CORRESPONDENCE

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Monitoring of mortality rates in primary care

Sir—In testing their pilot system for monitoring mortality rates in general practice, Paul Aylin and colleagues (Aug 9, p 485)[1] ran cumulative sum charts on mortality data, relating to the registered patients of 1009 family doctors working in five former Health Authorities in the UK between 1993 and 1999. The false detection rate (FDR)—the proportion of all alarms detected that is false—is presented as a key performance measure of the monitoring system. Aylin and colleagues note that, "An important feature of the false detection rate is that it depends on the true (but unknown) proportion of out-of-control units". Given that the number of family doctors with truly out-of-control mortality rates is unknown, Aylin and co-workers report FDRs that are modelled on the assumption that either 5% or 10% of family doctors' mortality rates are truly out of control.

Although we appreciate that these arbitrary assumptions with respect to the true proportion of out-of-control units have been made for illustrative purposes only, the assumed magnitude of practising family doctors with truly aberrant mortality rates is staggering. Aylin and colleagues offer no justification or evidence for their choice of these assumed true out-of-control proportions.

If 5% of full-time family doctors practising in England in 2002 had out-of-control mortality rates, this proportion would equate to 443 doctors with "truly unacceptable mortality rates".[2] We accept that to dismiss Harold Shipman as a one-off would be complacent, but find it harder to accept that more than 400 doctors in the UK potentially have unacceptable mortality rates.

We suggest that the number of family doctors with excessive mortality rates not accounted for by benign explanations, such as casemix of patients, is small. Consequently, the FDRs reported by Aylin and colleagues are liable to be underestimates, based on unrealistic assumptions with respect to the true underlying prevalence of aberrant mortality rates in primary care.

Given the rarity of doctors behaving as Harold Shipman did, the consequences of introducing a national monitoring system, which could trigger local investigations into the mortality rates of more than 300 doctors across England within each monitoring period, need much greater consideration than alluded to by Aylin and colleagues. Not least among these consequences would be whether primary care trusts would have the capacity and resources to undertake such local investigations and, indeed, whether the public-health and epidemiological expertise needed for such investigations would be better spent strengthening clinical governance and performance management mechanisms to ensure the delivery of high quality, appropriate primary care to patients.

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1 Aylin P, Best N, Bottle A, Marshall C. Following Shipman: a pilot system for monitoring mortality rates in primary care. *Lancet* 2003; **362:** 485–91.
2 Department of Health. Statistical bulletin 2003/03: statistics for general medical practitioners 1992–2002. London: Department of Health, 2003.

Sir—Paul Aylin and colleagues[1] have explored well the use of statistical process control (SPC) methods in the surveillance of mortality rates in primary care. We believe they have shown, but not stated, a basic weakness of using a fixed set of statistical rules to address a complex, adaptive problem.

Assume that family doctor A is identified as out of control with SPC. However, after careful consideration of all available information, including further detail of casemix, mortality of patients linked to doctor A is judged non-suspect. What do we do with the extra information from this verdict? By convention, we might reset the running total of a cumulative SPC chart for doctor A to zero to allow them to make a fresh start, or to some head-start value that puts doctor A on probation, so to speak. Such action does not, however, incorporate the newly found explanatory information into the prediction system for doctor A, it just resets a counter, therefore further false alarms that involve that particular doctor are likely. The workload involved with false alarms could consume a lot of resources and force down the sensitivity of surveillance due to the raising of trigger thresholds or the tendency to re-classify doctor A as non-suspect. Another potential loss of information from the examination of alarms arises if the overdispersion allowance for the unknown variation due to unmeasured explanatory factors is not reassessed. If the surveillance system had more power to detect unusual patterns over time (or other dimensions) linked to individuals or groups, then the potential loss of sensitivity by allowing for artificially generic overdispersion is reduced.

We believe the sensitivity and specificity of the alarm system could be improved through the application of machine or statistical learning techniques.[2] For example, methods such as cluster analysis, novelty detection, and independent component analysis might be used to identify family doctors with mortality rates that are exceptionally high with respect to other family doctors of a similar class (defined, for example, by casemix pattern derived from demographic data and hospital episode statistics) and to previously considered rates for those doctors. The perceived probability that a particular doctor's patients' mortality is suspect could then be incorporated into the detection system, for example by using Bayesian probability. There are various ways that SPC could be combined with such a system.

