Letters

Olfactory detection of human bladder cancer by dogs

Cause or association?

EDITOR—The study by Willis et al, testing whether dogs can detect signs of bladder cancer in urine, may be the occasion for an amusing cover for the *BMJ* but this should not be an excuse for relaxing intellectual rigor when assessing the experiment.[1] Neither the authors nor the commentator point out that the study design is unable to distinguish cause from association—a basic logical error.

The dogs may be detecting "tumour related volatile compounds" or they may be detecting a substance in the urine that is associated with an increased risk of cancer.

The most obvious candidate would be from cigarette smoking, which would be rather unoriginal, but it could also be other as yet unidentified substances.

Furthermore, while the dogs may only be 41% accurate at detecting urine from people already diagnosed with cancer, the results would also be consistent with a higher accuracy for detecting patients at risk of cancer.

The authors should follow up their interesting preliminary study rigorously and the *BMJ* should stick to the Christmas edition for letting down its usual standards of review.

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Competing interests: None declared.

1 Willis CM, Church SM, Guest CM, Cook WA, McCarthy N, Bransbury AJ, et al. Olfactory detection of human bladder cancer by dogs: proof of principle study [with commentary by T Cole]. *BMJ* 2004;329:712-5. (25 September.)

Authors' reply

EDITOR—We were well aware of the need to consider lifestyle and environmental factors associated with bladder cancer. As stated in our methods section, we collected comprehensive data on each participant, including occupation, dietary intake, hobbies, drug treatment, and, most importantly, smoking habits. We specifically designed the training regimen to take into account the association between smoking, bladder cancer, and the possible presence of tobacco related odours in the urine.

During training the dogs were taught to ignore the urine of control individuals who smoked, and they were presented with positive bladder cancer urine samples from non-smokers as well as smokers. In the evaluation tests all runs containing a patient with bladder cancer who smoked included at least two controls who were smokers.

We did not measure metabolites from tobacco in the urine, but based on self report there was no obvious tendency for the dogs to preferentially select the urine from smokers. Specifically, 41% of selected urine samples were from self described "current or recent smokers" compared with 43% of non-selected urine samples. Overall, 37% of selected urine samples were from individuals who reported smoking one or more cigarettes on the day before their urine sample, compared with 33% who reported smoking no cigarettes on this day.

Moreover, adjustment for smoking status has essentially no effect on the observed association between presence of cancer and odds of selection as indicated in the table.

None of the patients with bladder cancer whose urine was used during testing was in a high risk occupation for the development of bladder cancer. Furthermore, there was no over-representation in terms of dietary intake (including tea, coffee, or alcohol) or exposure to chemicals used for domestic purposes, such as paints, solvents, and pesticides, among this group.

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Competing interests: None declared.

Effect of adjustment for tobacco smoking status on the odds of selection

Model	Odds ratio*
Base (cancer)	4.1
+ Usual cigarettes per day	4.1
+ Cigarettes on day of urine sample	4.2
+ Time since stopping smoking in weeks†	4.2
+ Usually smoke (any amount)	4.1
+ Smoked on day of sample (any amount)	4.4

*Odds of selection among individuals with bladder cancer (transitional cell carcinoma) compared with among those without from a conditional logistic regression model.
†0 for current smokers and 100 for non-smokers or smokers stopping more than 100 weeks before sample.

Another cancer detected by "pet scan"

EDITOR—Before the study by Willis et al there was only sparse, anecdotal evidence suggesting that dogs might truly be able to detect human malignancies.[1] Their study complements a recent study in which dogs were trained to identify melanoma in tissue samples and were then tested for their ability to detect melanoma lesions on human subjects.[2]

In both investigations the dogs detected malignancies in supposed controls. These studies bolster the idea that dogs may someday prove useful in the early detection of cancer. Such experimental investigations are of great interest to me, as I had encountered a patient who claimed that her dog's incessant sniffing led to her finding of a breast mass that proved malignant. Owing to the lack of substantiating literature to back up her claim, most of her medical care team brushed this off as coincidence, particularly since the lesion was internal rather than cutaneous as in other anecdotal reports.

