs will kill most, if not all, *Mycobacterium leprae* in the tissues. Thus, chemotherapy cures the

infection, but not necessarily the disease, which requires further care, as the report highlights.

The microbiological cure is essentially meant for rendering the person non-infectious to others, or for the public-health purpose of the control of leprosy.^{2,3} What is seldom recognised is that many symptoms persist or become worse, often over a few years, after the completion of chemotherapy. Neuritis or nerve entrapment can cause wrist-drop, claw-hand deformity, foot-drop, or lagophthalmos; chronic neuropathic pain can be added to this list.¹ Sensory loss may persist and cause various well-known consequences. All these require diagnosis, treatment, and rehabilitation, commonly for a few to several years.

The emphasis on microbiological cure to control disease is based on the assumption that transmission is mostly from people with overt signs or symptoms of leprosy. In that case, leprosy should be controlled or eliminated by case detection and microbiological cure. This is the current approach of the WHO leprosy-elimination programme. If this assumption turns out to be incorrect, leprosy will not be controlled by this intervention.⁴ On the other hand, if careful and individualised care after cure is practiced, then the deformities due to leprosy can be almost eliminated.

People worry more about the consequences of leprosy, than about the infection itself. We do not go into the details of the pathogenesis and treatment of the persisting symptoms here, but we emphasise that we have the technology to ensure that no-one becomes deformed from leprosy. Since we are not sure that we know how to prevent infection, the more feasible global goal should be to eliminate deformity rather than leprosy infection per se. For that, care after cure is crucial.

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Risk of asthma

Sir—In his Oct 21 commentary,¹ Roni Grad calls for more research into the substantial increase in the prevalence of asthma over the past 30 years.

Atopic disorders such as allergic rhinitis, eczema, and asthma, as well as malignant diseases are characterised by a predominant T-helper-2 (Th2) immune response. Better housing and hygiene, the decline in infectious diseases, and current immunisation regimens might have contributed to the increase in these diseases.² There is, however, also an increase in T-helper-1 (Th1)-mediated autoimmune diseases such as insulin-dependent diabetes mellitus. But, of the environmental factors, early childhood vaccinations might be the important contributing factor, leading to an increase in these diseases of disordered immune regulation.

Thomas Ball and colleagues³ have shown that childhood infections, especially in the first 6 months of life, seem to prevent asthma later in life. Cells infected with a virus or intracellular parasites and tumour cells are destroyed by a Th1 response. Non-replicating vaccines do not, however, cause a vigorous Th1 response because they do not stimulate antigen presenting cells sufficiently in the maturing immune system of the neonate.⁴ Early childhood vaccines could, therefore, cause a disturbance in the immune regulation of the maturing immune system, priming it to react in a certain way.

Such an effect could explain the results of the International Study of Allergies and Asthma in Childhood study,⁵ which shows that the prevalence of asthma, atopic eczema, and allergic rhinoconjunctivitis is most consistently high in the UK, Ireland, Australia, USA, and New Zealand. These countries have long established vaccination programmes. Other observations show that, although foodborne and orofecal microbes are thought to protect against atopy, the prevalence of atopic diseases has increased in poor African cities, where hygiene has not had the same effect on these microbes as in the affluent countries. The implementation of immunisation programmes in these areas could explain this rising trend.

As a family physician I am becoming increasingly uncomfortable with the diseases to which vaccines might contribute later in life. I suggest the need for epidemiological studies to assess whether the currently perceived benefits still outweigh the long-term disadvantages. Consideration should be given as to whether vaccination should

be postponed until after the first 6 months of life. Especially in view of the increasing number of childhood vaccines, should we investigate with some urgency whether they are becoming too much of a good thing?

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Catalase deficiency, diabetes, and mitochondrial function

Sir—László Góth and John Eaton (Nov 25, p 1820)¹ report an increased frequency of diabetes in patients with catalase deficiency. They speculate that a deficiency of this enzyme leads, in the β -cell, to an increase in oxidative stress and, ultimately, to a failure of this cell type.

Góth and Eaton correctly point out that β -cells are rich in mitochondria and that this organelle might be a source of reactive oxygen species. However, the mitochondrial electron transport chain is also susceptible to damage by oxidising species² and such damage is exacerbated when antioxidant reserves are compromised.³ Since insulin release is an energy-dependent process,⁴ an impaired ability to generate ATP, through mitochondrial damage, is the mechanism whereby catalase deficiency can lead to diabetes.

