Antiplatelet therapy and atherosclerotic events. Commentary is inaccurate

Letters

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What do you think is a non-disease?

Pros and cons of medicalisation

EDITOR—The *BMJ*'s decision to extend participatory democracy to the question of disease is important not so much for the results but because it happened at all.[1]

To a previous generation the idea of asking consumers to decide on these matters would have been incomprehensible. Doctors decided which conditions were legitimate and which should be consigned to the outer darkness. In the debate about the nature of neurasthenia at the end of the 19th century all protagonists were in the medical profession and their debates were published in journals. The views of a few well educated and well heeled patients may be inferred from diaries and fiction, but their voices were largely unheard and unheeded.

Now of course medical authority is in retreat everywhere and the final arbiter of "non-disease" is fast becoming the patient.

All this is well and good, so why the outrage of so many respondents?[1] I suspect it comes from a failure to recognise the different concepts of illness and disease.

Taking chronic fatigue syndrome as an example from the debate,[1] few could now question that it is indeed an illness. It has a nosological status and is clearly associated with suffering, ill health, and disability. The patient's voice must be and is paramount. But is it a disease—that is, has a specific pathological process been identified to account for the above? Chronic fatigue syndrome is not yet a disease because no unambiguous evidence has yet been presented that has commanded widespread acceptance by the scientific community, which remains the arbiter.

Of course, the syndrome may plausibly make the transition from illness to disease like many other illnesses have done. Or it may not. The traffic is not entirely one way in which illness entities inevitably receive the stamp of scientific approval, usually after a period of being falsely labelled as psychological. Previously apparently sound entities have lost their disease status under the cold light of scientific scrutiny.

The concept of labelling also generated a lot of heat in this debate. People behave according to the labels that are ascribed to them, a process seen as largely negative. Some respondents rightly echo this, citing examples in which the act of labelling distress as something medical (pathological) carries with it a host of adverse consequences.[1 w1-w8]

But more commonly the act of giving a name to symptoms and disability brings relief.[w9-15] The acknowledgement by the medical profession that a patient's condition has a name and is a legitimate illness is immensely reassuring and enabling. It also ends the battle of diagnosis—"If you have to prove you are ill you can't get well."[w16]

Giving a condition a name is an intervention in itself with costs and benefits.[w17] Crudely handled, medicalisation can perpetuate disability and exclusion. But used constructively and appropriately it is the first step towards recovery.

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bmj.com *References w1-17 are available on bmj.com*

1 Non-disease. Results of ballot, and electronic responses. bmj.com 2002 (bmj.com/cgi/content/full/324/7334/DC1; accessed 4 April 2002).

Compiling list of non-diseases is medical arrogance

EDITOR—The arrogance of the concept of compiling a list of non-diseases is breathtaking.[1]

Had this list been compiled 50 years ago, which illnesses would have been listed? Multiple sclerosis, Crohn's disease, hypothyroidism? The medical community's inability to learn from past mistakes—namely, to acknowledge that most patients are honestly relating their symptoms and sincerely wish to recover—will doom generations of innocent people to the kind of humiliation and insult this ballot encapsulates.

Unable to perceive their own ignorance, these commentators will enjoy a brief moment in the spotlight sneering at the proponents of non-diseases, utterly failing to advance medical science.

And you wonder why the benighted sufferers of their non-diseases resort to alternative practitioners.

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1 Non-disease. Results of ballot, and electronic responses. bmj.com 2002 (bmj.com/cgi/content/full/324/7334/DC1; accessed 4 April 2002).

Defining non-diseases to avoid medicalisation is throwing the baby out with the bath water

EDITOR—Having read the list of non-diseases I am not sure I fully understand the rationale behind it.[1] However, as a person who experiences chronic fatigue syndrome, fibromyalgia, obesity, and several other conditions included on the list I have a vested interest in the outcome.

I agree that the medicalisation of certain diseases, illnesses, and conditions has impacted negatively on those who experience them. I also accept that it might be better not to treat certain conditions in certain circumstances. This is true of both diseases and non-diseases and I see no automatic correlation between disease and treatment and non-disease and no treatment.

Few people would probably argue that having big ears is a disease, so its inclusion as a non-disease poses few problems. This does not mean, however, that it automatically requires no treatment. That decision surely depends on various factors, including the extent to which the condition impinges on the life of the person experiencing it. Conversely, cancer is (arguably) a disease that often benefits from highly aggressive treatment, but in some cases less aggressive treatment or no treatment at all might be better.

Moreover, despite the best efforts of certain egotistical members of the medical profession to convince us that they have all the answers, many conditions are not understood enough to be able to label them disease or non-disease. Perhaps a condition should be labelled a non-disease rather than erroneously be called a disease. I think, however, that any rush to label a condition of unknown origin a non-disease could have negative effects.

Historically, conditions that have no known origin have attracted labels such as psychosomatic and psychological, stigmatising those experiencing them as lacking or weak at best and mad at worst and defining treatment. For example, before the organic origin of multiple sclerosis was discovered patients were often labelled as having psychological difficulties and treated inappropriately. This is still the case with conditions such as chronic fatigue syndrome and myalgic encephalitis.

Labelling conditions as non-diseases could also have more far reaching consequences. In the United Kingdom a person's entitlement to receive state and other benefits when unable to work because of ill health is largely dependent on the recogni-

tion of a pre-existing condition. Clearly, the label of non-disease might well negatively affect the amount of benefit paid.