Professor Hywel Williams's well-known case of a melanoma being detected by the patient's dog is now supported by experimental evidence.[3] Our unpublished case suggests that dogs, in rare situations, may also detect non-cutaneous malignancies. Work such as that by Willis et al should spur on further rigorous investigation into this intriguing area.

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1 Willis CM, Church SM, Guest CM, Cook WA, McCarthy N, Bransbury AJ, et al. Olfactory detection of human bladder

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Epidemiology of preterm birth

Delayed cord clamping used to be taught and practised

EDITOR—Tucker and McGuire point out that modern perinatal care and the specific interventions of antenatal steroids and exogenous surfactant have contributed to the improved outcomes for very preterm infants.[1] As an obstetric registrar in Ninewells Hospital, Dundee, in the mid-1970s I was taught and practised delayed cord clamping at delivery of preterm infants. This measure has since been shown to reduce the severity of respiratory distress syndrome[2] and neonatal morbidity.[3] Despite the evidence of benefit, timing of clamping the cord was not included in the 27/28 week inquiry into stillbirths and deaths in infancy (CESDI) project as a standard of care.[4] A recent postal survey of obstetricians regularly delivering preterm infants showed that only 47% practised delayed cord clamping.[5] Neither is this measure specified by Tucker and Mcguire in their review article.

I agree that prevention of preterm birth, or the need for it, provided by an adequate research based treatment, must be the ultimate aim. When prevention is not possible, every measure that reduces the morbidity and mortality of the infant must be given. Currently this does not seem to be the case in the United Kingdom.

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Authors' reply

EDITOR—In noting antenatal steroids and exogenous surfactants as two specific perinatal interventions that have contributed to trends in improved outcomes for very preterm infants, Hutchon thinks that we have omitted to include delayed cord clamping. We argue that whereas there is robust evidence from larger trials and systematic reviews for both prophylactic steroids and surfactants,[1 2] there is currently continued uncertainty in the published evidence base about the effect of delayed cord clamping on mortality and disability outcomes.

The recently published Cochrane review of this intervention identifies seven trials in which a total of 297 infants participated.[3] There is some evidence from meta-analysis of data from these trials that delayed cord clamping results in fewer infants receiving blood transfusions in the neonatal period, but there is little other evidence of benefit. Infants in the delayed clamping group had higher peak serum bilirubin concentration in the early neonatal period. There is insufficient evidence of effect on mortality, respiratory outcomes, the incidence of severe intraventricular haemorrhage or periventricular leucomalacia, or the incidence of necrotising enterocolitis.[3] Most importantly, there are not yet any data on the effect of this intervention on neurodevelopmental outcomes in the longer term. Further large trials are needed to provide these data in order to clarify whether the practice of delayed cord clamping for very preterm infants should be adopted.

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Competing interests: None declared.

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Colonoscopy completion rates

Technologies have evolved

EDITOR—In their quality improvement report on improving caecal intubation rates at colonoscopy Ball et al conclude that these improvements were due to three key measures: increasing appointment times, allocating the procedures to the most skilled operators, and improving bowel preparation in frail patients.[1] We have several issues related to each of their interventions.

Firstly, colonoscopy appointment times were increased from 20 minutes to 30 minutes. The Royal College of Physicians recommends that consultant gastroenterologists perform a maximum of six colonoscopies per notional half day ($3\frac{1}{2}$ hours)[2]; 30 minutes is therefore slightly less than the suggested minimum time per procedure. Perhaps increasing appointment times even further would have resulted in even better caecal intubation rates. Moreover, an appointment shorter than the recommended lower limit is unlikely to be adequate for training purposes.

Secondly, although it may seem sensible to allocate colonoscopies to the most proficient practitioners, this intervention could also have an impact on the training of junior doctors.