We appreciate that further statistical development of SPC could address some of the problems we have raised. Such developments would result in more precise selection of thresholds, and thus greater predictive power at the population level. There is perhaps more to gain from research into realistically complex methods to improve predictive values at the individual or unit level than from further refinement of SPC.

We suggest that cross-discipline research into machine learning,

especially unsupervised learning methods for clinical quality surveillance, for and beyond the simple case of all-cause mortality, is needed.

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1 Aylin P, Best N, Bottle A, Marshall C. Following Shipman: a pilot system for monitoring mortality rates in primary care. *Lancet* 2003; **362:** 485–91.
2 Hastie T, Tibshirani R, Friedman J. The elements of statistical learning. New York: Springer, 2001.

Authors' reply

Sir—Julie Billet and Nicholas Kendall question our choice of FDRs modelled on the assumption that either 5% or 10% of units are truly out of control. We point out in our report that these rates are for illustrative purposes only, and are parameters that help to inform the choice of alarm threshold. We also emphasise that we are referring to the proportion of units that are statistically out of control—ie, statistical true alarms. Follow-up investigation could reveal a valid explanation for many such units, in which case their signals could be seen as medical false alarms. Our aim is not only to detect illegal behaviour (such as Shipman's true medical alarm) but to uncover explanations for other extreme patterns of mortality to provide useful feedback towards improving overall quality of care.

We set out to develop a transparent and fairly straightforward monitoring system that could be used for a first-pass analysis of routine mortality data. The question of how best to adjust a control chart once a unit has signalled remains open. Further casemix information on all or a subset of units could be incorporated into the system as and when such information becomes available to reduce the number of false alarms. Iain Buchan, Stephen Marsland, and Paul Beatty suggest that machine or statistical learning techniques might improve the sensitivity and specificity of the alarm system. We agree that this area merits further investigation.

We also agree with Billet and Kendall that introduction of a national monitoring system, which could trigger local investigations into large numbers of family doctors across England, has implications for resources. However, there are various steps that could be taken before an intensive case-by-case investigation is initiated. Data quality and organisational factors, such as nursing homes in the area and other information about practice casemix, are obvious factors that should be examined first. Alarms could also be used to intelligently direct audit that is already being undertaken, currently on a random basis. We feel that this system would serve to strengthen clinical governance and performance management mechanisms.

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Importance of medicine-related problems as risk factors

Sir—Majid Ezzati and colleagues (July 26, p 271)[1] have done a great analysis on some of the risk factors that contribute to burden of disease. In May, 2003, WHO published Surveillance of Risks Factors (SuRF) related to non-communicable diseases,[2] a booklet and a CD-ROM, in which are presented prevalence data on non-communicable disease risk factors from WHO member states. WHO states that the risk factors covered are "those that make the greatest contribution to mortality and morbidity from chronic diseases". The organisation focuses its report on tobacco and alcohol use, patterns of physical inactivity, low fruit or vegetable intake, obesity, blood pressure, cholesterol, and diabetes; Ezzati and colleagues focus on 20 other risk factors.

In neither the article nor the WHO publication are medicine-related problems mentioned[3]—ie, negative clinical outcomes resulting from the use (or lack of use) of medicines—despite the fact that such problems fit the three conditions for inclusion as risk factors noted in the SuRF report—namely, they contribute to mortality and morbidity; can be affected by primary interventions; and can easily be measured in populations.

The potential danger of medicines is an important issue, on which much has been published. Most developed countries have implemented pharmacosurveillance systems to detect adverse events that arise at a population level, though drug ineffectiveness receives little attention despite being a greater contributor to burden of disease. These factors should be included in risk analyses so that interventions to prevent their occurrence are sought.

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1 Ezzati M, Vander Hoorn S, Rodgers A, Lopez AD, Mathers CD, Murray CJL. Estimates of global and regional potential health gains from reducing multiple major risk factors. *Lancet* 2003; **362:** 271–80.
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The euthanasia law in Belgium and the Netherlands

Sir—On April 10, 2001, the Dutch parliament legalised euthanasia and assisted suicide,[1] and on May 16, 2002, the Belgian parliament approved a law on euthanasia.[2] Whereas in the Netherlands euthanasia and physician assisted suicide are regulated as two possible end-of-life options, in Belgium the law only regulates euthanasia. In both countries the patient involved in such decisions must be an adult and mentally competent at the time of requesting help. Only the law in Holland contains special provisions for dealing with requests from individuals aged 12 to 18 years.

