judgment, but the thought crosses my mind that, apart from some criticisms on points of detail, which I am happy to accept, the reasons for rejection of these papers might in themselves be matters for comment. I imagine that Minerva, in her wisdom, will not overlook the Athenian principle that truth is most likely to emerge in temples whose columns are open for entry.

GORDON T STEWART

University Department of Community
Medicine,
Ruchill Hospital,
Glasgow G20 9NB

¹ Stewart GT. In: *International symposium on pertussis*. Washington, DC: US Government Printing Office, 1978:262-78.

Stress after amniocentesis for high serum alpha-fetoprotein concentrations

SIR,—In his review of maternal serum α -fetoprotein (AFP) screening in pregnancy (17 May, p 1199) Rodney Harris concludes that one potential benefit of population screening might be the identification of fetuses at risk of spontaneous abortion, low birth weight, or perinatal death. He bases this conclusion on the increased incidence of these problems among women who have a high maternal serum AFP concentration but a normal result on amniocentesis. The possibility that the prenatal diagnostic intervention may have caused the subsequent problems is discounted by reference to the significantly better pregnancy outcome of women who have amniocentesis for other reasons.

An outcome measure which receives no attention in Harris's review, but which I have found to be significant in differentiating women with high serum AFP concentrations from those with other indications for amniocentesis, is the woman's emotional reaction to the diagnostic intervention.¹ The data in the table are based on interviews with 90 women who had a normal result on amniocentesis. Although nearly all women were worried about

results ($p < 0.001$). This was sometimes a cause of further anxiety, in that women worried about the effect that their stress might have on their unborn child: "If they're inside you and you're worrying terrible it must affect them somehow"; "My husband's greatest worry was that the baby was perfectly normal but I would miscarry because I was so worried"; "I was worried about not eating—thinking I will miss the nutrition for the baby"; "I smoked a lot more and I was worried that it was not good for the baby."

Eight women (seven from the high serum AFP group) said they smoked more during the period of waiting for results. Four (three from the high serum AFP group) took tranquillisers. One woman with a high serum AFP concentration mentioned that although she normally drank alcohol only in moderation and on special occasions, she was drinking up to half a bottle of spirits a day during the time of waiting for the results.

There is evidence to suggest that stress during pregnancy is associated with both fetal death² and low birth weight.³ The hypothesis of the women just quoted, that the stress reaction to a false-positive result on a serum AFP screening test might contribute to poor pregnancy outcome, would seem no less reasonable than the assertion of Harris and his colleagues⁴ that "the greater fetal loss and low birth weight associated with pregnancies complicated by high maternal serum AFP concentrations appear to be an inherent feature of these pregnancies, rather than the result of amniocentesis."

WENDY FARRANT

Institute for Social Studies in Medical Care,
London NW3 2SB

¹ Farrant W. *Mims Magazine*, 15 June 1980, 55-63.

² Myers RE. In: Zichella I, Pancheri P, eds. *Psychoneuro-endocrinology in reproduction*. Amsterdam: Elsevier/North Holland Biomedical Press, 1979, 55-73.

³ Newton RW, et al. *Br Med J* 1979;ii:411-3.

⁴ Read AP, et al. *Br J Obstet Gynaecol* 1980;87:372-6.

Plasma exchange in severe rhesus haemolytic disease

SIR,—Intensive plasma exchange is now becoming a recognised and effective form of treatment for antibody and immune-complex mediated disease.^{1,2} Mr G R Barclay and others in their report (28 June, p 1569) suggest that the maternal concentration of anti-D increased despite intensive plasma exchange and that the procedure may have been deleterious by removing maternal "inhibitory" activity.

Although they feel that they were unable to control the secondary antibody response, it appears from the graph that each significant rise in anti-D concentration occurred during the two to three-day gaps in the exchange programme. When regular exchange occurred there was either a decrease in the rate of rise or an actual fall in the concentration of anti-D.