The classification of certain conditions as non-diseases to avoid the perils of medicalisation seems to be a case of throwing the baby out with the bath water. A holistic social approach to illness and disability that treats each person individually is far better than seeking a cover all solution replacing one label with another.

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Labels create legitimacy and produce dependence

Editor—The last decade has seen the development of an ever increasing role of patients as the primary decision maker in the management of illness. This approach has been encouraged by advocacy groups, the popular news media, and doctors who cater to the non-critical thinking population.

For those not trained to reign in their innate belief engines, the association of symptoms with a disease is encouraged only by the production of labels. A symptom complex described by physicians as fibromyalgia, which is nothing more than a descriptive term for pain in muscles and fibrous tissue, now has the legitimacy of a disease as opposed to a panoply of symptoms. The near mass hysteria displayed by like-minded believers when these labels are challenged adds to the dependency on the labels as being legitimate.

Having evolved a mind that is designed for pattern recognition, resists changing beliefs in the face of new information, and encourages the production of cause and effect relations in the presence of associative phenomena, some human beings will always need labels to support their continued suffering in an unfair world. These non-diseases clearly contribute to the development of co-dependent suffering.

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Diet, lifestyle, exercise, spirituality, and the search for meaning are ignored at our peril

Editor—Much evidence supports the organic nature of many of the diseases mentioned in the list of non-diseases, particularly for myalgic encephalitis-chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity.[1] Evidence also supports shared symptoms in these and other medically puzzling and taxing disorders such as Gulf war syndrome and irritable bowel syndrome.

Linus Pauling argued that all diseases have a molecular basis. The validity of this statement is substantiated by many who advocate the existence of non-diseases. Yet in prescribing antidepressants, antiepileptic drugs, and agonists and antagonists of the major biogenic amines and neurotransmitters, they are changing the underlying physicochemical and physiological properties of organs and body systems, particularly the brain.

Illich has written perceptively about the medicalisation of life and its origins and consequences. Medical ignorance and arrogance dominated by rationalism seeks explanations of puzzling signs and symptoms and ends up creating spurious diseases and disorders that put the blame on patients or their caring family and friends.

Numerous examples of, and articles about, non-diseases were published in the medical peer reviewed literature by eminent people of their day. They were wrong. The advancement of scientific and medical knowledge has now identified the underlying biochemical and physiological disorders of, for example, diabetes, parkinsonism, and multiple sclerosis. The sufferings of patients imposed by these arrogant and rigid attitudes demean both patients and doctors and create mistrust.

The consequence of the triumph of such attitudes is now seen in the abandonment of any responsibility for one's own health. Lifestyles, however destructive, are pursued in the belief that medicine will somehow provide an answer. The drug industry and much of modern medicine seek new agents to modify or offset the consequences of excesses—for example, new anti-obesity agents for the epidemic of obesity and maturity onset diabetes.

The food industry also contributes to modern health problems with the widespread use of pesticides, plant and animal hormones, and genetically modified crops. Thus, even eating a healthy diet leads to an increasing burden of new man-made toxins, many of which have not been toxicologically assessed.

Diet, lifestyle, exercise, spirituality, and the search for meaning are all parts of our human condition. We ignore them at our peril.

What is required is a change of heart and mind leading to a change of practice that embraces human values of mutual respect, careful listening, and use of modern drugs effectively and not randomly. It also needs to recognise the possible benefits of alternative treatments in constructive and critical ways, examine diet and nutrition, and allow patients to decide how they live and die with their illness.

Let's return to being fully human.

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1 Non-disease. Results of ballot, and electronic responses. bmj.com 2002 (bmj.com/cgi/content/full/324/7334/DC1; accessed 4 April 2002).

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Summary of responses

Editor—There were some who thought the exercise a joke, and in bad taste at that.[1] Others couldn't see the point and complained that deciding what was, or was not, a non-disease was unworthy of a serious medical journal and did little more than toy with semantics.

And some thought that the process trivialised genuine suffering and was an excuse for airing prejudice and ignorance. The stigma of having a non-disease could only make that suffering worse. But aside from the long list of possible contenders—from burnout to fibromyalgia, and high cholesterol—the issue provoked vigorous debate about the purpose of medicine and what some saw as a narrow understanding of illness and the limited scientific paradigm.

Respondents struggled with definitions of their own, and Kazem Zarrabi, a postdoctoral researcher at the University of Lund, Sweden, suggested that we should look to Darwin for guidance, regarding as disease any condition that interfered with our reproductive success and compromised our "inclusive fitness."

Medicalising natural processes, such as normal childbirth, the menopause, and bereavement was not a healthy option, countered several correspondents, serving to boost the profits of drug companies.

And much of what we classify as disease is really a byproduct of ageing, suggested Dirk Ulbricht of the Centre Hospitalier, Luxemburg, including osteoporosis, said Iona Collins, specialist registrar in trauma at the John Radcliffe Hospital, Oxford.

But de-medicalising disease could deny those who had them the right to research and treatment, said Alex McLaughlin, a writer from Red Hill in Australia, and they could be dismissed as "somatisers." The nub of the issue, she said, was whether medicine had the capacity and the moral authority to define what is and what isn't disease.

