Letters

Impact of postmenopausal hormone therapy on cardiovascular events and cancer

More women are excluded from treatment arm of such trials because of cardiovascular events

EDITOR—Elina Hemminki and Klim McPherson studied the impact of postmenopausal hormone therapy on cardiovascular events and cancer.[1] Meta-analysis has both potential and limitations,[2] and the authors comment on bias introduced when data are pooled from clinical trials designed to measure something different. Data on cardiovascular events and cancer "were given incidentally," mostly as "reasons for dropping out." The authors conclude that pooled data do not support the notion that hormone replacement therapy prevents cardiovascular events, but a more honest interpretation is surely that a much higher proportion of women are excluded because of cardiovascular events from the treatment arm of such trials. Given the difficulty of blinding patients and the culture connecting hormones with blood clotting, this is not surprising.

The best information we have on the relation between hormone replacement therapy and mortality comes from the nurses' health study.[3] In this study of over 120 000 women followed up since 1976, over 3600 women died, each of whom was matched with 10 controls. After adjustment for confounding variables, current hormone users had a lower risk of death; indeed, current hormone users with coronary risk factors had the largest reduction in mortality (relative risk 0.51; 95% confidence interval 0.45 to 0.57). While benefit decreased with long term use and was reversed more than five years after therapy (probably due to the increased risk of breast cancer and the "catching up" of postponed deaths), the overall impact of hormone replacement therapy on mortality was positive.

We calculated the numbers of deaths in two cohorts of 1000 women from age 55 (the average menopausal age), one of which took hormone replacement therapy for 10 years and was followed up for 10 more years, and the other of which did not take hormone replacement therapy. We used Northumberland's age specific death rates and relative risks from the nurses' health study[3] (table).

Although the relative risk of benefit was reduced during the second five years of therapy, the number of deaths prevented was more than in the first five years. Secondly, although in the final five years more deaths occurred in the cohort who had been given hormone replacement therapy, this group showed considerable benefit over the whole 20 year period. Thus the number needed to treat with hormone replacement therapy for 10 years to prevent one death was 54, compared with 70 for mild hypertension.[4] Even if it did not benefit patients through good effects on menopausal symptoms and osteoporosis, hormone replacement therapy seems to be a good public health measure for women.

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1 Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;315:149-53. (19 July.)
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Effects of hormone replacement therapy (HRT) in 1000 women given HRT and 1000 women not given HRT

	During HRT		After HRT	
	< 5 years	5-10 years	< 5 years	⩾ 5 years
Age group (years)	55-59	60-64	65-69	70-74
Relative risk of benefit*	0.56	0.6	0.81	1.16
Crude rate of death in Northumberland in 1995 (No/1000)	5.46	10.96	17.29	28.91
Calculated No of deaths:				
In cohort not given HRT	27	53	79	121
In cohort given HRT	15	32	67	149
No of deaths postponed	19			
No needed to treat	54			

*Relative risk in cohort not given HRT=1.00.

Search for studies was limited

EDITOR—Elina Hemminki and Klim McPherson's pooled analysis addresses the possible cardioprotective effect of hormone replacement therapy.[1] We are concerned, however, that the headline results of the paper had the potential to mislead practitioners and patients. Our main concern was the use of results from short term trials of hormone replacement therapy to refute a hypothesis, the cardioprotective effect of such therapy, which was generated from long term observational epidemiological studies. This confusion between short and long term outcomes does not help in clinical decision making on the use of hormone replacement therapy.

Our specific concerns focus on the selection of studies for analysis, the ascertainment of end points, and the method of analysis. The search for relevant trials seems to have been restricted to Medline, specific languages, and a limited time period. Other

Advice to authors

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When deciding which letters to publish we favour originality, assertions supported by data or by citation, and a clear prose style. Letters should have fewer than 400 words (please give a word count) and no more than five references (including one to the BMJ article to which they relate); references should be in the Vancouver style. We welcome pictures.

Letters, whether typed or sent by email, should give each author's current appointment and full address. Letters sent by email should give a telephone and fax number when possible. We encourage you to declare any conflict of interest. Please send a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

We may post some letters submitted to us on the world wide web before we decide on publication in the paper version. We will assume that correspondents consent to this unless they specifically say no.

Letters will be edited and may be shortened.

authors suggest that Medline may contain only 30-80% of relevant trials on a particular subject.[2] The reliance on published end points in the study meant that data on cardiovascular disease were not available for 13 of the 22 studies identified. Some of these data might have been available from direct contact with the authors. These factors are potential sources of bias in the pooled analysis which may be just as important as the possible selection bias in observational studies. Also, the validity of directly pooling studies that were heterogeneous in terms of intervention, population, and time for follow up was not addressed.

The main conclusions of the study were based on a P value of 0.04 from a test of significance on a hypothetical null hypothesis of an odds ratio of 0.7. The choice of null hypothesis is critical, and if an odds ratio of 0.8 had been chosen the results would not have been significant. This approach to analysis hides the fact that the sample size was too small to detect an odds ratio of 0.7. Our calculations suggest that a sample size of 50 000 would be required.

As the authors note, pooled analysis has the potential to enhance the usefulness of small trials. It is essential, however, that such analysis is conducted with adequate attention to the possible pitfalls and biases as these studies can greatly influence clinicians, decision makers, and the public.