Both laws define euthanasia as the act, undertaken by a third party, which intentionally ends the life of a person at his or her request, and in both countries euthanasia can only be effected by a doctor. Furthermore, both laws accept the evidence that euthanasia is an important medical practice.[3] The main aim is to bring these practices into the open, to apply uniform criteria for the assessment of each new case in which a doctor terminates life, and hence to ensure that maximum care is guaranteed in such instances. The decision to end someone's life on request is fixed within the patient-doctor relationship, and societal control has been established within a review procedure after death. A doctor can only proceed when they know the patient well enough to be able to assess whether their request for euthanasia is voluntary and well-considered,

whether the patient's medical situation is without prospect of improvement, and whether the individual's suffering is unbearable. The ability to refuse a request for euthanasia guarantees a doctor's freedom of conscience in both countries.

The public debate on euthanasia in the Netherlands began in the 1970s, and since 1984/1985, when undertaken by a doctor who has complied with the due care criteria, the act has been legalised.[4] In Belgium, however, the euthanasia law was voted in after only 3 years of debate in parliament and by the Federal Advisory Committee on Bioethics. Furthermore, by contrast with the situation in the Netherlands, no medical association supported the process in Belgium.[5]

In both countries, any patient who requests euthanasia has to be well informed about their situation—namely, their diagnosis, outlook, and treatment options. Before the attending doctor can comply with a request for euthanasia, they must first consult a colleague who is not connected with them or with their patient's treatment. Unlike in the Netherlands, in Belgium a second doctor must be consulted if the patient is unlikely to die naturally within a short period—ie, a procedure exists for non-terminally ill patients.

Euthanasia is legal only in the Netherlands and Belgium. We believe that robust empirical research should be done to assess the end-of-life care consequences of legalising euthanasia in these two countries.

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Addiction myths?

Sir—Mike Fitzpatrick (Aug 2, p 412)[1] seems to be quite a liberal chap. Unlike many family doctors, he does at least talk and listen to heroin addicts, so it is depressing that he displays so much "pull-your-socks-up" prejudice about their withdrawal symptoms. Because he has met patients who managed to stop using heroin without treatment and with only mild withdrawal symptoms, he believes that "this . . . confirms that 'cold turkey' is a myth" and that "perhaps breaking these bad habits is not as difficult as it is made out to be?" If giving up drugs is so easy, why is the completion rate for in-patient detoxification only 27% at one UK National Health Service (NHS) centre of excellence and commonly 50% or less elsewhere?[2] However, I write not to explain how these dismal figures can be easily improved, but out of concern that Fitzpatrick's evidence-free assertions will give even more doctors an excuse to ignore the real difficulties that some addicts experience.

Many alcohol abusers have minor withdrawal symptoms or none. Moderately severe withdrawal can often be easily managed at home, but a minority experience delirium tremens or convulsions, or both. Does Fitzpatrick think these too are mythical (or perhaps hysterical)? Similarly, only a minority of heroin addicts experience the worst manifestations of opiate withdrawal, but severe diarrhoea, colic and arthralgia, vomiting, suicidal depression, anxiety, and total insomnia are not myths either. Furthermore, unlike alcohol withdrawal, many components of the opiate abstinence syndrome often persist in lesser but still cumulatively demoralising forms for months afterwards.[3] That is one reason why relapse is so common.

Of course, psychosocial and personality factors are important in addiction, as in most conditions. Many heroin addicts, treated or not, mature out of their addiction in their thirties, just as adolescents often mature out of juvenile delinquency, but addicts can only mature-out if they stay alive. Far too many die needlessly from lack of basic treatment, among which opiate maintenance programmes are the most important. I suspect attitudes like Fitzpatrick's have helped to give Britain probably Europe's worst methadone programmes. The average maintenance dose is 52 mg daily[4] when the government's own guidelines advise that 60 mg should usually be the minimum and that 120 mg should be unexceptional. Results of clinical and pharmacokinetic studies[5] suggest that even these doses are too low. Averages of 285 mg per day can improve outcomes, and doses of more than 1000 mg are sometimes needed.

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Sir—To marshal some casually acquired anecdote and deploy it in support of an argument against one's pet annoyances is all too simple. Mike Fitzpatrick's Dissecting room piece[1] was a case in point, although one in which assertion stood in for the construction of even a rudimentary argument.