Others suggested that labels helped people cope better, gave them legitimacy, and signalled protected funding and physician time. Chronic fatigue syndrome was frequently suggested as rightfully belonging to the non-disease category, but it was also vigorously defended as having clear physiological changes.

And there were fears that state funding for disease that impaired mobility and the ability to work might be withheld if it were to lose its legitimate label. The UK government's refusal to recognise repetitive strain injury as a disease, suggested Martin Wilson of Glasgow, denied people financial help.

Respondents worried that definitions were founded on shaky ground, guided as they are by constantly changing criteria: (lack of) knowledge, different cultural perspectives, where you lived.

And they were also subject to fads and fashion. A case in point is obesity, which was regarded as a sign of prosperity a century ago, pointed out research professor of chemistry, Joel Kaufmann, from Philadelphia. New Zealand patients' rights cam-

paigner Gurli Bagnall was concerned about the prevalence of attention deficit disorder and the way in which Ritalin (methylphenidate hydrochloride) had been heavily promoted as a suitable treatment for it.

But several people suspected that the proposed list conveniently included many non-diseases for which there was little effective treatment, and even less understanding of their cause.

Public health physician Steve Hajioff commented: "This has been the case for many conditions throughout history … Crohn's disease, multiple sclerosis, and coeliac disease are good examples." Others given were asthma and lupus.

Raymond Colliton of Philadelphia pointed out that the purpose of medicine was to reduce human suffering, irrespective of the labels given. And Elmer Fudd agreed that "disease is a very slippery concept," but added "So is medicine."

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1 Non-disease. Results of ballot, and electronic responses. bmj.com 2002 (bmj.com/cgi/content/full/324/7334/DC1; accessed 4 April 2002).

Editorial on CFS was biased, inaccurate, and misleading

Editor—As a member of the chief medical officer's working group on chronic fatigue syndrome, I consider that Straus has failed to appreciate the difficulties of deciding what constitutes evidence in an illness as uncertain and heterogeneous as this.[1] He also misunderstood, or took out of context, some of the key conclusions and recommendations in the chief medical officer's report.

Although it was agreed that evidence should not just be limited to the results of randomised controlled trials, the findings of the York systematic review were frequently cited. It was therefore disingenuous of Straus to state that information from this review did not influence the report's conclusions about a wide range of therapeutic interventions. It did.

Equally, it would have been a serious omission if the report had failed to refer to the feedback from patients contained in three large surveys on attitudes to management, as well as two events where patients and carers met with the working group. All three surveys concluded that graded exercise as is currently being done made more people worse than any other intervention. Pacing, however, was found to be beneficial by around 90% of respondents. By dismissing such views as anecdote, Straus fails to appreciate that the Department of Health is encouraging patients to enter into a therapeutic relationship with the medical profession in the management of chronic conditions such as this.[2]

The recommendation that an incipient diagnosis of chronic fatigue syndrome should be considered after six weeks of characteristic symptomatology was taken out of context. Current diagnostic criteria for the syndrome have been heavily criticised for their emphasis on selecting patients for research rather than routine clinical assessment, and there was widespread agreement that early diagnosis with advice on management could reduce long term morbidity. Does Straus believe that these patients should have to endure six months of quite severe ill health before they can be offered a presumptive diagnosis and advice on management? The report clearly concluded that this should no longer be the case.

Despite his generally dismissive view of much of the section on management, Straus nevertheless welcomes the main conclusion: that this is a genuine and disabling illness that can no longer be ignored by clinicians and researchers.

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Gulf war syndrome may be post-conflict dysfunction

Editor—We have read the results of the questionnaire based study by Chalder et al from the Gulf war research unit at King's College.[1] They found that 17% of the 2961 Gulf war veterans believe themselves to be suffering from Gulf war syndrome, although the group has found no evidence to support such a syndrome.[2] The veterans' belief was reinforced if they knew someone with similar symptoms. We believe that this represents post-conflict dysfunction expressed according to health beliefs prevailing at the time the questionnaire was administered.

Hyams et al investigated the health of veterans without organic disease from conflicts since the American civil war ("disordered action of the heart").[3] He showed that veterans complained of a range of physical and cognitive symptoms, the nature of which was independent of the conflict and gained diagnoses based on the then current aetiological beliefs. The Gulf veterans' medical assessment programme of the Ministry of Defence now provides a robust clinical base.[4] Of the 3000 who have attended (6% of the deployed force), 80% are well. The 20% who are ill account for about 1% of the deployed force.

Unwin et al showed that self reported physical functioning in Gulf veterans is broadly similar to that in a control group of non-deployed forces and Bosnia veterans but that the perceived quality of their health is reduced.[5] The difference between the 17% of Chalder et al and our clinical findings may be explained by the disordered health perception and related behaviour.[1] We think that this, and the syndromes discussed by Hyams and others, constitutes post-conflict dysfunction.[3]

Chalder et al speculate that social networks, usually protective of health, worked perversely in the case of the Gulf war veterans. A major omission in their discussion was a lack of consideration of the role of the media in reporting Gulf veterans' illnesses. Although we are not suggesting that the media are solely the "infective agent," their function as the "vector" of disease in the Gulf war syndrome deserves comment. Media distortion and oversimplifications of the issues are the rule and were exemplified when the *Daily Telegraph* of 31 August 2001, commenting on the paper by Chalder et al, ran the headline "One in six veterans has Gulf war syndrome." We have taken histories from many veterans who attended the medical assessment programme because of fears fanned by ill informed and unbalanced media speculation. Some of these men have post-conflict dysfunction, but no Gulf war syndrome.