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1 Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;315:149-53. (19 July.)
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Paper's main conclusion is no longer justified when data from all trials are considered

Editor—Elina Hemminki and Klim McPherson's meta-analysis concluded that hormone replacement therapy does not protect postmenopausal women against cardiovascular events.[1] This finding is shocking: not only did it conflict with the results of large observational studies[2] but the meta-analysis also managed to obtain such an apparently definitive conclusion from relatively few patients (4000) and cardiovascular events (17). These assertions seemed, however, to be based on odds ratios calculated without data from the most recent and largest trial.[3] (Their table of odds ratios gave a total of 2859, while their abstract talked of 4124 patients. The difference is the exact number in the latest trial.) Repeating their analysis on the data from all the trials gave odds ratios of 0.95 (95% confidence interval 0.31 to 3.1) for cardiovascular events and 2.0 (0.23 to 45) for thromboembolic events. In contrast to the reported odds ratios of 1.39 and 2.89, these odds ratios were consistent with hormone replacement therapy reducing cardiovascular events by 30%. Hence the main conclusion of the paper is no longer justified when data from all the trials are considered.

Regardless of the actual odds ratios, however, I am concerned about the reliability of the data and the methodology used in the meta-analysis. Firstly, the study used data from trials designed to study outcomes other than cardiovascular disease and cancers. There is no guarantee that the reporting of adverse events in the hormone and control groups would be unbiased.

Secondly, only seven of the 23 trials reported any cardiovascular or thromboembolic events. Strictly, only these trials provided information on the effect of hormone replacement therapy in patients compared with a control group. However, data were analysed as if they came from one large trial, which they clearly did not.

Thirdly, the meta-analysis was prompted by the high incidence of cardiovascular events in one trial[4]; in fact, without this trial the meta-analysis contained too few events to provide any useful, additional, information on the issue.

Fourthly, the study included strokes among the cardiovascular events. Yet observational studies suggest little protective effect of hormone replacement therapy against stroke.[2] Considering strokes and coronary heart diseases separately, however, again leaves too few events to be useful.

In conclusion, the meta-analysis provided no evidence to suggest that hormone replacement therapy does not protect postmenopausal women against cardiovascular events. Publication of this meta-analysis despite its low power, methodological weaknesses, and possible errors reinforces the need for caution and scepticism in interpreting results from meta-analyses of predominantly small trials,[5] particularly those reporting controversial results.

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1 Hemminki E, McPherson K Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;315:149-53. (19 July.)
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Combining thromboembolic events with cardiovascular events does not support odds ratio of 0.7

Editor—One of the key messages in Elina Hemminki and Klim McPherson's paper was that there was insufficient evidence to suggest that postmenopausal hormone therapy prevents cardiovascular events.[1] This conclusion, however, is based on the pooling of adverse thromboembolic events with cardiovascular events. The meta-analysis reported in table 2 of the paper shows that the odds ratio of a cardiovascular event alone was 1.39 (95% confidence interval 0.48 to 3.95), which does not rule out the true odds ratio of 0.7 (P = 0.1); combining thromboembolic events with cardiovascular events raised the odds ratio to 1.64 (0.65 to 4.18), which does not support an odds ratio of 0.7 in the population (P = 0.04). Thromboembolic events are a known side effect of hormone replacement therapy,[2] and adding them to cardiovascular events would inflate the figures. In fact, the postmenopausal oestrogen/progestin interventions (PEPI) trial, which was quoted as an inspiration for the authors, shows only five events for cardiovascular disease compared with 10 for thromboembolic disease among the treatment groups.[3] The nurses' health study of nearly 60 000 women studied over more than 600 000 person years has shown a large decrease in the risk of major coronary heart disease among women taking hormone replacement therapy.[4] Hemminki and McPherson's paper fails to contradict that finding.

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1 Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;315:149-53. (19 July.)
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Inclusion of one particular study was inappropriate

Editor—We have concerns about the appropriateness of the methodology that Elina Hemminki and Klim McPherson used in their meta-analysis.[1] The methods section describes 22 studies on 4124 women, but table 1 gives details of 23 studies on 4164 women. The main results (table 2) seem to relate to an unspecified number of studies on 2859 women. In that table the odds ratio for cardiovascular events is given as 1.39, which suggests that women who receive postmenopausal hormone therapy may be at increased risk and certainly do not have the benefit of a 0.3-0.7 relative risk, as many authors have claimed.[2-4]

The three cardiovascular events attributed to the 1973 paper by Aitken et al[5] relate to a high dose of the oestrogen mestranol, which has not been used for over 20 years. Mestranol is generally agreed to be unacceptable for use postmenopausally. In Aitken et al's study, women underwent oophorectomy premenopausally and were recruited after a variable period ranging from six weeks to six years; although they were matched to the placebo group for

height and weight, they were not matched for cigarette smoking or concomitant drug treatment. Smoking is fundamental here since it is particularly harmful to users of mestranol even at young ages.

Non-selective analysis of all the studies in table 1 gives an odds ratio of just under 1.0, and if Aitken et al's study is removed the odds ratio approaches 0.7. Clearly, little can be said with certainty if these studies are examined in isolation.

In making these calculations of different odds ratios we have followed the methodology adopted in the paper of summing the events and numbers of women across the studies. This, however, is a non-standard method that has the potential to be misleading. The more usual approach is to maintain the distinctness of the studies and to pool their findings by using a Mantel-Haenszel estimate or similar technique. This approach is preferable since it assumes only that the odds ratios are constant across studies; the absolute risks of a cardiovascular event may differ. The authors' method of analysis makes sense only if the studies are similar in all respects, such as inclusion criteria, doses, and length of follow up.

The authors seem to have ignored the considerable volume of recent literature, which includes not only epidemiological data but also other direct intervention studies.

The selected studies contain little information about the real impact of postmenopausal hormone therapy on cardiovascular events. Given the impact of such evidence based conclusions, it is disappointing that the methodology was not more rigorous.

