Letters

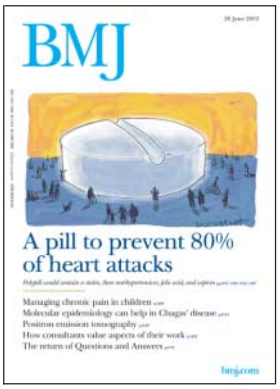
"Polypill" to fight cardiovascular disease

Patients before populations

EDITOR—Wald and Law's provocative paper and the accompanying editorial on the "Polypill" was disappointing in focusing only on the advantage to the population and ignoring the individual's views of the benefit he or she would wish to see from taking preventive drugs.[1 2]

The median threshold of absolute risk reduction below which patients would not wish to take a preventive drug may be as high as 30% over five years. This is far higher than the benefit of the Polypill, which offers a meagre 7% reduction over 10 years if started at age 55.[3] We and others found this benefit would be acceptable to only one in 10 healthy people.[3] If only one in 10 take the Polypill the effect on the population will be negligible.

It all comes down to accurate numerical presentation and framing of the benefits of drugs to patients. As the patient's treatment broker, doctors are duty bound to inform their healthy 55 year old patient that if he or she takes the Polypill for the next 10 years the chance of benefit will be less than 1% per year and that of side effects 6% overall, some of which (such as aspirin related gastrointestinal haemorrhage) may be life threatening.[1]



Furthermore, if the Polypill is successful their patient's chance of dying from cancer, trauma, and degenerative brain disease will increase with the effectiveness of the Polypill, as even with Polypill treatment, mortality will remain stubbornly 100%.

Some patients will do anything to prevent a heart attack or stroke. Some will take any treatment if their doctor recommends it. In the modern health service, whose focus is increasingly on health promotion rather than treating disease, doctors need to be numerically well informed and to be able to present data on drug effectiveness which are relevant to their patient as a person.

Journal editors have a tremendous responsibility to support doctors in this task by insisting that authors emphasise figures denoting the reduction in absolute risk. Given these figures for the Polypill, most doctors and patients will be considerably less enthusiastic than the authors of this paper and editorial.

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Competing interests: None declared.

1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)
2 Rodgers A. A cure for cardiovascular disease. *BMJ* 2003;326:1407-8. (28 June.)
3 Trewby PN, Reddy AV, Trewby CS, Ashton VJ, Brennan G, Inglis J. Are preventive drugs preventive enough? A study of patients' expectation of benefit from preventive drugs. *Clin Med* 2002;2:527-33.

Now who's playing God?

EDITOR—The implications of Wald and Law's paper are truly monumental.[1] Although they are scientifically brilliant and Nobelian in their relevance, they are simultaneously unsettling and alarming.

The impact of such a low cost initiative on individual and population based health parameters is potentially enormous. But having, at a stroke (to coin a phrase), slashed the risk of cardiovascular disease—what then for humanity? Will everyone be that much healthier, happier, and productive in his or her life?

As general practitioners, we have many patients nowadays whose cardiovascular problems have been managed by controlling their blood pressure, reducing their low density lipoprotein cholesterol concentration, and taking aspirin. Yet they continue to get older and develop other problems—often of a serious, debilitating, and long term nature.

Having "lost" the cardiovascular market to the low cost generic "Polypill," pharmaceutical companies will surely then concentrate their efforts on other avenues. So is it only a matter of time before Polypill mark two is suggested? Perhaps containing glucosamine and chondroiton, a COX-2 inhibitor, a proton pump inhibitor, a calcium homoeostatic agent, a memory enhancing agent, and others? And, for this part of the world, something to prevent the total failure of the skin induced by exposure to ultraviolet rays? How long will it before the Polypill becomes a part of veterinary science?

We are all still mortal, and perhaps this is the most important message for clinicians to remember. Which is more important: quality or quantity of life? How do we achieve a balance? Because it's not science that poses the hardest questions: it's the ethics and morality of what we are doing.

Doctors used to be accused of playing God, although for a generation or more society has done its reasonable best to knock that out of us. But, perhaps its time has come again?

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Competing interests: None declared.

