while at the same time favouring the use of another anaesthetic agent or technique which may have even greater dangers. The fact that the Medical Research Council (27 July, p. 268) is prepared to support prospective studies on this aspect serves to emphasize that, whatever some doctors may care to believe, no cause-and-effect relationship has yet been established between halothane and hepatic damage.

Finally, since Dr. Spalding is neither an anaesthetist nor an expert on liver diseases, perhaps he would declare his interest in this matter.—I am, etc.,

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SIR,—"If a man will begin with certainties, he shall end in doubts; but if he will be content to begin with doubts, he shall end in certainties" (Sir Francis Bacon, *The Advancement of Learning*, 1605).

Dr. J. M. K. Spalding (9 November, p. 345) cannot have his cake and eat it. He condemns as unethical a prospective trial in which randomly selected patients would receive either multiple halothane or multiple non-halothane anaesthetics for their operations. On the other hand he states that "it remains the duty of the anaesthetist to give the anaesthetic which he thinks most suitable for his patient."

Dr. Spalding's argument is based on his point that "many responsible and informed doctors believe in an association between repeated exposure to halothane and liver disease." However, strongly held beliefs are not necessarily correct. For example, in 1953 other eminent and distinguished neurologists successfully imposed their beliefs on a learned High Court judge regarding paraplegia following spinal anaesthesia[1]—a significant disservice to the care of patients by anaesthetists. It is generally accepted that the same opinions would achieve little credence today.[2]

Other responsible and informed doctors acknowledge the possibility of a cause-and-effect relationship between halothane and postoperative liver damage but find the evidence unconvincing. Numerous retrospective surveys have failed to clarify the position and the recent publication of data collected by the Committee on the Safety of Medicines,[3] which has been so widely criticized, has only added to the confusion. It is for these reasons that a prospective study is urgently required. Indeed, having considered the evidence and taken further expert opinion, the Medical Research Council has concluded that this controversy can only be resolved by just such a study. Thus it is not, as suggested by Dr. Spalding, that anaesthetists "are anxious to conduct trials"; indeed, the idea was first suggested by a physician with a particular interest in gastroenterology.[4]

Despite his welcome interest in anaesthesia, Dr. Spalding apparently fails to appreciate that halothane remains the most suitable agent for rapidly repeated short surgical procedures, and in the absence of convincing evidence to suggest that repeated halothane is more likely to be associated with postoperative liver damage than repeated non-halothane anaesthetics the former agent will, rightly, continue to be widely used in such circumstances. Hopefully, as a result of a prospective survey anaesthetists would be in a better position to make a proper decision about the choice of anaesthetic, graciously acknowledged by Dr. Spalding to be their responsibility.—We are, etc.,

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1 *The Times*, Woolley and Roe v. Ministry of Health. 21 October 1953, p. 12.
2 Lee, J. A., *Anaesthesia*, 1967, **22**, 342.
3 Inman, W. H. W., and Mushin, W. W., *British Medical Journal*, 1974, **1**, 5.
4 Davies, G. E., *Proceedings of the Royal Society of Medicine*, 1973, **66**, 55.

SIR,—Dr. J. M. K. Spalding (9 November, p. 345), in elaborating his argument against the ethical propriety of conducting prospective clinical trials involving multiple halothane administration, makes the following statement: "The patients receiving repeated halothane would, however, be exposed for the purposes of experiment to something which has been suspected of causing illness and even death and the other group to something which has not been so suspected."

This statement appears to have missed the heart of the controversy, for it should read: "Each group of patients would of necessity be exposed to something which is known to be associated with illness and death; the object of the trial would be to establish whether one group of patients is more 'at risk' than the other."—I am, etc.,

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Uticillin

SIR,—I read with interest the views expressed on Uticillin (carfecillin sodium) by Dr. M. J. Bendall and Drs. H. R. Ingham and J. B. Selkon (9 November, p. 344). I would like to reply to some of the points raised in their letters.

Your correspondents state, quite rightly, that following oral administration carfecillin (the phenyl ester of carbenicillin) is hydrolysed in the body to produce carbenicillin. This hydrolysis by non-specific esterases takes place in the gut wall, portal blood, and liver to release carbenicillin, which enters the systemic circulation and is eventually excreted in the urine in an active form. The indanyl ester of carbenicillin (carindacillin) is also converted to carbenicillin in the body. In both compounds the carboxyl group which is esterified is that which is attached to the α-carbon atom of the "side-chain" rather than to the "nucleus" and therefore both the phenyl ester and indanyl ester of carbenicillin are penicillins with intrinsic antibacterial activity. This activity, however, is of no clinical relevance since the parent compounds never appear in the systemic circulation following ingestion.

The oral administration of 500 mg of carfecillin produces peak concentrations of carbenicillin of approximately 10 μg/ml in the serum and 800 μg/ml in the urine. Such concentrations in the urine are far in excess of the minimum inhibitory concentrations for most urinary pathogens. The serum concentrations are obviously inadequate to treat systemic infections due to *Pseudomonas aeruginosa* and, as Dr. Bendall indicates, such infections are usually treated with high intravenous doses of carbenicillin sodium, often together with gentamicin.

Though sulphonamides remain the primary treatment for acute urinary tract infections in general practice, carfecillin has advantages over many other agents available and is particularly indicated for the treatment of urinary infections complicated by recurrence or relapse or those in which *Ps. aeruginosa* is the offending organism. The availability of an oral antibiotic which is effective in the treatment of pseudomonas infections of the urinary tract allows earlier discharge of patients and incidentally reduces the reservoir of this organism in the hospital environment. Furthermore, patients who in the past have had to be admitted to hospital repeatedly for the treatment of recurring pseudomonas urinary tract infections can now be treated in domiciliary practice. The appearance of pseudomonas in sites other than the urinary tract would necessitate the use of carbenicillin sodium in high dosage and under no circumstances should carfecillin be used.

The introduction of Uticillin presented a dilemma inasmuch as it was essential to limit its use to the treatment of urinary tract infections. In order to identify Uticillin specifically with the urinary tract and to avoid misuse, it was considered that for the bacteriological testing of urine, discs should be provided containing carfecillin. Such discs give zone diameters comparable to those given by carbenicillin discs since carfecillin hydrolyses extensively to carbenicillin during the course of the test. The resulting sensitivity report would, however, refer to "carfecillin" rather than "carbenicillin," thus associating the use of carfecillin with the treatment of urinary tract infections only. It is unfortunate that this approach to the dilemma appears to have been misunderstood.—I am, etc.,

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John Locke

SIR,—Professor M. V. C. Jeffreys (5 October, p. 34) gives the impression that Locke, "exiled in Holland during the reign of the restored King Charles II," spent the period 1660-89 in enforced exile there. This was not the case. In 1659 he was appointed senior student of Christ Church, Oxford, a position which he continued to hold until 1683. In 1660 he was lecturer in Greek and in 1662 lecturer in rhetoric. In 1665 he was secretary in Sir Walter Vane's embassy to the Elector of Brandenburg. In 1666 he attempted to obtain a dispensation from the University of Oxford to become a doctor of medicine without becoming a bachelor, and Fox-Bourne has it that "the request of Lord Clarendon [to this end] was not heeded, probably owing to the fact that Locke belonged to the puritan party."

I see no reason to attribute this failure to Shaftesbury, of whom Professor Jeffreys