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1 Hemminki E, McPherson K. Impact of postmenopausal hormone therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;315:149-53. (19 July.)
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Study's conclusions were incorrect

EDITOR—After pooling data from randomised clinical trials examining the effect of postmenopausal hormone replacement therapy on cardiovascular events and cancer, Elina Hemminki and Klim McPherson concluded that the "data do not support the notion that postmenopausal hormone therapy prevents cardiovascular events."[1] This conclusion is at odds with multiple previously published meta-analyses of observational studies. After reviewing the original studies that were pooled in this analysis we have several concerns regarding both the methods applied and the interpretation of the results. The authors did not use the standard accepted techniques for performing meta-analyses and for pooling studies, and they did not consider differences in dosing regimens and duration of follow up. In calculating the odds ratio for cardiovascular events related to hormone use they included numerous "non-informative" studies that contained no information about whether patients, in fact, experienced such an event. Additionally, two of the 12 reported cardiovascular events among users of hormone replacement therapy were misclassified: one was an episode of palpitations associated with chest pain without myocardial infarction, and the other was an episode of superficial thrombophlebitis.[2] Finally, the authors compared their calculated odds ratio for cardiovascular events (which includes cerebrovascular events) with the odds ratio for coronary heart disease (which does not) from previous studies, blurring the distinction between cardiovascular events and coronary heart disease.

We repeated their analysis using their pooling methodology, but we corrected the two misclassifications and limited the at risk group to those studies that specifically noted the presence or absence of cardiovascular events (decreasing the hormone replacement therapy arm from 1818 to 1142 and the placebo arm from 1041 to 497). For comparison, a recent meta-analysis of observational studies found a relative risk of 0.65 of hormone replacement therapy on coronary heart disease,[3] identical with that found in the current dataset (table).

Even though the odds ratios in this analysis are based on a small number of coronary heart disease events (six among 1142 users of hormone replacement therapy and four among 497 non-users) and the confidence intervals are broad, there is a 71% probability that the true odds ratio for hormone replacement therapy on coronary heart disease is <1.0 and a 53% chance that it is <0.7. Our concern is that the authors' conclusions may be given undue weight by doctors and women, thus denying some women the potential benefit of hormone replacement therapy. Just as selection bias may affect results from observational studies, the lesson to be learnt here is that misreading and misclassifying data from randomised trials can lead to incorrect conclusions.

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Odds ratio (OR) of various cardiovascular events occurring with postmenopausal hormone therapy

Event	OR (95% CI)	Probability of obtaining this OR if true OR is: <0.5	<0.7	<1
Cardiovascular event (stroke, TIA, or CHD)	0.87 (0.30 to 2.56)	0.25	0.38	0.59
CHD	0.65 (0.18 to 2.32)	0.41	0.53	0.71
Completed stroke	0.43 (0.03 to 6.96)	NA	NA	NA
Stroke or TIA	1.74 (0.19 to 15.64)	NA	NA	NA

TIA=Transient ischaemic attack. CHD=Coronary heart disease. NA=Not applicable.

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Author's reply

EDITOR—The purpose of our work was not to make a synthesis of all the evidence concerning benefits and harms of postmenopausal hormone therapy. Its focus was narrower: simply to examine what can be learnt from published randomised trials of such therapy. The nurses' health study potentially suffers from possible selection bias, as do all non-experimental studies.Our study has its own problems, as discussed in our paper and in the letters by Sunil Shah and Leonaura Rhodes and by Valerie Seagroatt. However, the literature search was more extensive than Medline alone, as suggested by Shah and Rhodes. We did consider contacting the authors of papers not reporting adverse effects. Such an approach also has its problems, including selective response and costs, but it would clearly be worth while. We did not test whether the calculated odds ratios were significantly different from unity (as suggested by Shah and Rhodes); instead we tested how likely it is to find such odds ratios by chance, if the true ratio was 0.7 or 0.5—more sensible null hypotheses.

We grouped different types of serious (potentially life threatening) cardiovascular diseases, because for decisions whether to use postmenopausal hormones this is sensible. We kept superficial phlebitis and thrombophlebitis separate, because they have different clinical implications and are likely to be diagnosed and reported less consistently. The PEPI trial had only four thromboembolic events, not 10 as cited by Torbjorn Sundkvist (six were phlebitis).

The allocation method in Aitken et al's study is not clear, but random allocation is more likely than matched. As Farook Al-Azzawi and colleagues say, it concerned women who had undergone oophorectomy and took an atypical hormone, but it is included in our paper. We did not misclassify two cases, as suggested by Nananda F Col and colleagues. The three cases from the study by Aitken et al included in table 1 comprised one death from cerebrovascular catastrophe (reported in methods), one case of transient hemiparesis, and one case of prolonged chest pain requiring treatment

(termed ischaemic attack in a footnote to table 1). Exclusion of this study did not change our results.

Seagroatt and Al-Azzawi and colleagues wonder what the denominators were. The study by Speroff et al contributed only to the odds ratios of breast cancer, because it was not specific for other outcomes (see methods). It certainly would have been clearer to have a footnote to this in table 2. One cannot calculate odds ratios for cardiovascular diseases as suggested by Seagroatt or Al-Azzawi and colleagues. Col and colleagues seem to have interpreted non-informative studies differently from us, but they do not specify the trials they have excluded. Since we excluded none that fitted our criteria we still are more confident with our analysis than theirs. Reducing the denominators, unnecessarily excluding the two cardiovascular events, and breaking the outcomes into small subgroups seem to explain their different results.

We found two new trials only after we had completed the final manuscript. Unfortunately, when we added their data we failed to correct a few numbers. The correct number of trials is 23, and the number of women is 2899 without Speroff et al's study and 4164 with it. These inaccuracies do not influence our results, but we apologise for the confusion they caused for readers.