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ICD and DSM are contemporary cultural documents

Editor—In their riposte to my critique of post-traumatic stress disorder Mezey and Robbins cite me as advocating a "stiff upper lip" approach to adversity.[1 2] This is disingenuous: I was pointing to the tension between aspects of British identity traditionally grounded in stoicism and composure and the emergent demands of an expressive individualism.

Mezey and Robbins pay lip service to the role of social factors, but their argument runs the other way. Their core defence is institutional: post-traumatic stress disorder must be valid because it is in the books—in psychiatric classification systems such as the *International Classification of Diseases* (ICD) and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). By this token they would happily have diagnosed homosexuality as a mental illness during the years when it was classified as such in the ICD or DSM.

Psychiatrists serve neither society nor patients with psychiatric difficulties when they uncritically endorse the medicalisation of life

(though they may well serve the pharmaceutical industry, with its vested interest in the medicalisation of the human predicament: some antidepressants are now being specifically marketed for post-traumatic stress disorder). It is academic shallowness and complacency that may permit sociocultural (and often political) values and expectations to be dressed up as medicopsychiatric facts.

What comes to be presented as psychiatric knowledge is as much constructed as discovered. The ICD and the DSM categorise phenomenological constellations, but this is not synonymous with scientific validation. The classifications are not atheoretical and value free—for example, they contain ontological notions of what constitutes a real disorder, epistemological notions about what counts as scientific evidence, and methodological notions about how research should be conducted.[3] They are contemporary cultural documents. Awareness of this helps refine our clinical gaze.

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Non-cardiac chest pain

Patients need diagnoses

Editor—We are concerned about one of the sweeping conclusions in the editorial on non-cardiac chest pain.[1] We do not agree that "providing a diagnosis may be less important than addressing a patient's concerns and fears." Providing a diagnosis is probably the most important part of the care of such patients.

Evidence shows that angiography fails to relieve the anxiety of patients,[2] but the psychological and psychiatric complications of chest pain may be at least partially related to general practitioners' inability to provide a definite diagnosis. Continued prescription of antiangina drugs, and possibly failure to investigate further, contribute to continued anxiety. Patients with chest pain of non-cardiac origin need a label to hang on to.

Because there is often more than one diagnosis, we suggest using the label "chest pain of unexplained origin." A multidisciplinary approach could be useful, with particular attention being paid to psychological factors.[3] Nijher et al say that an alternative non-cardiac diagnosis can be difficult to make, but it is often possible: a definite diagnosis can be reached in up 85% of patients.[4] The impact of chest pain clinics is uncertain, and follow up for patients with non-cardiac chest pain may be of value.[5] Certainly, as the authors say, these clinics might worsen the situation if adequate follow up is not arranged.

Adequate investigation for other physical causes of chest pain must be part of a comprehensive approach to this difficult problem.

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Rapid access clinics lead to deskilling of general practitioners

Editor—In many ways the editorial about non-cardiac chest pain indicates the increasing problem of overspecialisation.[1] General practitioners are good at stopping the juggernaut of investigation at source, but this takes nerve and is sometimes seen as not doing enough. Of course the general practitioner who boldly states that chest pain is non-cardiac at the first consultation is not seen to be doing very much; the decision may be made on no more than a hunch and experience, but the potential savings in time, money, and neuroses are huge. The trouble is that the system is unforgiving if the hunch was wrong.

Rapid access clinics, be they for chest pain, breast lumps, or rectal bleeding, deskill general practitioners in dealing with these symptoms because they give easy access to decisions taken with much more information. However, the editorial shows the negative side of this process. Our hospital colleagues are less good at taking decisions with no tests, as they have to be seen to be doing everything.

I have always thought that the general practitioner system works well only because general practitioners half do things, but the benefits to patients can be huge and the savings immense. It is a question of where to draw the line. Deciding that there is probably nothing wrong takes nerve and courage. Rapid access clinics deskill this process, and the implications for the NHS are considerable in terms of resources. It is not helped by empire builders who state in the public domain that patients with certain symptoms always need extensive investigation and referral. It leaves general practitioners even more exposed.

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Hormone replacement therapy and the breast

Studies must determine the evidence

Editor—As active members of the Australasian Menopause Society, we are disappointed at the conclusions that Dixon drew in his editorial on hormone replacement therapy and the breast.[1] Although it may be true that hormone replacement therapy makes mammograms harder to interpret, it is far from clear that it causes breast cancer.

A recent overview by Bush et al emphasises the weakness of Dixon's argument, based, as it is, almost entirely on level three observational studies.[2] Unlike Dixon's selection of studies with the highest odds ratio, Bush et al's review was of 45 studies assessing the association between use of hormone replacement therapy and risk of breast cancer. It found that risk was reduced (relative risk < 0.9) in 20% of the studies, did not change in 47% (0.9-1.1), and increased in 33% (1.1-2.0). In no study did relative risk increase above 2.0, and in the 20 studies where the relation between risk of breast cancer and combined oestrogen and progestin therapy was studied only four reported a significant difference in relative risk, with two showing an increased and two a decreased risk.