The immunoglobulin produced in the secondary response is in the IgG class, of which only 44% is in the vascular compartment. When the balance between the intravascular and extravascular space is disturbed by rapid reduction in the intravascular concentration of IgG then equilibration will occur when plasma exchange is withdrawn. In addition, immediate rebound in antibody synthesis may be expected owing to feedback stimulation of the clone of lymphocytes producing the antibody.³

Graham-Pole *et al*⁴ demonstrated reduction of anti-D concentration with intensive plasma

exchange in severe rhesus disease but there was a rapid return of antibody between courses of exchange. This also accords with our own experience in treating patients with factor VIII inhibitors following essential surgery. These inhibitors are also IgG antibodies and plasma exchange is required daily to control the inhibitor level until such time as the clinical state resolves (data to be published, available on request). Our patients also receive high-dose factor VIII concentrates daily, which may provoke further antibody stimulation but by contrast may have led to immunological tolerance.⁵

Haemolytic disease of the newborn differs from other antibody-mediated disease in that the fetus can benefit only indirectly from plasma exchange. The beneficial effects depend on the free passage of antibody between fetus and mother. IgG levels in the newborn infant are frequently higher than in maternal serum.⁶ The level of anti-D may vary from 2% to 30% of that in the mother.⁷ The level in the latter is not, therefore, an accurate assessment but is only a guide to the severity of the disease. The placenta does not act as a simple filter but bears Fc receptors and appears to be the rate-limiting point in antibody transfer.⁸ It selectively and directionally transfers IgG against a substantial concentration gradient. The rate of transfer is relatively slow⁹ but better from mother to fetus than from fetus to mother, and acute changes of antibody concentration in the mother due to plasma exchange will not be reflected in the fetus unless the improvement is sustained by frequent exchange. If the problem in haemolytic disease of the newborn is purely related to antibody production then on theoretical grounds we have not yet been treating affected women sufficiently intensively to expect significant benefit.

A C NEWLAND
B T COLVIN
B E DODD

Department of Haematology,
London Hospital,
London E1 1BB

¹ Anonymous. *Br Med J* 1978;ii:1011-2.

² Lockwood CM, Rees AJ, Pussell B, Peters DK. *Exp Haematol* 1977;5, suppl:117-36.

³ Brystry J, Schenken I, Uhr JW. In: Amos B, ed. *Progress in immunology*. New York: Academic Press, 1971:630-6.

⁴ Graham-Pole J, Barr W, Willoughby MLN. *Br Med J* 1977;ii:1185-8.

⁵ Dresser DW, Mitchison NA. In: Dixon FJ, Kinkell HG, eds. *Advances in immunology*, vol 8. New York: Academic Press, 1978:129.

⁶ Kohler PF, Farr RS. *Nature* 1966;210:1070-1.

⁷ Hughes-Jones NG, Ellis MJ, Walker W. *Vox Sang* 1971;21:135-40.

⁸ McNabb T, Koh TY, Dorrington KJ, Painter RH. *J Immunol* 1976;117:882-8.

⁹ Gitlin D, Kumate J, Urrusti J, Morales C. *J Clin Invest* 1964;43:1938-51.

Social environment and relapse in schizophrenia

SIR,—Your recent leading article on social environment and relapse in schizophrenia (19 July, p 173) gave an accurate and useful summary of the research carried out by members of this unit. It is difficult, however, in presenting the results of such work to avoid an emphasis on factors that predict relapse, while factors that predict a good outcome receive less attention. In particular, the fact that a majority of the families we have studied provide a helpful and supportive environment, associated with a low relapse rate, tends to be left out of consideration. Professional people concerned with the long-term management of

Emotional reaction to the experience of waiting for the result of prenatal diagnosis, according to indication for amniocentesis

	Indication for amniocentesis	
	High serum AFP	Other
Found the experience:	(No = 33)	(No = 57)
Not distressing	3%	17%
A little distressing	6%	39%
Moderately distressing	12%	30%
Very distressing	21%	12%
Extremely distressing	58%	2%
Could stop self worrying:	(No = 33)	(No = 56)
Yes	33%	87%
No	67%	13%
Suffered from:	(No = 31)	(No = 55)
Depressed mood	71%	24%
Crying	71%	9%
Irritability	57%	20%
Poor concentration	53%	7%
Headaches	35%	16%
Sleep disturbance	61%	16%
Loss of appetite	65%	5%
> 3 of the above	71%	9%

All differences between groups are significant at the $p < 0.001$ level (χ^2 , 1 df).
AFP = α -fetoprotein.

the test outcome, the anxiety of the high serum AFP group was more generalised and more disabling. Sixty-eight per cent of this group, as compared with 22% of those who had amniocentesis because of their age or their obstetric or family history, felt that their health had suffered during the period of waiting for

schizophrenia can learn a great deal from these families, and the efforts of organisations such as the National Schizophrenia Fellowship to promote the welfare of patients and their families deserve professional encouragement and collaboration.

