CORRESPONDENCE

Proposal to outlaw the term "negative trial"
I Chalmers, FRCP 1002

Prolactinomas
R Hall, FRCP, and others; A Grossman, MRCP, and G M Besser, FRCP 1002

Convulsions associated with cyclosporin A in transplant recipients
R J Polson, MRCP, and others 1003

Misuse of published reports in propaganda
Jennifer Harding, BA 1003

Lectins
E-N M A Lalani, MB, and M Wells, MRCPATH; P M Gaylarde, and I Sarkany, FRCP 1004

Any review is a good review
D Paterson; Anne Copley and others 1004

Leptospirosis
Margaret A Forwell, MRCP, and others ... 1005

Morbidity and survival in neonates ventilated for the respiratory distress syndrome
R R Gordon, FRCP; Anne Greenough, MRCP; P Morrell, MRCP, and E Hey, FRCP 1005

The COMA report: what it left out
Jean Marr, SRD; J H Baron, FRCP 1006

AIDS guidelines too stringent?
Sheila McKechnie 1006

Animals in research
Sir Geoffrey Slaney, FRCS 1007

Are low cholesterol values associated with excess mortality?
J P Vandenbroucke, MD; Clare E Salmond, MSC 1007

Precipitation of laryngeal obstruction in acute epiglottitis
P A D Williams, FFARCS, and others 1007

City of the plain speaking
P Bailey, BM 1007

Correction: Avoiding AIDS with autologous transfusions (James *et al*) 1007

Because we receive many more letters than we have room to publish we may shorten those that we do publish to allow readers as wide a selection as possible. In particular, when we receive several letters on the same topic we reserve the right to abridge individual letters. Our usual policy is to reserve our correspondence columns for letters commenting on issues discussed recently (within six weeks) in the BMJ.

Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue. We may also forward letters that we decide not to publish to the authors of the paper on which they comment.

Letters should not exceed 400 words and should be typed double spaced and signed by all authors, who should include their main degree.

Proposal to outlaw the term "negative trial"

SIR,—Minerva seems somewhat ambivalent about negative trials. In 1983 she thought that they "have never made riveting reading,"[1] while more recently she thought that they "are (almost) always worth putting on record" (23 February, p 644). She has come round to the right way of thinking of course, although she might have added that there is no such thing as a "negative trial." All trials that have been well conceived and well conducted[2]—whatever their results—represent positive contributions to knowledge.

I suspect that the concept of a negative trial derives from an inflated reverence for differences between trial groups which achieve some rather arbitrarily chosen level of statistical significance. The adverse consequences of this phenomenon were recognised long ago,[3] and Dr J Stuart Pocock recently made excellent suggestions for confronting it (5 January, p 39-42). One important implication of Dr Pocock's recommendations is that investigators, referees, and editors should not exercise favouritism in respect of those trials which have results which they regard as "positive."

The magnitude of the "selective publication bias" which results from editorial designation of trials as negative or positive is unknown, so there is currently no basis for dismissing it as unlikely to be important. My colleagues and I would like to try to assess the extent of selective publication bias in perinatal medicine. We have established what we believe to be a fairly complete register of published reports of controlled trials in perinatal medicine which have appeared since 1950.

We would be most grateful to anyone who could let us know about any perinatal trials which have been conducted over this period but which have never appeared in print. By comparing the results of published and unpublished trials we would hope to obtain some estimate of the extent to which diligent readers of published reports are being misled by the selective suppression both of negative trials and possibly of "positive trials" which challenge prevailing hypotheses (and are thus perceived in some powerful quarters as negative in quite a different sense).

It is particularly important to derive estimates of the magnitude of selective publication biases if the exciting new possibilities presented by "meta-analyses" of data pooled from independently mounted, but similar, trials are to be exploited in a manner which is as scientifically rigorous as possible.

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2 Mosteller F, Gilbert JP, McPeek B. Reporting standards and research strategies for controlled trials: agenda for the editor. *Controlled Clinical Trials* 1980;**1**:37-58.
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Prolactinomas

SIR,—We feel that Dr A Grossman and Professor G M Besser (19 January, p 182) have taken an overpessimistic view of the value of surgery in patients with prolactinomas. Their success rate, using radiotherapy, as judged by restoration of serum prolactin to normal in "about one third,"[1] is certainly substantially worse than surgery and on long term follow up may reveal a higher rate of hypopituitarism.