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It is right to publicise recent advances in the media

EDITOR—Given his own flirtation with the media over the IVOX device (a little known research cul de sac), Tom Treasure was being disingenuous in his implied unhappiness over our public enthusiasm for our contributions to innovation in cardiac surgery.[1] Why, in purporting to review recent advances, did he disregard recent evidence that was certainly available to him—wringing his hands meanwhile over its alleged absence? What, if any, was the significance of his parting shot at the results of our initial efforts at ventricular reduction? The three deaths in our first four cases were no scoop for Treasure. In the now 18 month old television programme which seemingly ruffled his feathers, we reported the deaths fully and openly. In March this year we also reported to the Society of Cardiothoracic Surgeons of Great Britain and Ireland on our next 10 ventricular reductions; nine patients survived. Treasure was in the audience, and we responded promptly to his subsequent request for documentation of our more recent work.[2,3] We also sent copies of the abstracts from other respectable institutions, including the Cleveland Clinic (albeit this is outside London), which have cooperated over the past 18 months towards filling just those alleged gaps in functional and clinical assessment about which Treasure was so eloquent.[4,5]

There has surely never been any need for the would-be expert to dread the embarrassment of being "upstaged by friends and colleagues who heard the latest advances on the radio before breakfast." Before the advent of the internet, the abstracts of the specialist societies were a good source of information on truly recent advances—to say nothing of the good will of colleagues in the same specialty. Besides, there is nothing wrong with ignorance, provided it is genuine.

By contrast, cautious conservatism based on wilful economy with the truth erodes colleagues' good will. It also denies patients the chance to judge for themselves on matters that might be life or death to them. The paying public surely has a right to hear about potential advances at least as urgently as medical academia. Television is nowadays the most universal source of such information, and is increasingly used by medical and other enthusiasts. There is of course an onus on enthusiasts to lay out their wares honestly and in good faith, but the same onus should fall on their detractors. Candidates for novel treatments will choose their own confidence level for rejecting null hypotheses, and may well prefer to hear from enthusiasts rather than rely on conventional wisdom based on reviews as unsystematic and uninformative as Treasure's time expired offering.

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Finding of relation between epidural anaesthesia and long term backache remains valid

EDITOR—Robin Russell and Felicity Reynolds conclude in their editorial "that in no prospective study has the use of regional anaesthesia been associated with an increased risk of chronic backache."[1] The path to this conclusion and to the reassurances based on it involves stigmatising our investigation in 1990[2] (and their own previous study) as "retrospective" in design. They then attach to this the well known hazards of this approach and infer that women, in retrospect, falsely "choose to blame the epidural."

For a more judicious conclusion, we must point out that our own investigation was in fact prospective in design and based on antenatal registration of an entire cohort of women delivered at a single hospital. A concurrent record was made of all anaesthetic procedures in a form designed specially for the purposes of follow up and linked at the time with obstetric and other data. The prospective follow up was based on these prior registrations. We made no retrospective inquiries about the perceived origins of any symptom at the time of follow up. The women were asked about many different symptoms, with no emphasis on backache. They knew nothing of the inquiry during the period relevant to symptoms, and the design meticulously avoided the dangers of suggesting particular responses (for example, through too-narrowly specific inquiries). Variations in follow up intervals did not influence the differential recording of new postpartum backache in women who had and had not had an epidural. There was at that time little public perception of a possible relation between epidural anaesthesia and subsequent long term backache; we did not know of it ourselves.

It follows that the findings were not an artefact of outcome sampling, biased retrospective ascertainments of preceding hazards, or women's false attributions of the origins of their symptoms. The only "retrospective" element arises from the necessity that long term symptoms must have already occurred before they can be ascertained. Our report of a strong relation between epidural anaesthesia and subsequent long term backache was based on far more women and far more follow up years than all subsequent reports put together,[3-5] and the finding remains valid.

The conclusion of the editorial is as wrong as the arguments on which it is based. There is no justification for any global reassurance.

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Lowered risk of dying of heart attack with third generation pill may offset risk of dying of thromboembolism

EDITOR—Several reports have indicated that there is no risk of myocardial infarction associated with the use of third generation oral contraceptives containing the progestogens desogestrel and gestodene, and

Matched comparisons of use of oral contraceptive* and risk of myocardial infarction

Comparison	Myocardial infarction: Cases (n=182)	Myocardial infarction: Controls (n=635)	Odds ratio† (95% CI)	P value
No use of oral contraceptive (reference)	125	479	1.00	
Use of any oral contraceptive *v* no use	57	156	2.26 (1.32 to 3.86)	0.003
Use of first generation oral contraceptive *v* no use	14	22	4.66 (1.52 to 14.33)	0.007
Use of second generation oral contraceptive *v* no use	28	71	2.99 (1.51 to 5.91)	0.002
Use of levonorgestrel *v* no use	22	57	3.38 (1.63 to 7.00)	0.001
Use of third generation oral contraceptive *v* no use	7	49	0.85 (0.30 to 2.39)	0.758
Use of third generation oral contraceptive *v* use of second generation oral contraceptive	7	49	0.28 (0.09 to 0.87)	0.028
Use of third generation oral contraceptive *v* use of levonorgestrel	7	49	0.24 (0.07 to 0.78)	0.018

*First generation oral contraceptives contain ⩾50 μg ethinyl oestradiol; second generation oral contraceptives contain <50 μg ethinyl oestradiol and a progestogen other than desogestrel or gestodene; third generation oral contraceptives contain <50 μg ethinyl oestradiol and the progestogens desogestrel or gestodene; and compounds containing norgestimate are classed as second generation oral contraceptives.
†Adjusted for smoking, hypertension, hypercholesterolaemia, diabetes, family history of myocardial infarction, and duration of use of current oral contraceptive.

