Correspondence

Commentaries on thromboprophylaxis in hip replacement surgery

Sir—The recent commentary on thromboprophylaxis in hip replacement surgery by Christopher Bulstrode (Acta Orthop Scand 1998; 69: 343-344) cannot be allowed to pass unchallenged. His article was presumably intended as a provocative response to the review in the same issue by Ola Dahl on new frontiers and future strategy in thromboprophylaxis in hip arthroplasty. Like Bulstrode, I should also declare an interest. I am a retired hematologist and, like him, I am not receiving funds from the pharmaceutical industry, and have never carried out a clinical trial on their behalf. He may have views on the role of the pharmaceutical industry in funding clinical trials, but that does not entitle him to take such a lofty and disdainful view of those who carry out such trials in partnership with industry.

In my view, most hematologists and experts in the field of thrombosis and hemostasis would consider that Dahl's article was a well-balanced and fair analysis. Bulstrode, of course, is entitled to disagree with Dahl's assessment of the risk of thromboembolism after hip surgery, and he may be correct in his view that reducing DVT by drug thromboprophylaxis has not been shown to affect significantly the morbidity and mortality of patients after total hip replacement. Reasonable people may well disagree on this, and certainly no final answers are yet available. But what I take exception to is Bulstrode's highly objectionable remarks that hematologists working in this field are in the pay of the pharmaceutical industry, who he seems to think are their masters. Indeed, I am dismayed that a prominent orthopedic surgeon should take it upon himself to write in such disparaging terms about his professional colleagues. To claim that those who use drug prophylaxis are "gullible" and "captives of the pharmaceutical industry" is little short of defamatory, and certainly does nothing to help the ongoing debate about the best way to reduce thromboembolism after surgery. In my experience, most doctors engaged in clinical research are honourable "seekers after the truth", and it will be a sad day when we cannot make that assumption about our colleagues.

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Sir—Dr. Thomas has done me a great honor in responding to my Editorial, as it is always disappointing to receive no response to an article about which one feels strongly. He also does himself and his specialty great honor. He clearly sets very high standards for himself and expects the same of his colleagues. This Editorial was not in any way intended as an attack on the morality of hematologists. It was an attempt to open up the problems of determining the truth in research when there are very strong financial issues at stake.

A great deal of hematological research is sponsored by the pharmaceutical industry. Those who are involved in the peer review of research grants and of original papers for publication are not obliged to declare to what extent they are under the influence of pharmaceutical companies. Indeed, they may not even be aware themselves of the extent to which their ability to make objective decisions on scientific evidence is affected by underlying financial interests. The problem occurs in all specialties. In orthopedics, the problem arises when advising patients whether or not to have surgery if medical care is on a fee-for-service basis. Some orthopedic surgeons assure me that their decision to advise the patient to have surgery is not affected at all by the fact that they will earn much more if they do operate than if they do not. I have

to say that I find their naiveté touching, but not seriously credible.

There has been a paucity of studies on the relationship between deep-vein thrombosis and death from pulmonary embolus. There has also been an extraordinary paucity of studies on the side-effects of prophylactic anticoagulation. In contrast, there have been a very large number of studies on the reduction of the DVT rate in patients who are given anti-coagulants after total hip replacement. One plausible hypothesis to explain this peculiar distribution of scientific papers is that funding for research is focused on areas which suit the pharmaceutical industry. Many of us orthopedic surgeons have a touching faith in pronouncements made by physicians on complex subjects, such as thromboprophylaxis. The purpose of my Editorial was merely to cast a question mark over the assertions that there is clear evidence that thromboprophylaxis benefits patients after total hip replacements. The jury is still out, but I very much doubt that the definitive trial will be performed, because it is not in the interests of the pharmaceutical industry to allow it to happen.

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Thromboembolism—An academic concern or a clinical reality?

Sir—Recently Christopher J.K. Bulstrode was invited by the Editor-in-Chief to comment on the article by Dahl (1998) concerning thromboprophylaxis in hip replacement surgery. Bulstrode's opening statement will not be commented on, except to state that trials conducted by ourselves but funded by the pharmaceutical industry have been conducted correctly and reported accurately without undue influence from the companies concerned. Further, intellectual property rights have at all times remained with the authors and/or their host universities and not transferred to any third party.