1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)

Universal polypharmacy goes against recent beliefs in prescribing practice

EDITOR—Your advocacy of universal polypharmacy—as evidenced by the paper by Wald and Law[1]—is somewhat against recent beliefs in prescribing practice. Has there been sufficient emphasis on the fact that the proposal is a theoretical construct (admittedly enticing), based on extrapolation of data from many disparate studies, rather than on a trial itself? Indeed, why bother with new trials if one can find such apparently definitive answers so conveniently from existing data?

Apart from immediate practical considerations—such as a reliable source and supply system—little thought seems to have been given, among other matters, to:

- Potential adverse events (particularly in certain population groups, such as those with asthma or allergies)
- Duration of benefit and possible implications on further treatment should it be required
- The effects on those unable to tolerate such a Polypill or on the 20% who would not benefit, and how to identify them
- Adverse lifestyle behavioural changes that might occur were it to be perceived that a universal cardiovascular panacea might be available to pick up the pieces of adverse lifestyle choices
- Alternative causes of death, which may substantially reduce any putative gains.

This is a worthy idea, meriting future debate and research, but I fear that it will meet the fate of many such papers in the public and media viewpoints—namely, that publication in a reputable scientific or medical journal is the end point of research and a finished piece of wisdom, rather than the start of a process of refutation or affirmation that might, at some future date, lead to an acceptable truth (if such there is). I wonder how many doctors were asked for the magic heart pill on the day after this paper was published.

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Competing interests: MP has worked for medical journals that received money for advertisements for pharmaceutical advertisements.

1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)

Old joke has element of truth

Editor—There has always been an element of truth in the old and slightly cynical description of "Gerifix" and "Gerifix Forte"—the common collection of drugs that many elderly patients find themselves taking in and after hospital. Outside hospitals, in the effort to achieve reductions in premature or avoidable cardiovascular death and disability, many people are actually taking all or most of the components of the "Polypill,"[1] and we as doctors have reasonable grounds to believe in a mass benefit from doing so.

Incredulous senior house officers may yet hear of all these things and may also learn that meta-analysis is commonly more reliable than inspecting the results of a single trial, particularly if its power is low.

Wald and Law have produced a good paper.[1] There are a lot more bits of wisdom camouflaged as cynicism in the profession, and subjecting these "folk stories" to scientific analysis is at least entertaining.

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1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)

Birthday present was much appreciated

Editor—As a citizen of one of the "developing countries" quoted by Wald and Law,[1] I enjoy the free access to bmj.com, but I was amazed at the "collector's issue" of 28 June, published on my 55th birthday.[2]

I wonder whether the Editor's choice commentary is a product of astonished admiration, faithful friendship, or a critical view.[2] This renewed tailored recipe, like that of the old eminent doctors, is now the new paradigm of epidemiological and trial based science: no more costly evaluations, risk stratifications, control visits. We don't even need doctors or to treat patients: we'll treat populations. Let's begin with developing countries, and after that treat them all. The next step will be delivering "Polypills" to babies in their bottles.

The basis of Wald and Law's outstanding paper is an incredible intellectual achievement because the authors quote themselves 14 times in the references, and no doubt remains that they are worthy of owning the patent for the Polypill.

Medicine is and should remain a patient based practice. Strategies that forget the essence of the doctor's job are forgettable, and good ideas such as combination treatments deserve encouragement and to be implemented in clinical practice; Wald and Law's proposal smells only to profitable business.

Anyway, I enjoyed reading the responses to this article instead of beginning my Polypill treatment on my birthday. I eagerly wait the next magic bullet of "007BMJ." This might be—and why not?—the final solution to all human health problems.

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Competing interests: None declared.

1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)
2 Smith R. The most important *BMJ* for 50 years? *BMJ* 2003;326:0. (Editor's choice.) (28 June.)

Interpretation of trial data is optimistic

Editor—Rarely has the demand for empirical evidence of treatment benefit been as necessary as in the prevention of cardiovascular disease. Wald and Law doubt this approach, saying that a "Polypill" containing six drugs would reduce events of ischaemic heart disease by 88% and stroke by 80% and might therefore be given with impunity to everyone aged 55 and older and to everyone with existing cardiovascular disease.[1]

They think that this might have a greater impact on the prevention of disease in the Western world than any other single intervention.

That's impressive.

But a note of caution.