Although we share with Fitzpatrick a certain critical stance toward the addiction industry and the moves to bring everything from sex to shopping within its remit, we base our critique on reason and research, and on 20 years of personal experience of heroin use.

Fitzpatrick is convinced a priori that he is right, and therefore feels able to dispense with the tedious details of empirical methodology. Perhaps this tactic derives from some radical epistemology with which he plans to regale us in a further exposition, or perhaps it demonstrates the familiar tendency to locate items of anecdotal flotsam that reinforce one's prejudices.

Certainly, opiate withdrawal comprises psychosocial components that affect and can modify the ways in which different individuals cope. But the withdrawal syndrome is not a myth, at least in anything like the sense in which Fizpatrick would have us believe. Rather, it is a complex set of pharmacological, physiological, and neurological events grounded in the objective world.

The notion that opiate addiction is

just a bad habit, which can be discarded if only one has enough will-power is, moreover, hardly a novel one. Such a stance was adopted at the inception of prohibition by the federal law-enforcement authorities in the USA—with a legacy both tragic and enduring. Such a position is also taken up by the American antipsychiatrist Thomas Szasz,[2,3] in whose writings it has, at least, the virtue of being argued rather than simply stated as a truth. The argument depends, however, on Szasz's political and philosophical commitment to a model of individuality abstracted from the world of material, biological, and social interdependencies in which we all live.

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Oral contraceptive and smoking mortality

Sir—Between 1968 and 2003, Martin Vessey and colleagues (July 19, p 185)[1] noted no increase in mortality from any cause, except cervical cancer, in women who used oral contraceptives between the ages of 25 and 74 years. The most common cause of death among the study population was breast cancer.

Results of other studies[2] indicate that use of combined oral contraceptives can double the risk of breast cancer in young women, especially when users are compared with carefully confirmed never-users of hormones. Furthermore, the findings of the Million Women Study[3] show that women on hormone-replacement therapy (HRT) have increased mortality from breast cancer and those taking progestagen/oestrogen combinations have double the risk of breast cancer compared with those who are not taking HRT.[3] How can these contradictory results be explained?

We believe that Vessey and colleagues underestimated mortality associated with hormone use, and that the comparison in their study between smoking mortality and hormone-related mortality is misleading for two reasons.

First, there are problems with the reference groups. Numbers for never-takers of hormones and never-smokers are not provided. Also, whereas no one would categorise menopausal smokers as never-smokers, individuals classed as never-takers of oral contraceptives are not necessarily never-users of HRT. Most deaths recorded were of women older than age 45 years. How many of the 83 women who never used oral contraceptives and died of breast cancer had, therefore, taken HRT? Combined oral contraceptives and combined HRT contain progestagens and oestrogens, and have the same effect on the body; progestagens are breast carcinogens because of how they act, not because of the reason they are prescribed.

Duration and type of HRT are not detailed, except for the mention that, compared with never-users of oral contraceptives, slightly more longer users (for 8 years or more) were also longer users of HRT (for 2 years or more). If more never-users of oral contraceptives took progestagen HRT, and more users of oral contraceptives took oestrogen-only HRT (which has less risk of breast cancer[3]), a falsely negative breast-cancer risk would be obtained.

Considering HRT as a separate entity can also obscure long-term morbidity and later mortality from earlier use of oral contraceptives; short first-time hormone use could be particularly risky for intolerant women at whatever age it occurs.

Second, the numbers of deaths associated with smoking for up to 48 months, 96 months, or longer, were not compared with the numbers of deaths related to use of oral contraceptives alone for the same periods, including the first 5 months. Such information is needed to make valid comparisons. Rises in breast-cancer incidence in developed countries match increases in hormone use, despite fairly short overall exposures.[4] For example, the results of two collaborative reanalyses showed that breast-cancer risk increased with contraceptive and menopausal hormone use for an average of only 3 and 2 years, respectively. Conversely, 93% (50 of 54) of deaths from lung cancer were in older current smokers, suggesting that decades of smoking are needed before risk is raised.

Vessey and colleagues describe the higher frequency of deaths from uterine sarcomas than from endometrial cancer as unexpected. However, many individuals with breast cancer enrolled in the study would have been taking tamoxifen, which is linked to increases in uterine carcinosarcomas.[5]

Though probably more socially convenient to believe that smoking is more lethal than taking oral contraceptives, this study does not prove this pattern.