The heterogeneity of these data is in stark contrast to the homogeneity of the data on mortality from breast cancer in users of hormone replacement therapy that were reviewed: all 11 of the studies reported a reduction in risk. Unlike Dixon, the authors concluded that the likelihood of an adverse effect of hormone replacement therapy on breast cancer must be small.

The Australasian Menopause Society is a sponsor of the women's international study of long duration oestrogen use after the menopause (the WISDOM trial), a large prospective 15 year randomised placebo controlled trial. The results of this trial, together with those of the women's health initiative in the United States, will be needed to answer the question of whether hormone replacement therapy has any effect (beneficial or adverse) on breast cancer.

Until then strong opinions will continue to be held about hormone replacement therapy and its relation to risk of breast cancer, often derived from selective quoting of the available literature. These opinions heighten the anxiety of women who have valid reasons for taking hormone replacement therapy and do not afford them the opportunity of informed choice.

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Competing interests: AHM is editor in chief of *Climacteric*, the journal of the International Menopause Society. He has received research grants to conduct phase 1 and phase 3 trials of various products for managing the menopause and its sequelae and is the principal investigator of WISDOM, Australia. BL is involved in three clinical trials of hormone replacement therapy in postmenopausal women and receives funding from the Medical Research Council in the United Kingdom for the WISDOM trial. RJB has received research grants to conduct phase 2 and phase 3 clinical trials on the effects of various types of hormone replacement therapy, selective oestrogen receptor modulators, and phytoestrogens in postmenopausal women.

The WISDOM trial in Australia is sponsored by the UK Medical Research Council, Australian National Health and Medical Research Council, Australian Heart Foundation, South Australian Anti Cancer Foundation, Australasian Menopause Society, and Royal Australian and New Zealand College of Obstetricians and Gynaecologists.

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Women still want to have hormone replacement therapy

Editor—I was dismayed to read Dixon's editorial about hormone replacement therapy and its effect on the breast[1] and have been provoked to respond by the anguished cries for help by both patients and colleagues. Dixon, in the words of Bernard Levin, has become a single issue fanatic. There's more to women's health concerns than breast cancer.

Frightening women off hormone replacement therapy could have many unpredicted consequences. The lifetime risk for women of dying of breast cancer is only 1 in 26, with between three and 10 times that risk of dying from heart disease, depending on whether they are smokers or non-smokers.[2] For all we know, hormone replacement therapy could protect more women from death due to cardiovascular disease and osteoporotic fractures than the worst estimates for the increased incidence of breast cancer. Furthermore, as Dixon concedes, many of these cancers in women receiving hormone replacement therapy are of a favourable phenotype. It is therefore altogether perverse to criticise hormone replacement therapy for making screening mammograms uninterpretable.

Surely, given an informed choice, most women would be glad of the excuse to opt out of the national screening programme, which is of questionable value,[3] in favour of an intervention that improves short term and long term quality of life. Of course many women taking hormone replacement therapy have mastalgia and nodularity, but most of my patients are happy to live with this in exchange for the sense of wellbeing that they get from taking the therapy. Hormone replacement therapy also improves skin elasticity, mood, sexuality, and cognitive function.[4]

Are we really asking women to give all this up so as to make the life of our screening radiologists more comfortable?

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Author's reply

Truth or tact? You have to choose, most times they are not compatible

Eddie Cantor

Editor—The recent qualitative review by Bush et al is the basis of the objections of Baber et al to the conclusions I drew on the effects of hormone replacement therapy on the breast of postmenopausal women.[1]

This review took no account of the quality of studies included, it did not consider type of hormone replacement therapy used, its mode of delivery, or the age at which women started taking it. Figure 2 in their publication did, however, confirm that four of the five most recently published studies have shown an excess risk of breast cancer for combined regimens in postmenopausal women. Bush et al doubt whether oestrogen is important in breast cancer development and propose that some additional, as yet unidentified, factor is secreted from the ovary.

New data from over 9300 women with early breast cancer randomised to receive five years of treatment with adjuvant tamoxifen alone, anastrozole alone, or tamoxifen and anastrozole combined were presented last year by Baum. They show that after 33 months, there were five new invasive contralateral breast cancers in the 3112 patients taking anastrozole compared with 30 in 3116 women receiving tamoxifen and 23 in 3125 in the combination arm—a significant reduction in contralateral breast cancers with anastrozole compared with tamoxifen (hazard ratio 0.42 (0.22-0.79), $P = 0.0054$). These data explode the myth of an unknown factor proposed by Bush et al and confirm the importance of oestrogen in the development of breast cancer.

It was not my intention to try to frighten women off taking hormone replacement therapy. The US Food and Drug Administration removed the treatment of osteoporosis as an indication for oestrogen replacement therapy in 1999 because of lack of evidence from randomised trials. There are new specific and better drugs for this condition.[2] "Hormone replacement therapy should not be prescribed for the express purpose of preventing cardiovascular disease."[3] In the heart and oestrogen/progestin replacement study women over 65 taking hormone replacement therapy had worsening urinary incontinence and an increased risk of fatal stroke.[4]

Baum is inconsistent. He believes that women should be provided with all available data on screening so that they can make an informed choice yet he would deny them all available information on hormone replacement therapy. There is no doubt that oestrogen significantly improves the quality of many women's lives. The challenge for women and their clinicians remains to control menopausal symptoms and to deliver the benefits of oestrogen while minimizing the problems that continue to be reported with these preparations.[4 5]

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Competing interests: None declared.