Thirdly, admitting frail patients for bowel preparation may not be a cost effective measure. The authors do not state how many extra admissions this created; however, as 14% of patients attending for colonoscopy are 75 or older,[3] frail patients requiring admission may represent a sizeable burden for many hospitals. Computed tomography without bowel preparation is likely to identify gross pathology in such patients and may be a viable alternative. In addition, inpatient bowel preparation is, in our experience, often less effective than that performed at home: we agree with Ball et al that admission to wards with expertise in this area is important.

Finally, colonoscopic technology has improved notably over recent years: carbon dioxide (instead of air) insufflation and variable stiffness colonoscopes are likely to improve patients' comfort and completion rates. Ball et al do not say whether any of their equipment was updated between audit periods.

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1 Ball JE, Osbourne J, Jowett S, Pellen M, Welfare MR. Quality improvement programme to achieve acceptable colonoscopy completion rates: prospective before and after study. *BMJ* 2004;329:665-7. (18 September.)
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Should less successful endoscopists be removed or retrained?

EDITOR—Ball et al report their low colonoscopy completion rates, performing an audit to identify areas for improvement.[1] The use of audit in colonoscopy is invaluable and the points highlighted are undoubtedly relevant to other colonoscopy units.

The paper notes a considerable interoperator variation in completion rates (34% to 100%). They do not say whether the least successful colonoscopists were trainees or consultants, and if trainees, whether they were supervised during the sessions. Surely, removing the worst performers from colonoscopy without the opportunity of further training or supervised sessions is merely ensuring that they never have the chance to improve their skills.

The best way to improve performance is through training. Would it not have been preferable to educate the worst performers, either by way of attending formal colonoscopy courses or with colonoscopy sessions supervised by the best performers? Removing the worst performers from the equation

is a quick fix, resulting in an automatic improvement in the statistics without solving the heart of the problem. Although the authors' actions resulted in an increase in completion rates, this is merely a short term solution to the problem.

What will happen to the completion rates when the best performers leave their current positions or retire, leaving only the poorer performers who have been starved of further training? The paper highlighted one individual whose completion rates improved from 79% to 95% over four years. It is a shame that the poorer performers were not given the chance to increase their skills likewise.

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1 Ball JE, Osbourne J, Jowett S, Pellen M, Welfare MR. Quality improvement programme to achieve acceptable colonoscopy completion rates: prospective before and after study. *BMJ* 2004;329:665-7. (18 September.)

Author's reply

Editor—We agree that the more time the better, and ideally we could lengthen our appointments still further. Royal college guidance is clear, but few data are adhered to and discussions with other consultants and trainees show that appointment times vary considerably and trainees do not always have adequate time for training. Our report was true for our unit and the 20 minute appointments were historical. Clearly adequate arrangements need to be made for trainees and guidelines should be followed by having a well-performing trainer present at all times with trainees until their performance is good enough for independent practice.

This now happens in our unit, and trainees are not excluded from colonoscopy. However, colonoscopy training should be undertaken only by those with sufficient time and at an appropriate time in their career to learn this skill. With the reduction in training times resulting from the European Working Time Directive, some groups of trainees may not choose to learn colonoscopy.

Patient selection is clearly important, with function being more important than age. Simply changing the ward on which inpatients receive their preparation, rather than increasing the number of inpatient preparations, should have no cost implications. Computed tomography may replace colonoscopy in some instances. Space prevented us from detailing other changes, but we did upgrade our colonoscopy equipment, which may have played an additional part.

The issue of retraining *v* concentrating colonoscopy in the hands of those more successful is raised by Laban and Elewa and by others on bmj.com.[1] We offered further training to everyone and did not compel anyone to give up colonoscopy. Some people chose to concentrate on other aspects of their career, and presumably they were in the best position to know whether it was likely that retraining would be effective. If the more successful colonoscopists stop doing simple procedures and concentrate on colonoscopies then the total number of colonoscopy appointments available might well go up so it is not merely a quick fix.