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1 Vessey M, Painter R, Yeates D. Mortality in relation to oral contraceptive use and cigarette smoking. *Lancet* 2003; **362:** 185–91.
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Authors' reply

Sir—Ellen Grant and colleagues make several criticisms of our report, based largely on misinterpretation of our analysis and results.

Our findings with respect to breast-cancer mortality are described as contradictory, which is incorrect. First, there was little use of oral contraceptives before first pregnancy among women in the Oxford-FPA study,[1] which makes reference to the study by Hemminki and colleagues largely irrelevant. Second, although tempting, oral contraceptive use should not be equated with use of HRT. The findings in the Million Women Study should not be extrapolated to the Oxford-FPA study. The gold standard reference for the effects of oral contraceptive use on breast cancer continues to be the Collaborative Group report,[2] which summarises the results of 54 epidemiological studies worldwide. This report relates to similar kinds of women, similar patterns of pill use, and similar types of oral contraceptive to those represented in the Oxford-FPA study. In the report,[2] the risk of a diagnosis of breast cancer was shown to be increased by 24% in current oral contraceptive users compared with never-users, with risk declining steadily after discontinuation of use.

This finding is statistically compatible with our results, as discussed in our report.

Grant and colleagues also mention "problems with the reference groups". We disagree. In our analyses of the effects of oral contraceptive use on mortality, we allowed for the effect of smoking and many other factors, using a well established and valid method. There was only a modest association between smoking and oral contraceptive use in our study anyway, with pill users being somewhat more likely to smoke than non-users. Our information on HRT use is incomplete, but we showed in our report that such use was slightly greater among oral contraceptive users than non-users. Both these weak associations—ie, between pill use and smoking, and pill use and HRT use—would tend to show mortality in oral contraceptive users in an unfavourable light rather than the reverse as Grant and colleagues seem to believe.

Grant and colleagues think we should compare the effects of smoking for given periods of time with the effects of oral contraceptive use for the same periods. We again disagree. Our comparisons are valid since oral contraceptive use usually extends over a moderate number of years, while smoking, sadly, often extends over a lifetime. We considered the effects of oral contraceptive use and of smoking in the way the two exposures arise in the community.

Finally, none of the women in our study who died from endometrial cancer or uterine sarcoma had breast cancer, so the comments about use of tamoxifen are irrelevant.

Our results offer reassurance about the effects of oral contraceptive use on mortality, both in the short term and in the long term. They refer, however, mainly to oral contraceptives used in the 1970s and 1980s, and further information is needed about more modern preparations.

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Genetic influence of hormone-replacement therapy on venous thromboembolism

Sir—Pierre-Yves Scarabin and colleagues' findings (Aug 9, p 428)[1] indicate that oral but not transdermal oestrogen-replacement therapy is associated with risk of venous thromboembolism (VTE) in postmenopausal women.

Among many risk factors for hypercoagulability—eg, malignant disease, immobility, smoking, obesity, diabetes, advanced age, heart failure—genetic variations in certain genes could explain the interaction between oestrogens and VTE risk. Mutations in coagulation factor II (prothrombin G20210A) and in coagulation factor V (Factor V Leiden) are, for example, associated with raised risk of venous thrombosis.[2]

Vandenbroucke and colleagues[3] noted that premenopausal women who took oral contraceptives and who were carriers of the factor V Leiden mutation had a raised risk of deep vein thrombosis, and Psaty and co-workers' results[4] indicate an association between hormone-replacement therapy (HRT), prothrombotic mutations, hypertension, and risk of incident non-fatal myocardial infarction in postmenopausal women. In view of these findings, we believe the interaction between transdermal HRT, genetic variants, and VTE should be investigated in postmenopausal women.

With respect to the effects of oral and transdermal HRT on haemostatic factors in postmenopausal women, Scarabin and co-workers[5] have reported that oral HRT can result in coagulation activation and increased fibrinolytic potential, whereas transdermal HRT does not seem to substantially affect haemostasis. Thus, we propose that there might not be an interaction between transdermal HRT, genetic variants, and VTE in postmenopausal women, since there is no association between VTE risk and use of transdermal oestrogen.[1]

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Edmonton's islet success has indeed been replicated elsewhere

Sir—As co-principal investigators of the Immune Tolerance Network multicentre clinical trial of the Edmonton Protocol, we wish to clarify the importance of the preliminary analysis.[1]

A 90% insulin-free rate was noted in three centres with long-standing expertise in islet preparation and in the clinical use of this immunosuppressant protocol, not only at the Edmonton site where the protocol originated. The average rate of insulin independence among the remaining six clinical sites was 23%, including one site with an interim success rate of 67%.