Further support for this suggestion comes from the observation that diabetes can be a characteristic of the mitochondrial cytopathies.⁵

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Changes in trial parameters

Sir—Michael Levin and colleagues (Sept 16, p 961)¹ report results of a placebo controlled trial of bactericidal/permeability-increasing protein (BPI) in children with meningococcal sepsis. Although the original primary endpoint of the trial, 60 day mortality, and a subsequently specified composite primary endpoint do not differ significantly between study groups, they conclude, on the basis of selected endpoints, that the trial demonstrated efficacy. Levin and colleagues are to be commended for studying this challenging and important issue, but their conclusion remains speculative.

The trial was designed to be able to detect a reduction in mortality from 25% in controls to 10% with BPI. During the study it became clear mortality was strikingly lower than expected, and, despite an expansion in size, the trial could detect no difference of the magnitude sought. As a result, the sponsor, XOMA, proposed to change the primary endpoint from mortality alone to a composite of mortality and morbidities to increase the event rate and, hopefully, the power. Since the elements of the composite were of dissimilar clinical severity, Levin and colleagues chose a ranked outcome assessment, with death as the worst outcome, followed by recovery with specified moderate to severe morbidities, followed by recovery with mild or no morbidities. Given the rarity of this disease and that the database remained masked, the Food and Drug Administration accepted the sponsor's proposal.

Levin and colleagues state that the sponsor did not consult them about the change of endpoints and that the case-report forms were not optimum for assessment of the new primary endpoint. We concur that these deficiencies are unfortunate, and note that it is the sponsor's responsibility to ensure communication with trial investigators and to properly collect trial data.

Despite the inability to detect significant differences between BPI and placebo by the original intention-to-treat mortality analysis and the modified primary endpoints, as well as many other secondary outcomes, Levin and colleagues conclude from analyses of selected retrospectively defined, secondary outcome measures, including mortality rates in patients who completed treatment, that BPI has beneficial effects. However, although perhaps representing a trend toward benefit, neither this analysis nor the purported reduction in patients needing severe amputations were significant, despite being described as "much lower" and "a striking reduction", respectively.

When there is good cause (in this case, an unexpectedly low mortality rate and inability to adequately expand the trial), the Food and Drug Administration might allow changes to analytical plans before revealing data. When there are many potential analyses (eg, various outcome measures, subsets, statistical tests, and analytic approaches), even an ineffective therapy can, by chance, seem effective on one or more analyses. Thus, selection of analyses after data are revealed frequently introduces bias. When prospectively defined endpoints show no significant differences from placebo, as occurred in this trial, other analyses, even if encouraging, may be judged suggestive of benefit but should not alone lead to major and definitive conclusions, such as that a product is effective.

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- 1 Levin M, Quint PA, Goldstein B, et al. Recombinant bactericidal/permeability-increasing protein (rBPI₂₁) as adjunctive treatment for children with severe meningococcal sepsis: a randomised trial. *Lancet* 2000; **356**: 961–67.

Does lung cancer need a lapel ribbon?

Sir—Your Oct 7 editorial¹ highlights an important issue and we identify with your concerns. The size of the issue is underestimated. Lung cancer causes more deaths in the USA and western Europe than colorectal, cervical, and breast cancer combined.² In addition, the rate of lung cancer is increasing in UK women.

Of course, there is certainly no lack of guidance on how to organise services for cancers. Guidance available includes the Calman Hine report,³ British Thoracic Society (BTS) recommendations,⁴ and the National Health Service Cancer Plan,⁵ which notes that at least one in three people in England will develop cancer at some stage in their lives and one in four will die from cancer.

In Walsall, UK, we have undertaken a joint audit with the local acute hospital to assess delays in referral times for patients with lung cancer. As a standard we used the BTS recommendations and the National Health Service requirement of a 2-week waiting time from referral by a family physician, if cancer is suspected, to being seen by a respiratory physician. Preliminary results show that there are delays at all stages of management once lung cancer is diagnosed.

You suggest that the low profile of lung cancer might be explained by the view in some cases that the disease is self-inflicted. In addition, tobacco industries have their own agenda and we depend on the government to apply sanctions and restrictions.

The UK Government has made a commitment to target lung cancer. Since Walsall is a health-action zone, huge efforts are being channelled into smoking cessation. In Walsall 37 (50%) family physician practices provide intermediate-level support in the smoking cessation scheme in primary care. Five (8.3%) pharmacists provide a similar service. We have in place specialist smoking cessation clinics to further tackle local inequalities. In the first quarter of 2000–01, the rate of stopping smoking for intermediate-level services was 36%. 1361 people have set a date to stop this year and 363 have already stopped at 4 weeks.