For large prolactinomas we agree with Bergh *et al* that bromocriptine is the treatment of choice to reduce prolactin, induce fertility, and decrease tumour size.[2] Thereafter it can be used to control possible expansion in pregnancy in the knowledge that the drug has no adverse effects on the fetus.[3]

The authors' objections to surgery appear to be based on one paper by Serri *et al*,[4] which gives a recurrence rate of 50% after surgery for microadenomas. It should be pointed out, however, that these results were obtained in an early series of cases, when surgery for prolactinomas was in its infancy and the importance of a wide excision of the tumour was not appreciated. It is not surprising that limited removal in the form of "selective adenomectomy" as practised in the series of Serri *et al* should result in some recurrences. We are of the opinion that after a decision to treat surgically has been made the correct operation for prolactinomas is a partial hypophysectomy which includes a wide margin of normal tissue around the tumour rather than selective microadenomectomy. In our series of patients in whom normoprolactinaemia was restored by partial hypophysectomy (26 out of 35) there have been no recurrences up to a maximum of five years among patients with microadenomas (10) or macroadenomas (16) (paper in preparation). Although our follow up period is not yet five years for all patients, our findings contrast strikingly with those of Serri and colleagues.

We consider that Dr Grossman and Professor Besser have taken too gloomy a view of surgery and we agree with Teasdale *et al* that transsphenoidal surgery for prolactino-

mas is extremely successful[5] and its role in the management of these patients should be re-evaluated.

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1 Grossman A, Cohen BL, Charlesworth M, *et al.* Treatment of prolactinomas with megavoltage radiotherapy. *Br Med J* 1984;**288**:1105-9.
2 Bergh T, Nillius SJ, Wide L. Clinical course and outcome of pregnancies in amenorrhoeic women with hyperprolactinaemia and pituitary tumours. *Br Med J* 1978;i:875-80.
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4 Serri O, Rasio E, Beauregard H, Hardy J, Somme M. Recurrence of hyperprolactinemia after selective transsphenoidal adenomectomy in women with prolactinoma. *N Engl J Med* 1983;**309**:280-3.
5 Teasdale G, Thomson JA, Macpherson P. Treatment of prolactinomas with megavoltage radiotherapy. *Br Med J* 1984;**288**:1538-9.

**The authors reply below.—ED, *BMJ*.

SIR,—We are grateful for the opportunity offered by the letter from Professor Hall and his colleagues to elaborate on some of the points that we alluded to in our review article on prolactinomas. We also feel that Professor Hall and colleagues may have misconstrued some of our treatment stratagems. We argued not that surgery, radiotherapy, and medical treatment were mutually exclusive forms of therapy but that they were usually complementary approaches to the patient with a prolactinoma. We have argued that external radiotherapy, delivered by a linear accelerator, has been effective in lowering serum prolactin concentrations in all patients with prolactinomas but we currently reserve its use for patients with microadenomas.[1] Although to date a normal serum prolactin concentration has been obtained in only one third of patients, the fall has been progressive in all and the number with a normal prolactin value will progressively increase. In most series the cure rate for surgery in macroadenomas is 50% or less. However, we did emphasise in our review that an alternative approach to the patient with a large prolactinoma is to administer bromocriptine to induce pregnancy and then to reintroduce bromocriptine during pregnancy should there be evidence of tumour expansion.

For the patient with a prolactin secreting microadenoma our current advice is to try dopamine agonist therapy, such as bromocriptine, in the first instance. Only in patients who are either intolerant of, or resistant to, dopamine agonist therapy is surgery then advised. Our enthusiasm for surgery has certainly been tempered by the results from Hardy and his colleagues showing that their high initial success rate is followed by a 50% recurrence rate by five years.[2] We indeed await with interest other largescale long term studies of recurrence rates after transsphenoidal removal of microprolactinomas. In the most recent abstract published by Professor Hall and his colleagues (presentation 36 at British Endocrine Societies' 4th Joint Meeting, March 1985, Oxford), out of 29 patients the number of surgically cured patients followed up for more than two years was two. We do not therefore feel that, on present data, transsphenoidal surgery should be the first line treatment of choice for small prolactinomas. Nevertheless, for the optimum treatment of all patients with prolactinomas we believe that all modalities of treatment should be available.