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Competing interests: None declared.

1 Electronic responses. Quality improvement programme to achieve acceptable colonoscopy completion rates. bmj.com 2004. http://bmj.bmjjournals.com/cgi/eletters/329/7467/665 (accessed 17 Nov 2004).

Life span and disability in Sweden and Russia

Paper highlights poor health among Russian women

Editor—Bobak et al in their paper on disability in Russia provide further evidence on the high level of morbidity in the Russian population, a finding that is consistent with our earlier reports using a similar method.[1 2 3] However, we disagree that these findings are consistent with the World Health Organization's healthy life expectancy project, which reported a male-female gap in healthy life expectancy of 11.5 years (52.8 years *v* 64.3 years).[4] This figure, for healthy life expectancy at birth, would correspond to at least an 8-9 year gap between the sexes at age 20.


PANOS PICTURES

Although Bobak et al do not report healthy life expectancy, their figures for the prevalence of good or fair health or good physical performance show no large gap between the sexes, again consistent with our findings. Computation of healthy life expectancy at age 20 from the table of age specific prevalence of poor health in the paper by Bobak et al produces figures of 34.5 years for men and 35.7 years for women. This is an even smaller gap than in our estimates of 36.7 for men and 40.6 years for women.[3] We therefore believe that the main message relates to the plight of Russian women surviving into middle and old age, a group that, as we have previously noted, suffers from high levels of disability and a strong probability of widowhood. Their limited protection from the worst effects of political transition is now under threat from reform of the Russian social security system.[5]

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Competing interests: None declared.

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Authors' reply

Editor—We are pleased by the consistency of our results with those of Andreev et al[1]; the fact that the two studies used entirely independent data (and partly different outcomes) on ill health supports the validity of both results.

The primary interest of our paper was the difference between Russia and Sweden. In this aspect, our results are consistent with the healthy life expectancy project, which shows, for both sexes, a difference in healthy life expectancy at birth of about 20 years between the two countries.[2] Differences between men and women were not a focus of our study, mainly because reporting by women of worse health than men is well known and our data are, in this respect, similar to those of other studies.

As McKee et al point out, our data do not show a major sex difference in disability free survival (and healthy life expectancy). This is because Russian women live longer than men but spend more of their lives with disability. We agree that a large number of elderly Russian women who are widowed or in poor health often live in difficult social circumstances. Papers such as the one by Andreev et al and ours may help to draw attention to it.

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Competing interests: None declared.

1 Andreev EM, McKee M, Shkolnikov VM. Health expectancy in Russia: a new perspective on the health divide in Europe. *Bull WHO* 2003;81:778-88.
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Completion lymphadenectomy may not increase in-transit disease in malignant melanoma

Editor—The arguments put forward by Thomas and Clark against the use of sentinel node biopsy in malignant melanoma have not changed over the past

four years.[1 2] However, data are now available to test the hypothesis that completion lymphadenectomy might increase the rate of in-transit disease.

We identified 10 studies, including our own, which report patterns of relapse separately according to sentinel node status.[3] Overall we found 701 relapses among 4713 subjects, of which 94 were nodal, 201 were either in-transit or local recurrence, and 406 were distant, giving an absolute rate of 2%, 4.3%, and 8.8%, respectively. In cohorts not subjected to selective lymphadenectomy the equivalent figures are 7.8% nodal, 3.4% in-transit, and 4.4% distant.[4] In other words, selective lymphadenectomy reduces the absolute rate of nodal relapse mainly at the expense of an increased rate of distant metastases. It is difficult to attach too much importance to the modest increase in the rate of in-transit disease as the cohorts subjected to selective lymphadenectomy commonly excluded patients with stage 1A disease, whereas the historical cohort was unselected.