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Schizophrenia in ethnic minority groups

Selection bias in prevalence data is difficult to rule out

Editor—To sociologists, Boydell et al's findings are counterintuitive.[1] One would expect economic deprivation (at neighbourhood level) to be a decisive factor for an increased incidence of mental illness. But it is surprising to learn that the lower the proportion of non-white ethnic minorities in a local area the higher the incidence of schizophrenia in those minorities (controlled for economic deprivation).

As an explanatory hypothesis the authors point to overt discrimination and institutionalised racism as sources of stress, which can be alleviated by people making use of social capital within the ethnic group. This hypothesis surely necessitates further testing and debate. It is a pity that non-white ethnic minority groups had to be considered as one homogeneous group on an aggregate level. The social networks and levels of social cohesion may be different for different ethnic groups, and follow up research should be able to distinguish these.

Boydell et al assume that all people with schizophrenia will come into contact with psychiatric services, but this requires closer attention. Members of an ethnic minority with a mental disorder who live in predominantly white neighbourhoods may be more likely to come into contact with psychiatric services. Probing for mental disorders might be more likely in predominantly white neighbourhoods than in non-white neighbourhoods. This is not necessarily ruled out by the fact that there is job mobility of clinical staff, since institutional cultures can both consciously and uncon-

sciously shape and influence individual professional practice (and in fact necessitate individual adaptation).

Different processes of self selection in contacting health services or looking for particular types of treatment may operate in different areas. It might be that in mainly non-white neighbourhoods, which often are also the most economically deprived areas, mental health issues among non-white groups are considered to be "luxury" problems compared with other health or social problems. As a result, incidences might be underestimated. The risk of being diagnosed as mentally ill in white (and often better off) neighbourhoods might be higher because of cultural-institutional factors.

The findings of this study are interesting. Sociologists signal different levels of tolerance, or willingness to label someone as deviant (for example, as "ill" or "insane"), according to the social setting.[2]

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Authors' reply

EDITOR—We agree that our findings are preliminary and demand both replication and further investigation. We are currently studying social capital in the area and hope to be able to measure this separately for the larger ethnic minority groups. Regarding the problem of selection bias, we examined incidence (number of new cases) not prevalence (total number of cases). Several studies, including one from the area we studied, have shown that a very high percentage of people with schizophrenia come into contact with psychiatric services.[1–3] Furthermore in our study most incident cases were admitted via emergency psychiatric services provided centrally for the whole area. We therefore consider it very unlikely that institutional factors and labelling phenomena have influenced our results.

As schizophrenia is still highly stigmatised we do not believe that non-whites in the smaller groups selected themselves for hospitalisation. Similarly, the very high rates of compulsory admission are against the view that schizophrenia is considered a "luxury" problem in our local community. It is, of course, never possible to completely rule out selection bias, as we discussed in the paper, but the magnitude of our findings give us confidence in the conclusion that the smaller the minority, the greater the incidence of schizophrenia.

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Antiplatelet therapy and atherosclerotic events

Commentary is inaccurate

EDITOR—We endorse the response of Baigent and others to Cleland's commentary on the Antithrombotic Trialists' antiplatelet meta-analysis.[1–3] We would like to add some further comments in response to Cleland's article and the editorial in the same issue.[4]

Both suggest that the data in the meta-analysis were revised retrospectively. But the overview methods were planned prospectively. Differences between the data in trial publications and the dataset used for the meta-analysis occurred where trialists provided additional information on the numbers of patients originally randomised, or on unpublished or subsequently available outcomes for small numbers of patients. Minor differences between the current and previous antiplatelet overviews generally relate to additional, unpublished data from a few trials and do not affect any of the results or conclusions.

The claim by Reilly and FitzGerald that the absolute reduction in vascular events with antiplatelet treatment is smaller in acute ischaemic stroke than in other high risk conditions is incorrect. For every 1000 patients treated, about 10 events are prevented in the first month after onset of stroke, and just over one event per month is prevented with long term treatment thereafter.[3]

Cleland finds it remarkable how seldom trials of antiplatelet agents have shown benefit on their selected primary outcome. Many early trials of antiplatelet treatment were too small to detect moderate benefits reliably, which is why the first meta-analyses were needed. Reilly and FitzGerald suggest that meta-analysis is no longer needed because large enough trials are now being done. This view fails to acknowledge that, firstly, meta-analysis of large trials can assess not just whether a treatment works but also for whom and by how much, and, secondly, trials comparing different antiplatelet regimens have rarely been large enough to detect the small differences expected.

Cleland says that inconvenient trials are ignored in the discussion section of the meta-analysis, citing an unpublished antithrombotic trial, which included fewer than 200 patients and recorded only about 50 vascular events in its comparison between aspirin and control. Including this trial in the meta-analysis would make no difference to the results. Cleland also cites an economic appraisal of aspirin, which he co-authored. Its first sentence, that aspirin is a cheap drug that is effective for the prophylaxis of cardiovascular events, contrasts with the views in Cleland's commentary.

Finally, unlike the Antithrombotic Trialists' meta-analysis, neither the accompanying editorial nor the commentary has been endorsed by hundreds of collaborating trialists worldwide. Furthermore, Cleland's commentary was published despite a reviewer pointing out that his views are maverick, and despite the fact that the conclusions of his article rely on basic errors of fact.[2]

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Competing interests: CS, PS, and CW are members of the steering committee of the Antithrombotic Trialists' Collaboration. CW participated in co-ordinating the current cycle of the collaborative overview and was a member of the writing committee for the antiplatelet meta-analysis.