Thus, the Edmonton Protocol has been replicated at other clinical sites and, in some cases, with a high degree of success.

Although these data are only preliminary, we view this result as a positive one, which confirms the great benefits to patients of islet transplantation and provides additional justification for the continued investigation of islet transplantation as a treatment for brittle forms of type 1 diabetes.

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1 Ault A. Edmonton's islet success tough to duplicate elsewhere. *Lancet* 2003; **361:** 2054.

Singular loyalties

Sir—Jerome A Singh (Aug 16, p 573)[1] argues that the treatment of prisoners at Guantanamo Bay by US forces is cruel, inhuman, or degrading, and contrary to the Tokyo Declaration. If he had not included "or degrading", his piece would be bemusing.

The Tokyo Declaration he mentions is not referenced, but I assume it is not one of the many Tokyo Declarations on Development, Information, Economics, the International Year of the Mountains, Global Renku, Work-related Stress, Higher Education, Health Environment and Culture, etc. I suspect he is referring to the Tokyo Declaration of the International Solidarity Forum,[2] professing to follow the Cairo Declaration to strengthen the international struggle against war and imperialism.

Singh's first problem seems to be semantic rather than substantive, and he even insinuates such treatment of prisoners might be forbidden by the Convention on Torture. Perhaps he should talk to some Iraqis to get a proper definition of the word torture. Most likely they would feel that Guantanamo treatment, being placed in a corner like a naughty child, would not fit the bill. Granted, being treated like a naughty child for months or years could be wearing and certainly is degrading, but, after all, it is a prison.

US military doctors in both Gulf wars treated Iraqi wounded just as well as their own, and they treat the prisoners satisfactorily too. Saddam Hussein's physicians were called on to undertake punitive amputations. Singh's admonishments seem oddly misplaced.

Then, there are the military tribunals he decries—undertaken under the same rules as apply to our own military personnel brought up on charges, with the exception of extra surveillance; surely appropriate?

Finally, "in bypassing the authority of the UN on the issue of invading Iraq, the US government displayed an isolationist, unilateral mentality", and rid the world of a horror whose dimensions are only now becoming clear. The non-isolationist multilateral mentality would have left it in place to re-arm and continue its Caligula-like activities. What moral courage. Not only does he not want to confront evil, he does not want anyone else to do so either. Singh might deride this "so-called war on terror", but if he is not lucky he might learn the hard way that we are all in this war together. War has been declared on us, and not just on the USA.

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Control of tuberculosis in India

Sir—In his Medicine and health policy piece, Haroon Ashraf (July 19, p 218)[1] comments on the possibly emerging tuberculosis/HIV crisis in India.

The Revised National Tuberculosis Programme (RNTCP) was launched in India nearly 10 years ago. Sadly, it does not enrol patients who have no proof of residence, so excludes all those individuals who need treatment but live in slums, on pavements, or who have no fixed address. The most successful centres, which provide the WHO's DOTS (directly observed therapy short-course) treatment strategy, exclude the highest proportion of people.[2]

Furthermore, India's RNTCP does not include treatment protocols for multidrug resistant (MDR) tuberculosis, despite the fact that 60% of all specimens sent to a particular mycobacterium laboratory in Mumbai in 1996 contained the MDR strain.[3]

Results of a survey[4] undertaken in 35 countries, including India, indicate that MDR tuberculosis is the major constraint to tuberculosis control. Non-inclusion of a treatment protocol for MDR in the DOTS programme will eventually lead to the overpowering of the sensitive strains with the MDR strain.

The frequency of co-infection with HIV-1 and tuberculosis and of infection with MDR strains of the bacterium is rising in India. If we do not make every effort to contain MDR tuberculosis, we could eventually reach a point at which even DOTS-plus, will be of limited effectiveness.[5]

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Smoking, iron, and tuberculosis

Sir—Vendhan Gajalakshmi and colleagues (Aug 16, p 507)[1] present important epidemiological data. However, they do not address the pathophysiological mechanisms by which smoking might increase the incidence of tuberculosis in smokers in India. We propose that iron loading in the bronchoalveolar macrophages, secondary to tobacco smoking, promotes the growth of *Mycobacterium tuberculosis*, resulting in severe clinical disease and eventually death.