Bulstrode's comments left the impression that thromboembolic complications after lower limb arthroplasty are probably of no clinical importance and that thromboprophylaxis is not cost-effective. Bulstrode and his co-authors found only a very low fatal pulmonary embolism rate in a meta-analysis they conducted. It is not unreasonable to question such a meta-analysis, since the authors had no access to source data and, even included retrospective studies in their analysis.

In their paper, Murray et al. (1996) state "In our meta-analysis, data were pooled from trials involving many different comparisons. This type of meta-analysis has previously been used to study thromboprophylaxis after THR and the results must be interpreted with considerable caution, since pooling is based on the assumption that patients and their management are similar in different studies." Moreover, it is worth pointing out that meta-analyses have been "demoted" on the Cochrane Collaboration ranking presumably because of the assumptions that must made unless source data are used.

Indeed, Petticrew and Kennedy (1997) in a pedagogical and debate article entitled, "Detecting the effects of thromboprophylaxis: the case of the rogue reviews" state that "The vital evidence is obscured by erroneous information—caused on this occasion by flawed methods". Furthermore, it should be noted that case-finding (typically using contrast venography) was an essential feature of thromboprophylaxis trials in patients undergoing elective hip surgery. Since the patients in the placebo group and prophylaxis group were identified as having venous thrombosis, they were treated with anticoagulant therapy. Thus, the no prophylaxis group and prophylaxis group outlined in the meta-analysis were in fact actively treated if they had deep vein thrombosis with treatment doses of anticoagulant regimens. For this reason, a difference in fatal pulmonary embolism in favor of the active thromboprophylaxis group would not be anticipated because of the active treatment effect.

Data from a National Confidential Inquiry into Peri-operative Deaths in the UK provide evidence that pulmonary embolism constitutes a significant cause of mortality following total hip replacement.

The interpretation of the majority of random-

ized clinical trials evaluating thromboprophylaxis in patients undergoing elective hip surgery is further confounded by the fact that pulmonary embolism, caused by the study design, was a secondary endpoint. Unfortunately, the autopsy rate was usually low in the patients who died. Indeed, recent autopsy data continue to show that the majority of the patients who die of pulmonary embolism, this diagnosis was not considered to be the cause of death prior to autopsy (Havig 1977, Sandler and Martin 1989, Karwinski 1995).

Thus, it is evident that meta-analytic techniques which have recently been widely criticized (Greenland 1994, Olkon 1994, Khan et al. 1996, Sacks et al. 1997), cannot be recommended. "Our study demonstrates that there is not enough evidence in the literature to conclude that any form of pharmacological thromboprophylaxis decreases the death rate after total hip replacement. For this reason guidelines which recommend their routine use to prevent death after hip replacement are not justified."

About 3000 patients have recently been included in 5 international prospective double-blind randomized studies (one is recently abstracted), using the best study design currently available (Bergqvist et al. 1996, Planes et al. 1996, Dahl et al. 1997, Hull et al. 1998, Lassen et al. 1998). All studies showed the same findings, a statistically significant reduced frequency of DVT if prophylaxis was continued with low-molecular-weight heparin (enoxaparin, dalteparin) up to 5 weeks after hip replacement surgery. To withhold thromboprophylaxis is to gamble with the patients welfare and life and should not be recommended.

"So what?"—It is a challenge for the future to design studies which reflect the clinical reality. If this should include loosening (septic/aseptic) of prostheses and infections, as suggested by Bulstrode, "to give the whole picture of benefit versus disadvantages" is not very obvious. Loosening of prostheses may be due to defective cement polymerization-cf. the Boneloc cement. The coagulation process is intimately linked to the inflammatory system and an infection and DVT may occur concomitantly.

However, in a small study, postthrombotic syndrome has been found to develop after subclinical DVT in a high percentage of hip-operated patients (McNally et al. 1994). Additional studies on that topic would be of great interest. Further, as previously pointed out (Dahl 1998), clinical trials including both venous and arterial thromboembolic events are warranted for a realistic view of the scale of posttraumatic morbidity and death caused by hypercoagulation.

With our present knowledge, posttraumatic thromboembolism is not an academic concern but a clinical reality. The consequences of such knowledge are summarized by J. Griffin, The Office of Health Economics, U.K., 1996: "The use of thrombolytic prophylaxis for the prevention of DVTs is a classic example of clinical and cost-effectiveness evidence about a therapy not being put into practice. At a time when evidenced-based medicine is receiving considerable emphasis in the National Health Service, it would appear from this research, that much could be achieved as regards cost savings and health gain, if prophylactic measures were implemented for surgical patients at high risk of developing a DVT".

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