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Risks and patients' values need to be included in decision about aspirin for prevention of coronary heart disease

EDITOR—The updated meta-analysis by the Antithrombotic Trialists' Collaboration confirms the benefits of aspirin in reducing non-fatal myocardial infarction, non-fatal stroke, vascular deaths, and total mortality in patients at high risk of vascular events.[1] High risk was defined as patients with previous occlusive events or predisposing conditions (for example, diabetes) that led to risks of having a vascular event that were greater than 3% per year.

On the basis of these findings, the authors recommended aspirin for patients with high cardiovascular risks and low or average risks of gastrointestinal bleeding. In their discussion, they also recommended aspirin for patients at intermediate risk of vascular events (annual risk of 2-3%), including those with peripheral vascular disease, stable angina, or atrial fibrillation. They then concluded by saying that for most healthy people, for whom the risk of a vascular event is likely to be substantially less than 1% per year, daily aspirin may well be inappropriate.

We performed a systematic review and meta-analysis of the effect of aspirin in adults with no previous history of cardiovascular events for the US Preventive Services Task Force.[2] On the basis of the results of five large trials that evaluated the use of aspirin for patients without cardiovascular disease, we concluded that aspirin reduced the risk of non-fatal myocardial infarction and deaths from coronary heart disease by 28%.

Aspirin had little effect on thrombotic strokes or all-cause mortality over the three to seven year duration of the trials. The risk of coronary heart disease of patients in the five trials ranged from 0.36% to 1.24% per year, well below the high risk patients studied in the *BMJ* review. We found that the harms of aspirin included increased risks of haemorrhagic stroke and gastrointestinal bleeding that were similar to the levels found in the trials with patients at high risk.

We concluded that the number of potential reductions in events of coronary heart disease exceeded the number of potential precipitated adverse bleeding events when patients have an annual risk of 1% or greater of events of coronary heart disease. Numbers of adverse effects approached the numbers of beneficial effects when the annual risk of coronary heart disease was 0.2% or less. The balance of beneficial and adverse effects was closer for patients with risks of 0.2-1.0% per year. Providers and patients can easily measure such risks by using any one of several cardiovascular risk calculators available on the web, including our own site (www.med-decisions.com). We recommend that providers and patients incorporate both risk and patient values about those risks into their decisions regarding whether or not to use aspirin.

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Fortification of flour with folic acid

Fortification has several potential risks

Editor—Wharton and Booth recommend caution and carrying out a field trial before a policy of fortifying flour with folic acid is implemented, but both they and the Department of Health's report understate the potential risks of the policy to the nervous system.[1]

In people with vitamin B-12 deficiency, giving folic acid does much more than mask any anaemia. The response of pernicious anaemia to folic acid is usually suboptimal and temporary and often followed by relapse. The vitamin precipitates not only neurological complications, sometimes after some initial temporary improvement, but also anaemia, although not necessarily to the same degree or in the same time scale.[2 3]

Can these problems with usually pharmacological doses of folic acid (1-50 mg daily) be avoided with minimum food fortification? The only evidence I know of is a review of 38 patients with vitamin B-12 deficiency treated with ⩽1 mg folic acid, 30% of whom showed a significant haematological response. None of 25 patients treated for 7-19 days developed nervous system disorder, whereas six of 12 treated for 90-930 days did. Isolated examples of a reticulocyte response and neurological deterioration occurred with doses as low as 0.3-0.5 mg daily.[4] Because of the very active blood-brain barrier for folate the vitamin enters the nervous system slowly and the duration of treatment is just as important as the dose, which is highly relevant to food fortification.[3 5]

Folic acid does much more than interfere with the metabolism of antiepileptic drugs. Experimental studies have confirmed that folates are highly convulsant if the blood-brain barrier is circumvented. The risk to patients is small because of the barrier mechanism, but the bigger the dose, the longer the duration, and the greater the damage to the blood-brain barrier then the higher the risk.

I do not agree that the benefits of fortification are clear. They may be relatively clear with respect to the prevention of neural tube defects, but not all such defects are preventable with folic acid. The Department of Health's report estimates that fortification with 240 μg folic acid/100 g flour would prevent a further 74 cases (41%) in the United Kingdom. Given the potential risks to others, the policy of universal food fortification seems disproportionate.

Other, potentially much greater benefits of food fortification exist (including in vascular disease and to mental health), which have yet to be clarified. The possible benefits for mood, cognitive function, and ageing are considerable but have not been evaluated.[3 5]

For all these reasons field trials are advisable before the whole population is exposed to a prolonged increase in folate intake.

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Fortification is needed now

Editor—Wharton and Booth raised several points about the safety of fortifying food with folic acid to prevent neural tube defects.[1] In my opinion, the negative effects of food fortification are overstated.

The risk of folate masking B-12 deficiency leading to spinal cord degeneration is probably low.[2] It is well known that neuropathies due to B-12 or folate deficiency can occur without megaloblastic anaemia. Surely an increase in cord degeneration would have been seen by now in the United States, where food has been fortified since 1998. Even if it was increased, this risk could be abrogated by food fortification with vitamin B-12 in addition to folate.[3]

Interference with antiepileptic drugs is unlikely to occur at the levels of fortification proposed. As the risk of fetal abnormality is increased in people with epilepsy who are taking drugs, especially in those taking sodium valproate, folate supplementation in this group is even more important.