Treatment effects are determined in randomised controlled clinical trials, taking non-compliance and the range of dose responses into account. You cannot extrapolate the result that would be expected with 100% compliance, counting only those with a maximum reduction in risk factors. Thus the expected 61% reduction in events of ischaemic heart disease from cholesterol lowering by using statins is about twice that yet seen in any trial.

Equally, blood pressure lowering trials reduced the risk of ischaemic heart disease by about 20%, not 46%. Trial evidence for antithrombotic treatment is weaker and does not exist for folate. Trial data on the Polypill are, of course, lacking.

How nice it would be to live in a Polypill world. One for heart disease, one for mood, and maybe even one for finding the right partner. In reality, however, we must deal with each problem in turn, often accepting a less than perfect result. There are no quick fixes, in life or in medicine, and lowering cardiovascular risk is no exception.

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1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)

Cost effectiveness of statins for primary prevention of cardiovascular events is questionable

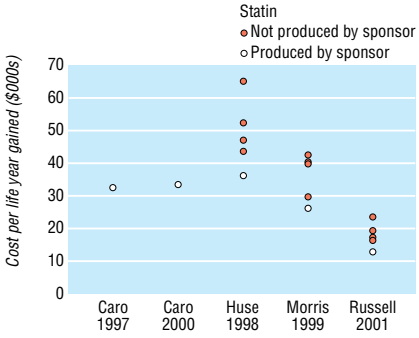
Editor—The presence of a statin in the "Polypill" implies a favourable cost effectiveness of the anticholesterol agent for primary prevention.[1 2] Medline reports 18 original studies (from 1995 to June 2003) evaluating the cost effectiveness of statins for this indication (8 independent, 10 sponsored[3]).

In the eight independent reports, the interstudy variations in the cost per life year gained are extremely wide ($C7700 to $US420 000 in men), which shows a profound uncertainty in the convenience of this indication of statins.

On the other hand, the 10 sponsored reports raise the question of whether the sponsor has any influence on the study. The results of these 10 papers are always in favour of the statin produced by the sponsor (10/10; 100%; P = 0.00098 by Signs test).

The figure summarises five studies; the other five (not presented in the figure because their results are not costs per life year gained) indicate an identical pattern, favouring the sponsor's statin. This impressive 100% rate implies that all of these 10 studies are biased by the presence of the sponsor.

One explanation is that the high level of uncertainty in the pharmacoeconomic indices (as shown by the "independent" costs per life year gained) generates a context where the sponsored studies can be guided towards the desired result. Another drawback is that the research question of eight out of 10 studies did not address the point of



Cost effectiveness of statins for primary prevention of cardiovascular events *v* no treatment in five studies sponsored by pharmaceutical companies.[3] Euros, Canadian dollars, and pounds were converted to dollars using rates as at 18 July 2003

contrasting statins compared with no statins (the most relevant one from a scientific viewpoint) but considered only comparisons of one statin with another (which is a much less interesting question).[3]

Regardless of clinical effectiveness, our data provide a negative picture on the scientific value of the pharmacoeconomic research on primary prevention with statins. Rigorous data on cost effectiveness are still needed before one can propose an indiscriminate use of statins in people aged 55 years or older.[1 2]

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1 Rodgers A. A cure for cardiovascular disease? *BMJ* 2003;326:1407-8. (28 June.)
2 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)
3 Messori A, Santarlasci B, Trippoli S, Vaiani M. Questionable cost-effectiveness of statins for primary prevention of cardiovascular events [electronic response to Wald et al]. bmj.com 2003. bmj.com/cgi/eletters/326/7404/1407#34612; correction bmj.com/cgi/eletters/326/7404/1407#34905 (accessed 31 Aug 2003).

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Summary of rapid responses

EDITOR—There were some enthusiastic champions of the concept, but, overall, respondents remained to be convinced that the "Polypill" issue was indeed a collector's item and a possible contender for the most important *BMJ* paper in 50 years, as the editor had indicated.[1–5] Images of the tooth fairy and April foolery were invoked, along with gasps of horror, astonishment, and incredulity that the hypothesis should be taken for anything approaching rigorous science.

This was proof, if any were needed, that the *BMJ* had finally lost the plot, judged several contributors.