that their risk profile compares favourably with that of second generation oral contraceptives containing primarily levonorgestrel.[1-3] We report the final results of the transnational case-control study on oral contraceptives and myocardial infarction.[3 4]

In an investigation patterned after the World Health Organisation study[2] women aged 16-44 who had had a myocardial infarction were recruited into the study between August 1993 and June 1996 in 16 European centres. At least one hospital control and one community control matched by five year age band and centre were recruited for each case. Altogether 182 cases and 635 controls were enrolled: 102 cases from the United Kingdom, 47 from Germany, six from Switzerland, seven from Austria, and 20 from France. The table shows the odds ratios for myocardial infarction in women who were current users of oral contraceptives compared with women who did not use them. These comparisons were obtained by matched analysis of women who used first generation oral contraceptives (odds ratio 4.66 (95% confidence interval 1.52 to 14.33)), second generation pills (2.99 (1.51 to 5.91)), and third generation pills (0.85 (0.30 to 2.39)). There is a clear decrease in risk from first generation to third in linear trend analysis ($\chi^2 = 8.537$; $P = 0.0035$). The odds ratio for current use of third generation oral contraceptives compared with current use of second generation pills was 0.28 (0.09 to 0.87). The odds ratio for the risk of myocardial infarction was 7.2 (4.6 to 11.4) when current smoking was adjusted for oral contraceptive use.

Our study confirms the results of other investigations that showed no risk of myocardial infarction associated with oral contraceptives containing the progestogens desogestrel or gestodene. We also found a significantly reduced risk of myocardial infarction associated with third generation oral contraceptives compared with former generations.[1 2] The baseline risk of myocardial infarction in this population of young women is small, ranging from 0-3 per 100 000 women per year in 25-34 year old women and from 6-14 per 100 000 women per year in 35-44 year old women in Germany.[5] Myocardial infarction is, however, associated with a case fatality of 50% in women in these age groups.[5] Although both second and third generation oral contraceptives are safe when recommended with careful consideration of cardiovascular risk factors, the expected reduction in deaths from myocardial infarction with third generation oral contraceptives could offset any excess deaths that might be associated with venous thromboembolism.

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The investigators were accountable only to the Scientific Reference Board which approved the protocol, received periodic reports, and conducted audits on the field and of the data before submission (members listed in Lewis et al[4]).
Funding: Unconditional grant from Schering AG, Berlin.
Conflict of interest: Study funded by Schering AG, Berlin.

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Treating shoulder complaints in general practice

Authors' diagnostic system is unclear

EDITOR—On what grounds do the authors of the study on treating shoulder complaints assert that "other diagnostic classifications, such as those by Cyriax..., were not suitable for diagnosing shoulder complaints in general practice."?[1] I have been using Cyriax's methods of diagnosing and treating shoulder disorders in general practice for over 20 years,[2] with consistently good results[3]; they are quick and simple to use, being based on applied anatomy.

In contrast, the diagnostic system of Jan C Winters and colleagues is unclear. Although the authors refer to another paper, in which "the three diagnostic groups have been described in detail," this is of no help to the general reader because it is in Dutch. In the *BMJ* article the definition of shoulder complaints is too wide, encompassing pain felt anywhere from the neck and upper thorax to the wrist. Furthermore, no explanation is given of how the complicated procedures of "measuring the active and passive range of movement of the glenohumeral joint, cervical spine, and upper thoracic spine and palpating the muscle tendons on the head of the humerus, the acromioclavicular joint, and the upper ribs" resulted in patients being assigned to either a "synovial" or a "shoulder girdle" diagnostic group.

The synovial group is said to have "consisted of patients with pain or limited movement...of the glenohumeral joint." But what is the evidence for saying that "these complaints originated from disorders of the subacromial structures, the acromioclavicular joint, the glenohumeral joint, or combinations of these"? The shoulder girdle group included patients with very similar diagnostic criteria—namely, those "with pain and sometimes slightly limited range...of the glenohumeral joint." What is the basis for claiming that "these problems probably originated from functional disorders of the cervical spine, upper thoracic spine, or the upper ribs (the shoulder girdle)"? Incidentally, this sentence shows confusion about the meaning of the term shoulder girdle; it is the bony arch formed by the scapula and clavicle.

It seems to me that the results of studies of this sort—in which undiagnosed painful conditions are treated by a combination of non-specific methods applied to several different tissues—are meaningless.

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1 Winters JC, Sobel JS, Groenier KH, Arendsen HJ, Meyboom-de Jong B. Comparison of physiotherapy, manipulation, and corticosteroid injection for treating

shoulder complaints in general practice: randomised, single blind study. *BMJ* 1997;314:1320-5. (3 May.)
2 Cyriax J. *Textbook of orthopaedic medicine.* 8th ed, vol I. *Diagnosis of soft tissue lesions.* London: Bailliere Tindall, 1982:127-67. 11th ed, vol II. *Treatment by manipulation, massage and injection.* London: Bailliere Tindall, 1984:88-106.
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Diagnostic criteria must be used and therapeutic regimens standardised

EDITOR—Jan C Winter and colleagues, having recognised the high number of patients with shoulder disorders in the community, evaluated different treatment strategies.[1] There are, however, several limitations to their study, which make interpretation difficult.

The authors' oversimplification of the classification of shoulder disorders is likely to have resulted in a heterogeneous group of disorders within their study groups. The frequent lack of recognition of strict diagnostic criteria for specific shoulder disorders contributes to the confusion surrounding their management and prognosis.