Although it is mentioned in the editorial, not enough weight is given to the effect of folic acid in reducing plasma homocysteine concentration, an emerging risk factor for atherosclerosis. Many case-control studies show that patients with high homocysteine concentrations are at increased risk from ischaemic heart disease and stroke, probably because of direct vascular endothelial damage.[4] The potential positive effects of folate on the vascular endothelium have been shown in recent short term randomised controlled trials in high risk groups.[5]

More extensive trials are ongoing, but they will probably show a magnitude of benefit similar to that estimated by case-control studies. As 10-20% of the population have high homocysteine concentrations, and this proportion increases with age, the potential health improvements are large and are likely to much outweigh the theoretical negative effects mentioned in the editorial.

A controlled trial of folate fortification, as suggested, would have to be conducted over an extended period to show the positive and negative effects adequately. During this time, preventable morbidity and death from atherosclerotic disease would be likely and many women would have unnecessary second trimester terminations. Folic acid fortification should be started as soon as possible.

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Treatment of intersex needs open discussion

EDITOR—It is excellent to see surgery for ambiguous genitalia and intersex being openly discussed.[1–5] These articles prove what patients have been saying for years, that surgery can, and does, cause damage to sexual function. This research is long overdue and most welcomed by patients and parents. I agree that cosmetic genital surgery needs to be reassessed.

Parents and patients need to have all the facts explained before opting for irreversible genital surgery. This is especially so in the changing NHS that is aiming to be more patient led. Fully informed consent is important (particularly after the Bristol and Alder Hey scandals), and may be lacking in patients with ambiguous genitalia or intersex as surgery is often done on children before they can give consent. If parents are to make these decisions they need the full facts or they will end up with feelings of extreme guilt for damaging their child's sexual function by having early surgery. Ambiguous genitalia or intersex are nothing to be ashamed of; being more open can only help people lead better lives. More research is needed into whether leaving surgery until adolescence will have psychological effects compared with surgery in early infancy as is current practice in the thought that it reinforces sexual identity. This gives rise to the necessity for multidisciplinary treatment centres to treat the conditions with a more holistic approach encompassing surgery, endocrinology, and psychology.

Two conferences in 2000 brought together professionals and patient support groups to present their views. Universities have also invited patient groups to speak to medical students to learn from patients the effect on lives of people with ambiguous genitalia.

Support groups are professional and not disgruntled haters of doctors. They work closely with the medical profession to improve treatment, raise awareness, and support patients. Patients have the opportunity to air their views only in the media, which can often distort important issues.

When doctors come to our conferences and take time to listen to patients, parents, and support groups, they learn more than they do in the few minutes of a consultation. Patients are more likely to open up and talk to doctors who take an interest in how conditions affect people's quality of life and everyday living.

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Doctors' knowledge of radiation exposures is deficient

EDITOR—We read with interest Adams's personal view and share her concerns.[1] At one of our hospitals a young boy with splenic trauma received serial computed tomography scanning of his upper abdomen to assess the degree of splenic laceration. The scans were discussed at a multiple disciplinary meeting, and a query was raised regarding the radiation dose received by that patient. It became clear that the requesting doctors were unaware of the dose.

We compiled a simple questionnaire and interviewed 130 doctors of all grades, including consultant radiologists. They were asked for an approximate dose of radiation to the average patient having chest radiography. This was then used as a unit of 1 to calculate how many units a patient would receive for a wide variety of investigations carried out in a busy radiology department of a district general hospital (17 examinations in total).

The results were appalling. With a pass mark of 50% only three doctors (2%) passed, and that was with a generous marking scheme—20% error allowed and no negative marking. Many doctors were able to score at all only because they realised that ultrasound examinations do not use ionising radiation. The degree of knowledge was inversely proportional to seniority, with consultants scoring less than junior colleagues. It was clear and worrying that doctors have no real knowledge of radiation doses that their patients receive.

The fact that computed tomograms of the entire body can be performed on a single breath hold over a matter of seconds does not mean the patient is getting a lower radiation dose than they would have received 10 years ago. Although the Ionising Radiation (Medical Exposure) Regulations 2000 are in place, which means that it is a legal requirement to keep radiation exposures as low as possible and that they should be justifiable, it seems that knowledge is still seriously lacking.

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Prevalence of surnames in each letter affects order of authors

EDITOR—Chambers et al's study of the order of authorship in a study seems to be lacking in at least one way.[1] I have observed that surnames, especially those with a British origin, tend to begin with letters from the first half of the alphabet. For example, among the research group to which I belong, surnames begin with A, A, B, C, H, J, K, L, L, L, M, P, R, R, S, and S. According to probability, a random drawing of three of my colleagues' names to determine the order of authorship would be more likely to result in the first author having a surname beginning with a letter in the first half of the alphabet than in the second.

The graph in Chambers et al's paper presents only the percentages of names in their study; it does not indicate (except for Q and X) what the prevalence was for surnames beginning with each letter. Thus it unfortunately does not allow us to evaluate whether adjustments are needed. This study could be enhanced by adjusting the analysis for the higher prevalence of surnames that begin with first letters from the first half of the alphabet.

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