Chief among the concerns was the lack of trial evidence for the effectiveness of the Polypill, or any facsimile, for that matter. Wasn't the assumption that the six constituents would work cumulatively and in perfect synergy a foolish one to make on the basis of results from disparate trials? What about the effects of aspirin on people with asthma and allergies or the potentially serious side effects of each of the ingredients, some readers asked?

The merits of alternative combinations or additional ingredients were debated, and some inspired tongue in cheek varieties were suggested.

Some agreed that the hypothesis was at least worthy of testing, and others approved of the egalitarian stance of an all inclusive approach rather than simply targeting those most at risk. But many questioned the basis for the "spectacular claims." The 61% reduction in ischaemic heart disease using statins is around twice that of any statin trial to date, pointed out some respondents.

Others queried the absolute numbers needed to treat to obtain the population effects proposed by Wald and Law, especially in view of the well known difficulties of long term compliance with any drug. But some of those treating the elderly or diabetic patients suggested that all too often their patients were already taking drug cocktails, and that one combined dose would improve their quality of life and treatment compliance.

"Blunderbuss medicine," roared one reader, while milder responses said that mass prescribing ignores the differences in metabolism and blood rheology between younger and older people to say nothing of the racial and sex differences in responses to β blockers and angiotensin converting enzyme inhibitors.

Several considered the failure to include projected overall mortality data a major flaw in the hypothesis. Slashing rates of heart disease would simply increase the chances of dying from cancer, trauma, and brain disease, thought some. Others ventured that the data from the Framingham heart study on which the hypothesis is based were themselves flawed.

A widely held concern was the way in which a polypill might undermine personal responsibility for wellness and encourage unhealthy lifestyles. A sensible diet, exercise, and not smoking were the way to go; far from reducing the tendency to "medicalise" life, this "quick fix" would actually promote it. Others looked to the longevity of the Japanese, who manage perfectly well without the aid of a polypill.

Several contributors cautioned against the seductiveness of an attractive hypothesis, which might not automatically translate into benefit, citing hormone replacement therapy and beta carotene as examples. Others thought that the hypothesis was too good to be true and, as in the maxim, that probably meant it was.

But a few voices speculated that respondents had missed the point: the intention was to get people thinking, and as one contributor ventured: "This is not a panacea, but with minor changes it might be the face of secondary prevention to come."

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Competing interests: None declared.

1 Electronic responses. The most important *BMJ* for 50 years? bmj.com/cgi/letters/326/7404/0-f (accessed 21 Jul 2003).
2 Electronic responses. A cure for cardiovascular disease? bmj.com/cgi/eletters/326/7404/1407 (accessed 21 Jul 2003).
3 Electronic responses. A strategy to reduce cardiovascular disease by more than 80%. bmj.com/cgi/eletters/326/7404/1419 (accessed 21 Jul 2003).
4 Electronic responses. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. bmj.com/cgi/eletters/326/7404/1423 (accessed 21 Jul 2003).
5 Electronic responses. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. bmj.com/cgi/eletters/326/7404/1427 (accessed 21 Jul 2003).

Authors' reply

EDITOR—Your correspondents overlook the extent of the health gain achievable with the "Polypill" and of the large amount of evidence underpinning our estimates of efficacy and adverse effects.[1]

About one person in three would benefit, and the Polypill would offer many people important extra years of active and useful life, with benefits evident over decades. The adverse effects, on the other hand, would mostly be apparent after a few weeks, in which case a variant of the pill could be substituted—for example, one without aspirin.

Of course, the Polypill is not an alternative to adopting a healthy lifestyle such as not smoking or not becoming overweight: it is a complementary means of prevention. We agree that work on the Polypill needs to continue so that after the necessary clinical trials it can be made available.

Ramos's view, that medicine should remain a patient based practice, is too limited; it would forgo important preventive measures such as vaccination. The motivation in seeking a patent for the Polypill is to help ensure its development and to fund the necessary clinical trials, which will be costly.

The expected 61% reduction in ischaemic heart disease events from statins is not twice that yet seen in any trial, as stated by Assmann et al and highlighted by White as a "spectacular claim." Randomised trials have shown this directly.