In the authors' study the initial evaluation and classification were performed by one of seven practitioners, although a lack of diagnostic concordance between doctors when evaluating the painful shoulder has been reported.[2] Suitable diagnostic criteria do, however, exist and should be used to allow appropriate classification and further evaluation of specific complaints.[3] Treatment regimens must also be strictly standardised, and the use of "two of three" injection routes and "classic physiotherapy" by a group of physiotherapists causes more confusion in the interpretation of the treatments used and the results of this study. The study of treatment strategies for shoulder disorders is vital, but clear approaches to management can be devised only if specific disorders are considered as distinct entities and therapeutic regimens are strictly standardised.

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1 Winter JC, Sobel JS, Groenier KH, Arendzen HJ, Meyboom-de Jong B. Comparison of physiotherapy, manipulation, and corticosteroid injection for treating shoulder complaints in general practice: randomised, single blind study. *BMJ* 1997;314:1320-5. (3 May.)
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Study's results must be viewed in context of Dutch, not British, physiotherapy practice

EDITOR—I was pleased to read that all treatments of shoulder complaints (that is, corticosteroid injection, manipulation, and physiotherapy) "significantly reduced the patients' pain scores" in the study by Jan C Winters.[1] In this study, however, physiotherapy was defined as "'classic' physiotherapy—such as exercise therapy, massage, and physical applications." The use of "such as" creates some uncertainty over the specificity of the physiotherapy administered. Notwithstanding this, classic physiotherapy, based on the definition of Koes et al,[2] was listed as "exercise therapy, massage, and physical applications," and the authors emphasised that "no mobilisations or manipulations were allowed." Although Koes et al's definition of classic physiotherapy was seen as satisfactory and may represent Dutch physiotherapy practice, it misrepresents British physiotherapy practice. Firstly, the definition is misleading; physiotherapy is not prescriptive but is personalised to the patient's complaint. Secondly, the treatment options for British physiotherapists managing shoulder complaints would certainly include mobilisations and manipulations[3] (along with other options not mentioned—for example, taping and strapping, and muscle re-education techniques). The study states that for "shoulder girdle disorders, manipulation seems to be the preferred treatment." If mobilisations and manipulations had been included as a physiotherapy option for shoulder girdle disorders (as would have been the case in Britain) it is arguable that the results of physiotherapy would have been more favourable. Therefore, as this study misrepresents British physiotherapy practice it is important that readers view the results of physiotherapy in the context of Dutch practice.

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1 Winters JC, Sobel JS, Groenier KH, Arendzen HJ, Meyboom-de Jong B. Comparison of physiotherapy, manipulation, and corticosteroid injection for treating shoulder complaints in general practice: randomised, single blind study. *BMJ* 1997;314:1320-5. (3 May.)
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Author's reply

EDITOR—The criticisms in these letters mainly concern two points: diagnostic aspects and the treatments given. The Cyriax classification suggests that certain shoulder disorders can be recognised by specific findings on physical examination and that these disorders are specific entities that need a specific treatment and run their own course over time.[1] Although these assumptions are widely accepted, little research has been done to prove them (except in frozen shoulder).

In our study the criteria for a specific shoulder disorder were also fulfilled in other shoulder disorders.[2] In addition, a group of patients with shoulder complaints was found who did not have abnormalities of the range of motion of the scapulohumeral structures on passive physical examination (shoulder girdle group).

In a cluster analysis of 30 variables of medical history and physical examination of patients with shoulder complaints, only three stable clusters could be identified by the degree of restriction of scapulohumeral mobility (none, average, and severe).[3] No specific patterns in limitation of mobility could be found. Another study showed the correlation between the course of pain and restriction of mobility of the scapulohumeral joint.[4] Bamji et al found complete diagnostic agreement in only 46% of cases.[5] These findings show that specific shoulder disorders cannot be diagnosed properly (if they exist at all). The findings of the physical examination are overrated for diagnostic interpretation in a pathological-anatomical classification. They may be more useful for assessing the degree of inflammation or irritation of the joint or the adjoining structures than establishing the exact anatomical location of the disorder. Because of these arguments we devised a more superficial (and easier) classification (synovial, shoulder girdle, and combinations).

If a reliable specific diagnosis cannot be made then a specific treatment is unlikely, which means that injections in specific structures are not indicated. As there are only three principle structures (the joint capsule, the subacromial structures, and the acromioclavicular joint) we chose the multiple injection scheme, with the results described in the article. We used the definition of physiotherapy used by Koes et al; it is the same as that given by the Dutch healthcare department.

The aim of the study was to investigate what kind of physical treatment is indicated in patients with shoulder complaints. Our main conclusion was that manipulative treatment has a satisfactory effect, especially in patients with a shoulder girdle disorder. The other physical treatments had no effect. Our results show that, with a simple diagnostic classification and a simple therapeutic strategy, satisfactory results can be achieved.

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1 Cyriax J. *Textbook of orthopaedic medicine.* 11th ed, vol 1. *Diagnosis of soft tissue lesions.* London: Bailliere Tindall, 1984:127-58.
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GPs and health authority believe that locality commissioning will improve services

EDITOR—We agree with Christine E Hine and Max O Bachmann that the collaboration of general practitioners and health authorities at locality level has enormous potential for improving local services for patients.[1] A similar evaluation to the authors' was carried out in Ealing, Hammersmith

Perceptions of lead general practitioners (GPs)* and health authority link staff† of benefits of future involvement of GPs in locality commissioning (ranked in descending order of GPs' agreement). Figures are numbers (percentages) of those who agreed or strongly agreed