The picture, therefore, isn't all grey. There is, however, no room for complacency. We agree with your concerns all the same and would fully support a lung-cancer ribbon.

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- 1 Anon. Does lung cancer need a lapel ribbon? *Lancet* 2000; **356**: 1205.
- 2 Porter JC, Spiro SG. Detection of early lung cancer. *Thorax* 2000; **55** (suppl 1): S56–62.
- 3 Calman K, Hine DA. Policy framework for commissioning cancer services: a report by the Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales. London: Department of Health, 1995.
- 4 BTS recommendations to respiratory physicians for organising the care of patients with lung cancer. *Thorax* 1998; **53** (suppl 1): S1–S8.
- 5 The NHS Cancer Plan. Crown copyright. London: Department of Health, September 2000.

Sir—In your editorial,¹ you ask “Does lung cancer need a lapel ribbon?” Absolutely! In the USA a lapel ribbon to increase awareness of lung cancer has been available for the past 5 years. It was developed by the Alliance for Lung Cancer Advocacy, Support, and Education (ALCASE), a non-profit organisation solely dedicated to helping people at risk for and living with lung cancer. The ribbon can be ordered through our website (www.alcase.org accessed on Jan 22, 2001). The ribbon is made of transparent plastic to represent the invisible population living with lung cancer.

In the USA, the Alliance for Lung Cancer Advocacy has declared November lung cancer awareness month. Activities throughout the nation are focused on bringing the issues of lung cancer into the open. As you state, there is a stigma attached to this disease that infers it is self-inflicted. This stigma is even associated with people who have never smoked, a number that increases yearly. Such blame is misplaced.

Lung cancer is the number one killer by cancer in the USA for both women and men. More people die from lung cancer each year than from breast, prostate, and rectal cancers combined. Yet famous and influential people will not step forward and speak about lung cancer, even if they have been affected. Awareness is the key. The general public must be informed and motivated to demand substantial money for research, for screening, more effective treatments, and better supportive care. Increased awareness will save lives.

Join us! Wear the ribbon!

Betty Layne

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- 1 Anon. Does lung cancer need a lapel ribbon? *Lancet* 2000; **356**: 1205.

The Joy of health

Sir—I read initially with irritation and later with some sadness your Oct 28 item on the National Health Service Plan and Michael Joy's letter.¹ I read it early on a Sunday morning in the on-call room of our cottage hospital towards the end of a busy shift for our local family physician cooperative. I am approaching my mid-50s and still working as a full time family physician. I have read *The Lancet* for many years, partly for its outspoken views, but found those expressed in this unsigned editorial hard to stomach.

The disapproving representation of family doctors in the first few paragraphs is reminiscent of Kenneth Clarke's description of us “nervously reaching for our wallets” back in 1990. Many of us are more concerned with the low morale and poor recruitment to this branch of the profession than with remuneration. We are being asked, or ordered, to perform to higher and higher standards with no sign of the arrival of the heralded additional resources. Indeed, many innovative practices are finding their staff budgets reduced rather than increased at a time when, for example, National Service Frameworks on coronary heart disease and diabetes are likely to require more family-physician, nursing, and administrative time. There are promises of more doctors and nurses, but the number of extra family doctors quoted takes no account of the trend towards earlier retirement and the wish of many of the dwindling number of recruits to general practice to work less than full time. In any case, no one has yet detailed where this extra manpower is to be found before my retirement.

Over the past few months, I have, with my colleagues, been branded in the media as lazy, negligent, abusive of emergency admissions, unduly cynical about the NHS Plan, and now greedy as well. I find it hard to cope with the government's constant sniping and subtle criticism—look at what they have achieved with teachers—but even harder to accept it from people who might be expected to have more insight. The great and good of medicine still seem very willing to set out values of service and commitment to those still engaged in front-line practice when they themselves are no longer significantly involved in it. They also seem to be very easily seduced by promises backed up by little evidence of action and effective implementation.

I have not read the full text of Joy's letter. I suspect I would agree with most of it. Like him, I want more time

and resources to do the job properly. I hope that he too still draws sufficient satisfaction from the essence of the job, which is interacting with patients, most of whom are understanding and appreciative, and each of whom is unique and fascinating. They deserve better: more resources and happier less-stressed nurses and doctors.

Perhaps we might expect kinder treatment from people who do not have to spend the odd night deciding whether to send into hospital an old gentleman with atypical chest pain, which risks "abusing the emergency referral system", or whether to wait and see and risk severe self-criticism and possible allegations of negligence. I had two such cases last night and soon after reading the editorial, a young sick child possibly developing a non-blanching rash. The decisions and judgments involved in such cases are stressful and will remain so. Those who make them need support not constant criticism.