In all trials that lowered low density lipoprotein cholesterol by ≥1.5 mmol/l (on average 1.6) (see our table 6[2]) the average reduction in ischaemic heart disease events was 51% after two years of statin treatment. With a 1.8 mmol/l reduction the benefit will be greater, and evidence from cohort studies indicates a 61% reduction. Although individual blood pressure lowering drugs reduce ischaemic heart disease events by about 20%, the reduction will be greater when three drugs are used together in low dosage. Trials show an additive effect on blood pressure lowering (see our figure 3[3]), and the cohort studies show a greater reduction in disease events with greater reduction in blood pressure. Combining these two sets of data quantitatively yields the estimated 46% reduction in risk of ischaemic heart disease events.

The published estimates of cost per year of life saved by using statins summarised by Messori et al are too high for four reasons. The cost of simvastatin can be expected to fall since it has recently come off patent protection. The effect of statins in preventing heart disease has, in the past, been underestimated in trials and cohort studies as we described.[4] We propose that the Polypill be used without medical examination or blood tests, so these costs are largely avoided. It is more appropriate to consider years of life gained free from a heart attack or stroke, rather than simply years of life gained. If the daily cost of the Polypill were about £1 the estimates summarised by Messori et al would be about eight times too high.

On 3 September there were 88 rapid responses to our papers on bmj.com. We classified 24 as positive, 41 as negative, and 23 as raising related side issues. The responses ranged from rating the work as Nobelian to regarding it as a joke. We were

struck by the strength of negative feeling by doctors on the use of a daily pill to prevent major disease. The public seems to think otherwise. The CNN website asked, "Would you take the Polypill?" and 95% replied yes. As DePoy says in his tongue in cheek summary of the responses, some regard the Polypill as immoral, and some thought, illogically, that it might benefit the population as a whole but individual patients would be worse off on average.[5] White's summary concentrates on the hyperbole. She does not comment on the lack of scientific input to the debate but selects invalid assertions such as "lack of trial evidence," the work being based on "flawed Framingham study data," and she makes the incorrect assumption of "perfect synergy."

Your correspondents have not given reason or evidence against the concept of the Polypill. Many have not recognised the massive data available on the efficacy and adverse effects of the Polypill components or the evidence showing their independent effects which together form the basis of our estimates. The fact that the expected health benefit is large is a reason for supporting it, not a reason for disbelieving it.

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Competing interests: NW and ML have filed a patent application on the formula of a combined pill to simultaneously reduce four cardiovascular risk factors, as well as a trademark application for the name Polypill.

1 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003;326:1419-24. (28 June.)
2 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423-7. (28 June.)
3 Law MR, Wald NJ, Morris JK, Jordan RE. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 2003;326:1427-31. (28 June.)
4 Law MR, Wald NJ, Wu T, Hackshaw A, Bailey A. Systematic underestimation of association between serum cholesterol concentration and ischaemic heart disease in observational studies: data from the BUPA study. *BMJ* 1994;308:363-6.
5 DePoy JA. The nays have it. Electronic response to: A strategy to reduce cardiovascular disease by more than 80%. bmj.com 2003. bmj.bmjjournals.com/cgi/eletters/326/7404/1419#34902 (accessed 3 Sep 2003).

Do school exams predict doctors' success?

Career achievements are not only measure

Editor—McManus et al studied A levels and intelligence as predictors of medical careers in UK doctors.[1] It is important to know that A levels as a test of academic achievement can predict a successful career in medicine. The authors measured career success as more rapid career progression, greater research output, and opting for hospital based practice. As they acknowledge in their paper, they cannot comment on the interaction between doctor and patient. Neither could they comment on any important aspect of the hands-on practice of clinical medicine of those doctors in their study.

In important aspects therefore, this study looks at career success rather than success as a clinician. No information was presented to indicate that the doctor who becomes a consultant more quickly will be a better clinician than a more slowly advancing colleague, although this might well be the case. Although research in medicine is crucial, I doubt that the number of papers published is always an indicator that the research is actually of any great value.

This study emphasises the importance of selecting medical students to include those in the ranks of the academically most able. However, the medical profession cannot afford to look solely to career success as a measure of the doctor without considering what the public looks for in that doctor. I doubt that my patients care much about my career progress or my research.

In their discussion McManus et al note that A levels should not be the only basis for selection. This must be right. We cannot afford to use career achievements as the sole measure of our success as a profession.