As expected, the overall relapse rate among patients with a positive node was almost three times that of the cohorts negative node result (11.6% *v* 31%), but it is also instructive to compare patterns of relapse according to sentinel node status. Among sentinel node negative subjects, 16% of all relapses were nodal, 53% were distant, and 31% were in-transit. Among sentinel node positive cohorts 8% were nodal, 59% were distant, and 33% were in-transit. This small difference for in-transit disease is not significant and does not support the hypothesis that completion lymphadenectomy increases the likelihood of in-transit disease.

We also take issue with the statement that adjuvant treatment with interferon confers no survival benefit. The meta-analysis quoted by Thomas and Clark shows an unequivocal and dose related improvement for disease free survival ($P < 0.0001$) and, if the analysis is confined to the high dose studies, a marginal benefit for overall survival ($P = 0.05$).[5] The fact that the NHS is not prepared to fund this treatment owes more to cost than toxicity.

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Infectious diseases in Iraq have international implications

EDITOR—The deteriorating infectious disease situation in Iraq as outlined in the news item by Dyer should be of international concern.[1] Not only are there ethical arguments for assisting the Iraqi people but some "global public good" arguments relating to communicable disease control may apply.[2] Measles outbreaks for example could spread from Iraq to neighbouring countries. Even the outbreaks of typhoid in Iraq may pose a risk to people in other countries—given the evidence for the crossborder spread of typhoid via contaminated food products.[3]

These arguments support the case for a collective response by the international community and surrounding nations to assist Iraq to strengthen critical health-protecting infrastructure such as the provision of clean water supplies. There may also be a particular obligation for providing assistance on those governments whose military forces caused damage as part of action against the former Iraqi government—for example, to water treatment facilities and electricity services.

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1 Dyer O. Infectious diseases increase in Iraq as public health service deteriorates. *BMJ* 2004;329:940. (23 October.)
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NICE and BHS guidelines on hypertension differ importantly

EDITOR—The NICE guidelines on hypertension remind the public that hypertension is a major risk factor for cardiovascular diseases. Their added value to those who manage hypertension is, however, unclear, given the recent national and international guidelines from experts and primary care doctors with an interest in hypertension.[1-3] The NICE guidance is largely consistent with these guidelines, but it differs from those of the British Hypertension Society in several important ways, thereby leading to confusion and potentially suboptimal management of hypertension. However, if both sets of guidelines improve the control of blood pressure the differences between guidelines will become less critical.

The NICE recommendation to treat hypertension initially with a thiazide-like diuretic irrespective of age, ethnic group, and whether isolated systolic hypertension is present or not is not supported by best evidence. Small crossover studies and large randomised trial data show differential effects on blood pressure with different antihypertensive agents by ethnic group and age.[4 5 w1] In black patients these differences have been reflected in differential major cardiovascular outcomes by drug class.[w1]

Two large trials inform optimal practice in managing isolated systolic hypertension, so treating isolated systolic hypertension as if both systolic and diastolic blood pressures are raised seems unwise.[w2 3]

Dihydropyridine calcium channel blockers are incorrectly described by NICE as contraindicated in hypertensive patients with heart failure. Although the ALLHAT trial suggests other agents may be preferable for preventing heart failure,[w1] calcium channel blockers are often needed as part of the cocktail of agents used to control blood pressure in heart failure.

The proposals to substitute lifestyle modification for drug treatment in patients with well-controlled hypertension are, on average, likely to worsen wellbeing.

Practitioners should continue to use the ABCD algorithm for drug sequencing because it is simple, easy to remember, flexible, and logical.[3] It facilitates rapid and effective blood pressure lowering, is based on best currently available evidence, and advises how to change drugs without loss of blood pressure control in the 10% of patients yearly whom NICE recognises develop side effects with each drug.

Finally, the web based version of the NICE guidelines needs careful proofreading to correct some of the more obvious errors, such as coronary obstructive airways disease—presumably chronic obstructive airways disease is intended—and to ensure consistency in quoted blood pressure targets and thresholds.

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Additional references w1-w3 are on bmj.com