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1 Anon. The Joy of health. *Lancet* 2000; **356**: 1453.

Sir—You rightly commend Michael Joy for speaking out on behalf of the patients at his hospital who had been waiting on trolleys for 2 days because all beds were full.¹ Statements made by practising clinicians have a powerful impact and they are not made lightly. However, your claim that medicine will "lose its wish to be called a profession" unless its leaders constantly reiterate their commitment to patients is unfair and politically naïve.

The comment is unfair because much of the British Medical Association's (BMA's) work and lobbying activity is geared precisely to that end—securing better funding for the National Health Service, a better deal for patients and a medical workforce big enough to meet patients' needs. I think the BMA can fairly claim credit for its role in exposing the chronic underfunding of the health service and securing a commitment to start bridging the funding gap. That endeavour has been consistent over many years, alongside work to promote high ethical standards of practice and research, and lobbying on major public-health issues.

Of course, if we disagree with the Government, that point of conflict will be more prominently reported than statements supporting the *National*

Health Service Plan. In the run up to a general election, we would be naïve to expect otherwise. Of the 40 or more press statements issued by the BMA since the *NHS Plan* was published at the end of July, most relate to professional, ethical, and funding issues. Only half a dozen relate to pay or contractual matters. Many BMA members might prefer that balance to be reversed. They spend their working days and nights caring for patients and showing their commitment to the sick and vulnerable through sheer hard work. They rightly expected their leaders to stick up for them and ensure that they are fairly treated. Consultants and registrars have been angered by the Government's proposal to bar new consultants from private practice precisely because it implies that they are not fulfilling their professional commitment to their National Health Service patients and that, despite working flat-out in the service for 15 years, they still have a debt to repay.

If you want to attack medical leaders, that is your prerogative but I am confident that working doctors want to see me defending them and the patients they serve.

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1 Anon. The Joy of health. *Lancet* 2000; **356**: 1453.

Sir—You contrast the attitude of people who claim to speak on behalf of doctors with the worries of cardiologist Michael Joy, who is having difficulty treating his acute admissions.¹ The stimulus for your editorial was the issue of private practice for newly qualified consultants. This issue is something about which the BMA, with other organisations, and the government disagree.

On the other hand, the British Medical Association agrees with the government that doctors should be appraised annually. Although the government has now accepted that the underfunding and understaffing of the National Health Service will take years to correct, the distracting political and media focus on poorly performing doctors has forced the compulsory contractual introduction of appraisal systems. These systems will take much time and money to implement, will take clinicians out of their clinics, and we do not know that they will prevent bad practice. How likely is proper individual appraisal in a system that is not working properly? If Michael Joy has to treat his patients with acute

medical conditions two to a cubicle in the accident and emergency department, how will anyone sensibly be able to (quoting the recent BMA consultative document on appraisal) "review regularly [his] work and performance, using relevant and appropriate comparative performance data"? Under these circumstances, describing appraisal as "a positive employer led process to give consultants feedback on their performance, to chart their continuing progress and to identify development needs" is pathetic and beside the point.

It is too late, but our leaders, from the outset, should have stressed that the damage done by wilful or ignorant poor practice (which everyone admits is a small proportion) is far less but more obvious than the damage done by poor practice due to service constraints. The politicians cleverly exploited this, and the medical profession has now been backed into a corner. We should have refused to cooperate until the National Health Service was in a better state. Appraisal was always going to be difficult.

At a time of acknowledged strain and large changes in the National Health Service, we are having to implement a system that will put us and our clinical commitments under even greater strain. The time to look at individuals is when the service as a whole is better able to deliver good health care. Having accepted the idea of appraisal, we are now responsible for it; and we, and our patients, will be worse for it.

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1 Anon. The Joy of health. *Lancet* 2000; **356**: 1453.

DEPARTMENT OF ERROR

Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis—In this Early report by Ralf Koster and colleagues (Dec 2, p 1895), the second sentence in paragraph 2 of the Discussion should read "The in-stent restenoses were associated with clinical symptoms requiring repeat intervention in all of the hypersensitive patients."

Impact of laparoscopic cholecystectomy: a population-based study—In this Article by Andrew J McMahon and colleagues (Nov 11, p 1632), the 95% CI for the change in cholecystectomy rate in men aged 35–44 years (table 1, p 1634) should be "–6 to 11". The mean age for patients undergoing open cholecystectomy (table 3, p 1634) should be "58".