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Competing interests: AABC at A level; 7 years from qualification to membership; 11 years to consultant post.

1 McManus IC, Smithers E, Partridge P, Keeling A, Fleming PR. A levels and intelligence as predictors of medical careers in UK doctors: 20 year prospective study. *BMJ* 2003;327:139-42. (19 July.)

Is it not a retrospective study?

Editor—The title of the paper by McManus et al is rather misleading in saying that it is a 20 year prospective study.[1] By definition this would mean that the study was planned 20 years ago and the recruitment of subjects was over the same time. But the subjects were selected retrospectively over seven years only, and at the start no such study was planned.

A prospective study is planned at the start and then continuously followed up over the said period or concluded at the end of the predicted period. None of these criteria are filled here, and hence this study can hardly be classified as prospective. Furthermore, a study from entrants to one medical school cannot justify it as predictors of medical careers in UK doctors. Any such study should ideally be a multicentre study.

The grades at which many doctors entered during 1975 to 1982 may never be shortlisted today. We do not know of any school that takes BBB these days. The difference among the new entrants to any medical school in the United Kingdom is hardly two (AAA or AAB) points these days, and therefore grades can not be taken as predictors of career. The number of participants in this article is not representative of the total number of new entrants over seven years in the United Kingdom as a whole and that takes away the relevance of this project in this particular context.

The grades obtained at A level are based mainly on theoretical grounds, whereas career progression in medicine entails theoretical, clinical, and communication skills. Achievement at A level does not equate with achievement in professional career owing to differing criteria. How many medical schools require new entrants to take an intelligence test?

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1 McManus IC, Smithers E, Partridge P, Keeling A, Fleming PR. A levels and intelligence as predictors of medical careers in UK doctors: 20 year prospective study. *BMJ* 2003;327:139-42. (19 July.)

Author's reply

Editor—A levels should not be the sole basis for the selection of students. Our study assessed only some of the skills possessed by good doctors, and A levels predicted only some of them.

A casual reader might see the partial validation of A levels as the main finding of our study. Equally important though, with government and pressure groups arguing that A levels might be better replaced by "aptitude tests," is the negative finding of the minimal predictive value of intelligence. That matters when, to answer a question of Chaturvedi and Chaturvedi, medical schools in the United Kingdom and elsewhere are using tests such as GAMSAT and BMAT, which partly measure intellectual ability.

Chaturvedi and Chaturvedi say our use of prospective is rather misleading. If they have been misled it probably results from their own idiosyncratic definition of prospective. Dictionaries define prospective study as synonymous with cohort study, follow up study, and longitudinal study.[1 2] Bland describes how in a prospective design, "We take a group of people, the cohort … We then follow them over time."[3] That is what we also did.

Chaturvedi and Chaturvedi also say that at the start no prospective study was planned. The reality is that Chaturvedi and Chaturvedi

were not present in 1975, and their retrospective analysis of the late Peter Fleming's intentions is wrong; from my discussions with him from 1988 onwards, a long term follow up had always been intended.

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Competing interests: None declared.

1 Upton G, Cook I. *A dictionary of statistics*. Oxford: Oxford University Press, 2002.
2 Last JM. *A dictionary of epidemiology*. 3rd ed. New York: Oxford University Press, 1995.
3 Bland M. *An introduction to medical statistics*. 2nd ed. Oxford: Oxford University Press, 1995.

Research was evidence based

Editor—We appreciate Fitzmaurice's agreement with us that expert based information sources cannot be trusted.[1] We take strong issue with his notion that our research design lacks rigour and is susceptible to bias.

A careful scanning of the complete version would reveal that, although we labelled the design as a convenience sample, we actually studied the complete population of review articles meeting our criteria. We called it a convenience sample because of the difficulties identifying review articles in the grey (unindexed) literature. As outlined in the methods section, our search was not completed by us but by a medical librarian (see acknowledgement).

Once the articles were identified, each article was reviewed for content separately and independently by two researchers who were blinded to the author, institution, and journal source. As a result of pre-testing and using strict criteria, our agreement was very high. We believe this methodology represents the state of the art for this type of research.

