

Quinacrine method of family planning

SIR—In his news report Malcolm Potts (March 12, p 662) reviews our 46-month field trial of nearly 32 000 women who chose non-surgical sterilisation with quinacrine pellets. It is true that we abruptly halted our quinacrine programme in December. By then the programme had reached 33 provinces and was proceeding smoothly. Stopping of the programme was prompted by a letter from Dr F T G Webb of WHO to United Nations Population Fund director Linda Demers in Hanoi. Webb stated: "WHO experts and FDA [US Food, and Drug Administration] officials have said that they would be very surprised if quinacrine did not turn out to be carcinogenic". Although we were not aware of any scientific evidence that this drug causes cancer in man, and none was brought to our attention at that time, the government felt that we had to terminate this programme in view of the authority of WHO.

Potts notes that the FDA approved phase I clinical trials in US volunteers. FDA approval followed the completion of the required toxicology work at Johns Hopkins University and this work has been published. This phase I clinical trial took place in San Antonio, Texas, and the results were satisfactory. If there were objections to these toxicology studies or to the results of this phase I clinical trial, these objections were not expressed in publications. These facts weighed heavily in our decision to move forward with this method. Webb did not explain the inconsistency between FDA approval of the quinacrine toxicology work, the approval of the clinical trial, and the statements of the unidentified FDA officials that they "would be very surprised if quinacrine did not turn out to be carcinogenic".

No scientific evidence that this drug causes cancer in man has yet been presented to us. Our position has been the one stated by the panel of toxicologists asked by Family Health International (FHI) in 1990 to evaluate the carcinogenicity of quinacrine. Their conclusion was "the lack of positive *in vivo* data and, considering the extent of medicinal use, the lack of relevant human data, suggests that the risk for cancer may be quite small" (Tice RR, unpublished). This conclusion led us to undertake our investigation in 1990. In a collaborative study by FHI and Dr Jaime Zipper of Chile, the conclusion reads, "no evidence was found of excess cancer risk associated with quinacrine pellet transcervical sterilization" (Sokel D, unpublished). WHO did not mention this work.

We have not been given an opportunity to respond by either WHO or the Association for Voluntary Surgical Contraception (AVSC) to their criticisms of our paper; instead they distributed their criticisms widely on their own. These methods stifle proper scientific debate. At the AVSC (Dec 3, 1993) meeting in New York, which was attended by WHO, our *Lancet* paper (July 24, 1993, p 213) was the major topic of discussion and was criticised extensively. This meeting was attended by representatives of about 15 organisations, but the co-authors of our paper were not invited to the meeting. There have been a few warranted criticisms of our paper, but they are minor and we can justifiably say that both the methods and conclusions remain fundamentally sound.

We were both surprised and disappointed by the treatment given by the scientific community with respect to our *Lancet* report. Scientific debate should be out in the open. Unsubstantiated opinions of unidentified WHO experts and FDA officials should not be accepted by the scientific community in this attempt to undermine our decision to proceed with this method; nor should these opinions be allowed to obstruct the international evaluation of this most promising family planning method.

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Science unblinded

SIR—In your March 5 editorial you provide arguments why blinding in randomised clinical trials is not always possible or desirable. We draw attention to a clinical trial of drug treatment in which we deliberately abstained from double blinding.

In patients with transient ischaemic attack (TIA) or non-disabling ischaemic stroke aspirin reduces the risk of important vascular events (vascular death, stroke, or myocardial infarction) by 18%;¹ in recent trials in patients after myocardial infarction oral anticoagulants show a risk reduction of as much as 35% for these events.^{2,3} Hence, a group of Dutch neurologists embarked on SPIRIT (the Stroke Prevention In Reversible Ischemia Trial), which compares the efficacy of oral anticoagulants with that of aspirin in patients after cerebral ischaemia. Patients randomised to anticoagulants are referred to the local thrombosis service for dose titration at regular intervals, and those randomised to aspirin receive an open prescription for 30 mg of aspirin **daily**.⁴ Outcome events are classified blindly. In this way the two treatment strategies reflect future practice. Double blinding would mean the use of double dummies and all patients would have to visit a local thrombosis service; also, co-medication would have to be adapted to the use of anticoagulants in all patients. In that situation the study addresses the pharmacological question of whether tablets containing anticoagulants or aspirin are better in the prevention of vascular events. We, however, wish to know which strategy is best; this also allows a cost-effectiveness analysis, which would have been of limited value in the setting of a double-blind trial.

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- 1 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; 308: 81-106.
- 2 Smith P, Arnesen H, Holme I. The effect of warfarin on mortality and reinfarction after myocardial infarction. *N Engl J Med* 1990; 323: 147-52.
- 3 Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) Research Group. Effect of long-term oral anticoagulant treatment on mortality and cardiovascular morbidity after myocardial infarction. *Lancet* 1994; 343: 499-503.
- 4 The Dutch TIA Trial Study Group. A comparison of two doses of aspirin (30 mg vs 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. *N Engl J Med* 1991; 325: 1261-66.

Munchausen's-by-proxy

SIR—In your Feb 19 news item Clare Thompson (p 471) outlines recommendations by the inquiry into the Beverley Allitt case. Apropos the four recommendations made by Sir Cecil Clothier QC, we were alarmed by the one about candidates with "major personality disorders" not being hired as nurses.

First, what does "major" imply? DSM III-R makes no such distinction in its classification of personality disorders (major vs minor) (DSM III-R). Second, personality traits show a continuous distribution without a single discrete cutoff (which would divide them) from disorders. DSM III-R defines "disorder" using the notion of significant impairment. "Significant" is left undefined. Third, the patient's cross-sectional presentation is not necessarily an accurate reflection of long-standing patterns. Moreover, the patient's description of previous functioning may be retrospectively distorted by his current mood and/or the circumstances of the **moment**.² In any specific evaluation of personality the consultant has to judge whether the patient's behaviour is deeply ingrained or a