Bronchoalveolar macrophages, the primary residence of *M tuberculosis*, have a two-fold and an almost five-fold to seven-fold higher iron content in asymptomatic and symptomatic smokers, respectively, than in non-smokers.[2] This higher iron content in bronchoalveolar macrophages of smokers could be related to the high iron content of tobacco—ie, someone who smokes one packet of cigarettes per day inhales 1·12 μg of iron.[2]

In-vitro and in-vivo iron loading of macrophages results in an impaired host defence toward several intracellular microorganisms for various reasons, including a decreased synthesis of tumour necrosis factor α and nitric oxide, both of which are effector molecules important in containing the intracellular growth of *M tuberculosis*.[3]

This finding accords with the results of two studies, which indicate an association between iron overload in Africans and tuberculosis. In the first study,[4] the concentration of iron in the spleens of 604 black adults from southern Africa was measured semiquantitatively and iron grades 1–5 were assigned. Splenic iron, mainly in macrophages, was the variable most associated with death

from tuberculosis. The odds of death from tuberculosis in individuals with grade 5 iron concentrations were 16·9 times the odds in those with grades 1 and 2. The second study[5] was a prospective trial, assessing the possible relation between pulmonary tuberculosis and increased dietary iron. The investigators compared 98 patients with pulmonary tuberculosis with 98 matched controls in rural Zimbabwe. Lifetime consumption of traditional beer brewed in non-galvanised steel containers was used as an indicator of exposure to increased dietary iron. Logistic regression modelling indicated that, after adjustment for HIV status and liver function, increased dietary iron was associated with an almost four-fold increase in the estimated odds of developing pulmonary tuberculosis and a non-significant trend toward higher mortality in the patients with pulmonary tuberculosis exposed to high concentrations of dietary iron.

The results of these two studies indicate, in accord with our hypothesis, that iron acquisition promotes the growth of *M tuberculosis* and that clinical situations, resulting in iron loading in the reticuloendothelial system—eg, tobacco smoking that increases the iron content of bronchoalveolar macrophages—increase the risk and could worsen the outcome of tuberculosis.

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Alterations to STICH protocol

Sir—Protocol 99PRT/7 International STICH (Surgical Trial in Intracerebral Haemorrhage) on *The Lancet* website[1] has changed. It now includes a detailed description of how the primary outcome will be analysed. Data collection for the study should be complete by October 17, 2003. The database will be unblinded and analysis will start shortly after. Results from the study will be available in early 2004.

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The human thermostat

Sir—The body temperature of healthy individuals is constant, whereas pyrexia is a cardinal sign of illness. A study of normal body temperature reveals that life is suspended on a cooling curve.

Since its formation, earth has been cooling down. Aeons ago the earth's crust solidified from the molten state. When the surface temperature fell below the boiling point of water, the primeval ocean was created out of clouds of steam. As the planet continued to cool, life was born within a very narrow temperature range.

In evolutionary terms, one might anticipate that the ideal body temperature would be halfway between boiling and freezing. Instead, the human thermostat is set at 37°C. This temperature setting can be predicted from Isaac Newton's Law of Cooling. When water cools, its temperature falls along Newton's exponential curve. The mid point of an exponential curve is given by 1/e, not 1/2; e is the universal constant, and its value is given by the equation (where x=1):

$$e=1+x/1!+x^2/2!+x^3/3!+[\ldots]+x^n/n!$$

The value of 1/e on a temperature scale is 37°C or 98·4°F, precisely that chosen by nature.

In practice, there is a small diurnal variation in body temperature, ranging from 36·1°C in the morning to 37·2°C in the evening, the average being slightly below 37°C. When 1/e is calculated to several decimal places it also falls marginally below 37°C.

This optimisation of a physical principle by the human body is an elegant example of mathematical design in nature.

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DEPARTMENT OF ERROR

Norvig P. PowerPoint: shot with its own bullets. Lancet *2003:* ***362:*** *341–42*—In this Commentary (Aug 2), the figure should have appeared as below.