	GPs (n=40)	Health authority link staff (n=23)
Sharing of good ideas between GPs and health authority	32(94)	15 (88)
Better understanding by GPs of commissioning process	29(85)	17(100)
Sharing of good ideas between GPs	29(85)	17(100)
Meeting patients' (health) needs	28(82)	15 (88)
Improved quality of services	27(79)	16 (94)
Better understanding of primary care by health authority	27(79)	15 (88)
More equitable distribution of resources	25(76)	16 (94)
Increased range of services	22(65)	6 (35)
Shift of resources from secondary to primary care	21(62)	11 (65)
Mutually agreed evidence based guidelines	19(56)	12 (71)
Change of provider(s)	19(56)	8 (47)
Meeting standards in patient's charter	16(47)	3 (18)
Meeting Health of the Nation targets	9(27)	4 (24)
Too early to say	4(12)	1 (6)

* Lead GPs comprised 30 GP locality leads (two leads for each of 15 localities) and 10 other GPs who also sit on district wide GP commissioning executive.
† Senior managers immediately below level of executive directors.

and Hounslow Health Authority, involving the elected lead general practitioners in the 15 localities, members of the general practitioner commissioning executive, and health authority link staff working with general practitioners in localities. The evaluation was based on both responses to questionnaires and interviews carried out 15 months after the launch of locality commissioning. The response rates were 85% (34/40) and 74% (17/23) for general practitioners and health authority staff respectively.

Most of the benefits reported were in primary care and community services. These benefits included improvements in physiotherapy services, having a named contact for community psychiatric nursing, the availability of district nursing after 5 pm, and the redistribution of midwives according to need rather than historic practice. Both general practitioners and health authority staff agreed that locality commissioning would lead to many benefits (table).

As in Hine and Bachmann's study, the perceived barriers were lack of training for general practitioners and health authority staff, insufficient time for general practitioners, and the reluctance of general practitioner colleagues to take on extra work. An additional barrier was the lack of clarity about what locality commissioning was trying to achieve and how this differed from health authority commissioning and individual practice based fundholding.

The general practitioners were asked their views about holding budgets, setting priorities, and their future preferred model of locality commissioning. Twenty of the 34 respondents wished to be involved in setting priorities, and 16 wished to manage budgets. Fourteen wished to widen the membership of locality commissioning groups, most frequently to include practice managers and nurses.

Different localities wanted different models to be developed in the future. Some wanted to manage real budgets as part of an extended general practice fundholding model. Others wanted to be in an advisory role to the health authority, similar to that described by the National Association of Commissioning GPs.[2] The challenge now for both general practitioners and the health authority will be to allow flexibility in the development of locality commissioning while maintaining integrated care to all the local residents in Ealing, Hammersmith and Hounslow.

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Rapid opiate detoxification

Assessment is needed to exclude certain patients before detoxification

EDITOR—Susan Mayor's news item on rapid opiate detoxification brought confusion and unnecessary alarm to the subject by failing to distinguish clearly between the rapid detoxification method and the similar process delivered with anaesthesia.[1] Rapid detoxification in which naltrexone is used to precipitate withdrawal and clonidine is used to modify symptoms of withdrawal was described in detail as long ago as 1986.[2 3] Our service has had eight years' experience of detoxification based on these descriptions; in recent years clonidine has been replaced by lofexidine, with enhanced acceptability and a reduced side effects profile. It is the introduction of anaesthesia and polypharmacy to the process that has, we believe, quite unnecessarily introduced major hazards.

Our experience has clarified the importance of proper assessment before detoxification. The exclusion of patients who may inadvertently be withdrawing hazardously from other drugs, especially benzodiazepines and alcohol; patients regularly using large amounts of opiates or illicit drugs which cannot be quantified; and patients with serious physical disorders or a lack of venous access has led to the technique being highly acceptable and popular with patients and staff. Clinical trials of rapid detoxification with anaesthesia cannot be justified, but comparison of rapid detoxification with methadone reduction and with methadone reduction modified with lofexidine should proceed. Indeed, we are currently contributing to the development of a protocol for such trials.

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1 Mayor S. Specialists criticise treatment for heroin addiction. *BMJ* 1997;314:1365. (10 May.)
2 Charney DS, Heninger GR, Kleber HD. The combined use of clonidine and naltrexone as a rapid, safe and effective treatment of abrupt withdrawal from methadone. *Am J Psychiatry* 1986;143:831-7.
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Acute withdrawal of opiates is indication for anaesthesia

EDITOR—We are concerned that rapid opiate detoxification under general anaesthesia is undergoing trial by media. In her news item Susan Mayor reports the death of a patient treated by this method.[1] That this death occurred in a private clinic might lead many readers to imagine that this treatment is undertaken in a dubious and poorly supervised environment. Intensive care beds and consultant anaesthetists are expensive and limited in the NHS. This procedure needs the dedicated, continuous, and close supervision of a consultant anaesthetist-intensivist, which limits the availability of rapid detoxification under anaesthesia in the NHS.

We were approached to assist in rapid opiate detoxification. After ethical considerations and advice from independent experts we agreed to proceed. In addition, the regional health authority's licensing board approved the treatment after advice from its anaesthesia adviser, a professor of anaesthetics.

We have now treated 75 patients dependent on narcotics in three intensive care units, using rapid opiate detoxification under general anaesthesia, without morbidity. Patients were assessed by a consultant psychiatrist. In our opinion this procedure is safer than prolonged detoxification with benzodiazepine sedation under supervision by psychiatrists. Deep sedation techniques can result in agitated and obtunded patients with compromised airways. Our patients were prepared for general anaesthesia, intubated, and ventilated. Invasive cardiovascular and respiratory monitoring was started.

Anaesthesia was maintained with total intravenous anaesthesia (propofol) or closed circuit isoflurane. Patients were anaesthetised for between 6 and 12 hours. During the period of anaesthesia and recovery we found minimal haemodynamic changes. Gastrointestinal side effects were controlled with octreotide. Intensive care observations were continued until all signs and symptoms of pharmacological withdrawal had disappeared. The patient was then stabilised on oral naltrexone. Patients were discharged under the supervision of a responsible adult, who was to ensure the regular administration of oral antagonists.