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1 Grossman A, Cohen BL, Charlesworth M, *et al.* The treatment of prolactinomas with megavoltage radiotherapy. *Br Med J* 1984;**288**:1105-9.
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Convulsions associated with cyclosporin A in transplant recipients

SIR,—Like Dr M L P Gross and others (16 February, p 555) we feel that cyclosporin A alone may not have been the major causative factor in the patients of Dr M Beaman and others (12 January, p 139), who suffered convulsions while having high serum cyclosporin A concentrations. Six patients aged 14-55 years (5 women) have had convulsions after orthotopic live transplant operations in the Cambridge/King's College Hospital series since July 1982 (four have been reported on previously).[1]

These occurred one to four months after transplantation while the patients were receiving cyclosporin A. In four patients the convulsions were preceded by a recent change in immunosuppression, although this was for rejection in only one patient. The whole blood cyclosporin A values in all these patients were within the acceptable range of 250-750 mg/l. One patient had a history of convulsions associated with peritonitis and on this occasion her convulsions occurred within three days of the development of a Gram negative septicaemia. Likewise, only one patient had a history of renal impairment or hypertension. She had had a mild mesangiocapillary glomerulonephritis before liver transplantation and at the time of the convulsions her serum creatinine was 128 μmol/l (1·5 mg/100 ml) and her blood pressure was 170/100 mm Hg. Her convulsions were initially controlled with phenytoin, but two weeks later she developed chickenpox and was treated with intravenous acyclovir. Shortly afterwards her convulsions recurred and progressed to status epilepticus, her blood pressure at this time being 160/120 mm Hg. Examination of the cerebrospinal fluid showed no evidence of an infective cause. The convulsions were eventually controlled with intravenous diazepam and phenytoin, and she made an uneventful neurological recovery.

There was thus little to support the concept of "rejection encephalopathy" in our patients, with only one patient having evidence of graft rejection. Although renal impairment and hypertension were important features in young patients having convulsions after bone marrow transplantation and treatment with cyclosporin A,[2] only one of our patients had evidence of this. Unlike the patients reported by Dr Beaman and colleagues, all our patients had cyclosporin A blood concentrations within the acceptable range at the time of their convulsions, and on the few occasions when their drug concentrations were high they did not have further fits. Hypomagnesaemia has been reported to be associated with cyclosporin neurotoxicity,[3] but there was nothing to suggest that this was present in our patients at the time of their convulsions, and none subsequently required magnesium supplementation. Of possible importance is the fact that five of our six patients were being treated with corticosteroids concurrently and these could interact with cyclosporin A in several ways. Both drugs cause fluid retention, which may increase the risks of epilepsy. In addition, tissue concentrations of cyclosporin A might be increased by competitive inhibition of hepatic cyclosporin A metabolism[4] and possible displacement of cyclosporin A from binding sites within the central nervous system by corticosteroids.

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1 Powell-Jackson PR, Carmichael FJL, Calne RY, Williams R. Adults respiratory distress syndrome and convulsions associated with administration of cyclosporine in liver transplant recipients. *Transplantation* 1984;**38**:341-3.
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**This correspondence is now closed.—ED, *BMJ*.

Misuse of published reports in propaganda

SIR,—It seems that some members of parliament do not feel obliged to read published articles in full or feel justified in abstracting only those conclusions which can be bent to make a particular case, disregarding those that contradict it. I refer to the use made of a recent article by myself and my colleagues entitled "Prescribing: the power to set limits" (9 February, p 450) by the Conservative member for Hazel Grove, Mr Tom Arnold. In copious correspondence with his constituents Mr Arnold has quoted our article as confirmation of his own support for the government's proposed limited drug list. Mr Arnold also put the following question to the House (20 February): "To ask the Secretary of State for Social Services, if he will make a statement on the conclusions of the article 'Prescribing: the power to set limits,' by J M Harding and others in the *British Medical Journal* of 9 February," a copy of which he had received. In a written answer Mr Kenneth Clarke replied: "The article referred to by my Hon Friend concludes that: generic prescribing and a limited list of drugs may improve the quality of prescribing and be the only way to curb prescribing costs. We fully agree with these conclusions." (25 February.)

What do Mr Clarke and Mr Arnold think of our conclusions set in context? "Generic prescribing and a limited list for all drugs (not just the categories dealt with in the DHSS proposals) may improve the quality of prescribing and be the only way to curb prescription costs, which are inflated by some drug companies. But a restricted list must be flexible and responsive to patients' needs, and there should be a mechanism for consumer feedback. It should apply to all prescribing, as a division between private and NHS prescriptions furthers a two class system of health care in which the NHS may be seen as second class. Certain investigations and treatments are already influenced by ability to pay. If certain drugs are not suitable for prescribing on the NHS perhaps they are not suitable for all."

It should be clear to everyone reading our paper in full that we oppose the government's initial limited and subsequent expanded list of drugs on the grounds that they will "limit the