J K WING

Medical Research Council
Social Psychiatry Unit,
Institute of Psychiatry,
London SE5 8AF

Disturbed behaviour induced by high-dose antipsychotic drugs

SIR,—The account by Drs Thomas R E Barnes and Paul K Bridges (26 July, p 274) of disturbed behaviour related to high-dose antipsychotics raises some interesting questions. The suggestion that increasing anticholinergic activity is shown with increased neuroleptic doses receives support from some open studies of high-dose versus low-dose treatment,^{1,2} in which at very high doses extrapyramidal effects diminished or disappeared but were present when dosage was in the standard range. This could be regarded as being due to a continuing increase of anticholinergic activity after basal ganglia dopamine receptors had been blocked. However, several double-blind studies^{3,4} have failed to show this effect and increasing dosage merely resulted in increased extrapyramidal side effects.

The issue might have been partly resolved if it had been shown that the form of disturbance described was that which might be expected with anticholinergic toxicity. However, other than pointing out that both their patients and those reported by MacVicar⁵ became excited and aggressive the authors give no further information. The "toxic psychosis" to which they refer would presumably include disorientation in time and place together with a greater likelihood of visual hallucination than in non-toxic states. In addition, anticholinergic poisoning may cause blurred vision, dry palms, and flushed skin *inter alia*,⁶ none of which are mentioned.

The distinction is important, for if the change in the patients' behaviour was due to neuroleptics acting as dopamine agonists it is interesting that the form of the illness changed to one atypical for the patient. If it was due to anticholinergic activity of neuroleptics then we might expect to see some of the changes outlined above. If, on the other hand, increasing dosages merely increase extrapyramidal effects, then akathisia, a physical and mental restlessness which is a side-effect of neuroleptics, might have contributed to the excitement and agitation described.

STEPHEN BROWN

Maudsley Hospital,
London SE5 8AZ

¹ Ayd FJ. *Proc R Soc Lond* 1976;**69**, suppl 1:14-22.

² Rifkin A, Quitkin F, Carrillo C, et al. *Arch Gen Psychiatry* 1971;**25**:398-403.

³ Quitkin F, Rifkin A, Klein DF. *Arch Gen Psychiatry* 1975;**32**:1276-81.

⁴ Carscallen HB, Rochman H, Lovegrove TD. *Canad Psychiat Assoc J* 1968;**13**:459-61.

⁵ MacVicar K. *Am J Psychiatry* 1977;**134**:809-11.

⁶ Laurence DR. *Clinical pharmacology*. 4th edn. Edinburgh: Churchill Livingstone, 1973:16.

Prostaglandin E₁ in affective disorders and alcoholism

SIR,—In support of the theory of ethanol enhancement of prostaglandin (PG)_E synthesis

followed by a reduction in its synthesis, put forward by Drs D F Horrobin and M S Manku (7 June, p 1363), I report remission of severe hangovers in two patients whom I treated with safflower oil, a PGE₁ precursor.

Case 1—A 56-year-old man with chronic depression experienced debilitating hangovers characterised by dysphoria and lethargy following an evening's consumption of 170-227 ml (6-8 oz) of spirits. Isocarboxazid, 50 mg a day, remitted the depression but did not affect the hangovers. I introduced linoleic acid in the form of safflower oil, 4 g a day, and within a few days he was entirely free of hangovers. This benefit has continued during eight months of linoleic acid therapy.

Case 2—A 48-year-old man took lithium in an attempt to halt a 20-year history of episodic excessive drinking. Drinking 114-170 ml (4-6 oz) of vodka was followed by a tachyarrhythmia and an incapacitating hangover. After taking lithium 150 mg twice daily for two days he had a precipitous onset of anxiety, dysphoria, and polyuria, and an irregular pulse. He took 3 g of linoleic acid in the form of safflower oil and within 20 minutes these symptoms abated. Lithium was stopped and he continued to take linoleic acid, 5 g a day. The alcohol-precipitated arrhythmia and the hangovers have remitted on this regimen.