We too wish it were true, but current research does not support Fitzmaurice's contention that most doctors evaluate research data themselves rather than relying on expert assessment. From a recent paper (just one on a long list): "The decision to initiate a new drug is heavily influenced by 'who says what,' in particular the pharmaceutical industry, hospital consultants, and patients."[2] Unfortunately, review articles written by experts are one of the more common sources clinicians use to find out who says what.

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1 Shaughnessy AF, Slawson DC. What happened to the valid POEMs? A survey of review articles on the treatment of type 2 diabetes [with commentary by D A Fitzmaurice]. *BMJ* 2003;327:266-10. (2 August.)
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Dyspepsia results may not apply in primary care

Editor—Manes et al reported their trial of *Helicobacter pylori* test and treat *v* initial proton pump inhibitors.[1] Their results in secondary care are encouraging in that eradication treatment for *H pylori* reduced the relapse of symptoms by 33% compared with a short course of treatment to suppress acid. However, we doubt whether their findings have any relevance to the use of "test and treat" in primary care.

Manes et al used an aggressive investigative strategy of testing, treating, and endoscopy *v* proton pump inhibitor and endoscopy in patients with dyspepsia who attended a single hospital clinic. All patients in the trial had intensive monthly then two monthly follow up and underwent endoscopy if symptoms recurred after their initial treatment. This would not be usual practice in primary care, where trials have shown that only 25% of young dyspeptic patients undergo endoscopy within a year after consultation.[2]

In addition, the prevalence of *H pylori* was extremely high (61%), whereas the prevalence in most north European countries and North America may be only 20-30% in similar young patients.

Whether an initial strategy of *H pylori* test and treatment or acid suppression should be used is really an issue of cost effectiveness.[3] The CADET-Hp study showed a 14% absolute reduction in dyspeptic symptoms when eradication treatment was compared with proton pump inhibitors and placebo.[4] However, it enrolled only patients who were positive for *H pylori* and cannot therefore compare costs at strategy level, where the costs of testing and managing the *H pylori* negative patients must be included.[4]

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Competing interests: All authors are currently recruiting patients to a trial of test and treat *v* proton pump inhibitor from 55 practices in the United Kingdom, funded by the Medical Research Council.

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Smoke free hospitals

Withdrawal from cigarettes should not be confused with withdrawal from nicotine

Editor—As we showed in our editorial, there are many sound clinical reasons for stopping smoking, not least that it improves the chances of recovery (which is surely the aim of being in hospital). However, some responses to our editorial seem to confuse withdrawal from cigarettes with withdrawal from nicotine.[1]

For those unable to do without nicotine, replacement therapy will satisfy their craving while they are in hospital (as your correspondents note) while reducing the risk of fire or pollution of the environment. Most importantly, it will allow it to be administered in a controlled manner that takes account of its physiological effects on those whose body systems may already be compromised. In response to Head, it is unethical to enable patients who are seriously ill to self administer a potent drug, with no idea of how much they are taking or how it might interact with the other drugs they are receiving.[1]

The correspondents from the Royal Victoria Hospital also raise ethical issues.[2] Contrary to their assertion, smoking bans are achievable. The fact that many of their patients experience social disadvantage should be a reason to increase efforts to reduce smoking, not to despair that it is too difficult.

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Competing interests: MM, AG, and TN were the authors of the editorial to which the letter in the references responded.

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Rising to the challenge

Editor—W McKee et al defend the provision of rooms for smokers in response to the editorial by M McKee et al.[1 2] They draw attention to the fact that for smoking cessation to be effective with inpatients, a follow up of more than four weeks is needed. They argue that this cannot be provided in acute hospitals.

The Royal London Hospital's inpatient service provides an intensive behavioural intervention combined with nicotine replacement and outpatient follow up for at least four weeks. This is achieving four week validated continuous abstinence rates of 54%. A growing number of acute hospitals within the United Kingdom are providing a similar cost effective treatment.[3] The £390 000 spent on the smoking rooms could have funded such a service for a very long time.

Smoking rooms in hospitals also represent smoking cues and their existence may encourage smoking. Anecdotally, a number

of patients we treated reported that the presence of smokers' rooms sabotaged their attempts to stop smoking.

Several years ago separate funding was allocated to NHS smoking cessation services. Inpatients are one of their priority targets.[4] Hospitals should be able to offer intensive smoking cessation treatment and follow-up via dedicated staff funded by the smoking cessation service, and the presence of such provision should make a transfer to smoke free policies much easier.