As anaesthetists, we believe we are ethically justified in providing anaesthesia to the highest standard in any patient undergoing unpleasant and painful treatment. We include the unpleasant "cold turkey" of acute withdrawal of opiates as an indication for anaesthesia. Clearly, whether rapid detoxification with antagonists is appropriate remains controversial among psychiatrists dealing with opiate dependence.

The time has come for this treatment to be fully recognised and subjected to unbiased scientific evaluation. While this treatment may be seen to be extremely expensive in terms of the need for intensive care beds and anaesthetists, there are obviously long term global savings if patients who are dependent on opiates are to be humanely treated.

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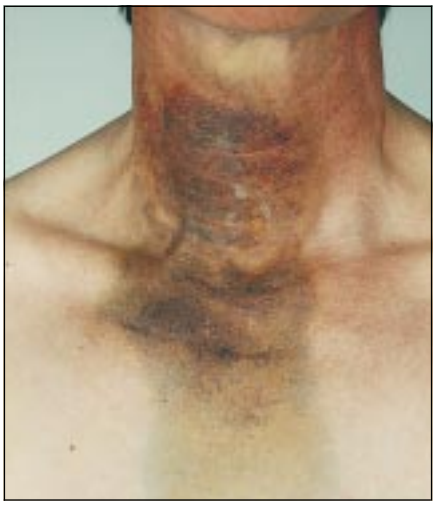
Ecchymoses may have been due to extracapsular haemorrhage from parathyroid adenoma

Editor—We would like to suggest a unifying diagnosis for the two recent reports of patients presenting with extensive ecchymoses of the neck and upper chest, associated with dysphagia and dysphonia[1 2]—namely, extracapsular haemorrhage from a parathyroid adenoma. We have recently reported and discussed the pathophysiology of this event in a woman who presented with exactly the same symptoms, as well as submucosal haemorrhage in the larynx and pharynx, ultrasound evidence of bleeding from a thyroid cyst, and hypercalcaemia (findings common to one or both of the cases above) (figure).[3]

Parathyroid adenomas may be very vascular, and extracapsular rupture will cause neck pain with dysphagia and dysphonia due to a mass effect followed by ecchymoses in both subcutaneous and submucosal tissues as a result of the tracking of blood. These adenomas may be difficult to pinpoint and can be located from the mediastinum up to the level of the internal carotid artery due to their embryological development,[4] which may explain why Walsh and Little found submucosal blood at the level of the nasopharynx.[1] It would be interesting to know if the serum calcium concentration was raised in this case. In the case reported by B G Issa and M F Scanlon the patient was already known to have primary hyperparathyroidism and a definite area of haemorrhage was found in the thyroid gland.



Ecchymoses of neck and upper chest from extracapsular rupture of parathyroid adenoma

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1 Walsh RM, Little JT. Minerva. *BMJ* 1996;312:1682.
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Inaccuracies in obituaries should not be ignored

Editor—I must correct some of the factual errors in the obituary on Gladys "Margaret" Pappworth (née Curtis).[1] I knew Margaret Curtis well in the 1960s and early '70s, and I trained her in the Family Planning Association's clinic in Attercliffe, in Sheffield. Our clinic was by then both efficient and professional; it was one of the first to start prescribing the pill, several years before Dr Curtis's arrival there, and was recognised nationally as a centre for training in family planning. Dr Curtis was one of five colleagues in Sheffield who pioneered the use of the intrauterine contraceptive device, and she soon became a senior training doctor herself. The Family Planning Association was way ahead of most medical organisations of that era in its compulsory training programmes, which included role play and peer review by video. These early courses were in London but became the pattern for a national network based on centres of excellence, of which Sheffield was one. Eventually Margaret Curtis became one of 20 or so senior doctors who went to other clinics to assess their suitability for training, but there was never a "chief inspector."

The takeover of clinical services by the NHS in 1974 was negotiated by Dr Margaret Watkinson from the Family Planning Association and Dr Stuart Horner from the BMA when Barbara Castle was at the Ministry of Health in a Labour government. Dr Curtis was one of a group who then formed the National Association of Family Planning Doctors. To her sorrow she was never chairman; neither was she president. The association became incorporated into the Royal College of Obstetricians and Gynaecologists in 1994 as the Faculty of Family Planning and Reproductive Health.

Margaret was not an easy colleague, but she was warm and generous with her hospitality. My family still remembers the Pappworths' Christmas parties with pleasure. She and her family were rarely without some major or minor drama in their lives, though I had not heard of her experiences up a crane which are mentioned in the obituary.

It may seem small minded to wish to make these corrections, but I do not think that inaccuracies should be glossed over just because the subject is no longer alive.

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1 Gladys Cotsworth ("Margaret") Pappworth (née Curtis) [obituary]. *BMJ* 1997;314:1488. (17 May.)

Pharmaceutical industry is invited to respond to amnesty for unreported trials

See p 622

Editor—Alan Maynard and Karen Bloor are correct to call for regulation of the pharmaceutical industry to ensure that all data from clinical trials are made publicly available.[1] It is now well established that underreporting of clinical trials is a potent source of bias in the medical literature on the effectiveness of treatment and that research by the pharmaceutical industry is associated with a low publication rate (27%).[2 3] The amnesty for unpublished trials announced today in the editorial by Smith and Roberts provides an opportunity for both non-industry and industry researchers, and the Association of the British Pharmaceutical Industry has been invited to respond positively to the initiative.

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1 Maynard A, Bloor K. Regulating the pharmaceutical industry. *BMJ* 1997;315:200-1. (26 July.)
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