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Competing interests: None declared.

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Diabetes may be independent risk factor for hyperkalaemia

EDITOR—Wrenger et al reported severe hyperkalaemia in patients taking spironolactone in combination with angiotensin converting enzyme inhibitors or angiotensin-II antagonists.[1] The strikingly high prevalence of diabetes in these patients (80%) is likely to be important.

In a study of the prevalence of hyperkalaemia in an unselected diabetic outpatient population we found that hyperkalaemia was comparatively common in patients with both type 1 and type 2 diabetes.[2] Among 1764 consecutive patients attending a hospital diabetic clinic over one year, serum potassium concentration was >5.0 mmol/l in 270 patients (15%) and >5.4 mmol/l in 67 (4%). Six patients had a serum potassium concentration >6.0 mmol/l. In contrast, only four patients had a serum potassium concentration of <3.4 mmol/l.

A comparatively small proportion of patients were receiving drugs that could increase potassium (20% of patients with hyperkalaemia) because angiotensin-II antagonists were not available and the use of ACE inhibitors in patients with diabetes was less well established.

These data indicate that diabetes is an independent risk factor for hyperkalaemia. Dangerous hyperkalaemia after taking ACE inhibitor drugs and potassium sparing diuretics is well described in diabetic patients,[3 4] and the *British National Formulary* advises caution prescribing amiloride for diabetic patients.

The report by Wrenger et al reinforces the concern that patients with diabetes seem to be particularly sensitive to the hyperkalaemic effect of drugs that block potassium excretion, particularly when used in combination. Doctors treating patients with diabetes should be aware of the dangers of precipitating life-threatening hyperkalaemia when prescribing for them, the combination of spironolactone with ACE inhibitors or angiotensin-II antagonists for heart failure being used with extreme caution.

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Be careful when extrapolating trial data to real life

EDITOR—Lenzer describes how stroke centres in the United states are under fire for their planned use of alteplase.[1] Most people who have a stroke are not young but old. What both groups have in common is the difficulty in understanding even basic risk and benefit information.[2]

In older patients there ought to be a concern about the use of thrombolysis in the presence of microhaemorrhages, a finding that is present in around 6% of healthy older people but in considerably more of those with clinical cerebrovascular disease.[3 4] These microbleeds are of relevance as they can mark people out as being at increased risk when undergoing thrombolysis.[5]

The people who are advocating this legislation should be able to explain to the public what would happen to 100 people at the end of 30 days or a year who present with each category of stroke (posterior circulation infarct, partial anterior circulation infarct, lacunar infarct, total anterior circulation infarct) and each modified Rankin score 1-5. Risk and benefit information for thrombolysis that is easy to understand is required to enable patients to give consent and make informed treatment choices rather than the introduction of legislation to allow doctors to do what they believe is in a person's best interest.

Thrombolysis may be the best option in some cases, but care is needed in extrapolating data obtained in trial conditions to real life, to all strokes, and to people of all ages.

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Competing interests: None declared.

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Confidentiality of patients' information must be guaranteed

EDITOR—During a recent research project we needed to contact a large number of patients, many of whom had not been seen since their last review appointment about 10 years previously. Consequently, the personal contact details on the hospital database were out of date.

We contacted the surgery of each patient's registered general medical practitioner requesting current telephone numbers and addresses. In each case the caller gave name and title—for example, Dr Smith, senior house officer in general surgery—and explained that the patient's hospital details were out of date and the current contact details were required to contact him or her for review. We noted the response of each practice to these requests.

We contacted 46 surgeries. Only one practice asked the caller to fax the request on headed hospital notepaper. Three practices asked for a contact number at the hospital to enable them to call back with the details. Six practices requested the last known address of the patient in question, and a further 11 asked for the date of birth. An alarming 25 surgeries gave the current contact details of the named patient without asking for any further information or verifying the caller's identity.

We became increasingly worried during this research that patients' information was so readily available. We commend the practices that seem to have implemented guidelines on the way to deal with requests for information and suggest that the gold standard should be that requests for patients' details be faxed on headed notepaper. We realise that there are financial and time implications for both the requester and provider of data, but this is no reason to abandon good practice.

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