Ethanol temporarily abolishes familial tremor and the tremor associated with alcoholism but after drinking stops the tremor intensifies.¹ The mechanism for this, as discussed by Drs Horrobin and Manku, could be an initial increase in PGE₁ synthesis, which abolishes the tremor, followed by a reduction in PGE₁ synthesis secondary to depletion of dihomogammalinolenic (DGLA) stores. Lithium inhibits the mobilisation of DGLA and its conversion to PGE₁² and in some patients linoleic acid appears to be an effective remedy for the tremor and other neurological manifestations of lithium toxicity.³

The time-honoured belief that eating an oily meal before heavy drinking mitigates intoxication and hangover may have had substance. Linoleic acid and other prostaglandin precursors may be of benefit in some alcohol withdrawal states.

JULIAN LIEB

Yale University School of Medicine,
New Haven, Connecticut, USA

¹ Critchley M. *Brain* 1949;**72**:113-39.

² Horrobin DF. In: Johnson FN, Johnson S, eds. *Lithium in medical practice*. Baltimore: University Park Press, 1978.

³ Lieb J. *Prostaglandins and Medicine* 1980;**4**:275-9.

Physical training and coronary risk factors

SIR,—It is a pity that exercise, as a possible preventive measure against coronary disease, should get an apparent let-down in the paper by Mr Antony W Sedgwick (5 July, p 7) before the possible benefits have had a chance to come to us across the Atlantic.

Fortunately, the authors admit that, firstly, they were looking at risk factors rather than the actual incidence of heart disease and, secondly, their criteria for the intensity of exercise may not have been stringent enough. On the first point, the quoted paper by Morris *et al*¹ uses far larger numbers, and reports the actual onset of coronary symptoms or death. Their figures indicate the protective effect of violent exercise. On the second point, Cooper, also quoted, gives us precise criteria for adequate exercise. His *Aerobics*,² a book for the public, advises the weekly acquisition of 30 "aerobic" points. This can be done cycling or swimming; but, as an example, a two-mile

jog in 16 minutes every Monday, Wednesday, and Friday is just adequate. And for those of us who are initially unfit he has a carefully graded programme for the first 16 weeks.

I understand that some ex-marathon runners have wide coronary arteries when examined post mortem, and there is also the suggestion that they only rarely die prematurely from infarction. As this specialty is taken up by the athlete late in his career, the implication emerges that wide coronaries can be acquired in the otherwise mature male—not a new idea, I'm sure, but surely good news if we all got our exercise just right?

Meanwhile would Minerva (28 June, p 1626) kindly stop knocking joggers? Of course, we look miserable—try looking happy with your jaw maximally open for air intake.

PETER MOFFITT

Hanham, Bristol BS15 3EL

¹ Morris JN, Chave SPN, Adam C, Sirey C, Epstein L, Sheehan D. *Lancet* 1973;**i**:333-9.

² Cooper K. *Aerobics*. London: Bantam, 1972.

Right bundle-branch block

SIR,—I was most interested to read your leading article on right bundle-branch block (14 June, p 1392). In 1948, aged 30 years, while teaching undergraduates I suddenly developed typical symptoms of coronary thrombosis unassociated with hypertension, previous coronary, vascular, or congenital heart disease, pulmonary embolism, or cardiomyopathy. Various cardiac symptoms and signs occurred during the succeeding two months, after which time I returned to normal hospital and university duties, eventually becoming a first-class life insurance risk. Details of this illness were published in 1971.¹

In 1977 I developed symptoms and signs of mild-to-moderate hypertension, which are well controlled by the effective treatment of colleagues. Since 1948 the currently accepted electrocardiographic criteria of right bundle-branch block have persisted.

E K BLACKBURN

Royal Hallamshire Hospital,
Sheffield S10 2JF

¹ Blackburn EK. In: Greene R, ed. *Sick doctors*. London: Heinemann Medical Books, 1971:63-4.

Propranolol and thyroid hormones

SIR,—We have read with interest the report of Dr Paul Heyma and his colleagues (5 July, p 24) in which they describe giving propranolol (DL-propranolol) and D-propranolol to six euthyroid subjects receiving L-thyroxine (T₄), and giving D-propranolol to six hypothyroid patients receiving T₄ replacement.

They conclude that the effect of DL-propranolol on T₄ to triiodothyronine (T₃) conversion is unrelated to its β -adrenergic-blocking activity and is related to its "membrane-stabilising activity". The lack of effect of atenolol, a cardioselective β -adrenergic-blocking drug devoid of membrane-stabilising activity, that we (unpublished observations) and others¹ have observed would seem to support this suggestion. We have also studied, however, the effect of oxprenolol, a non-cardioselective drug with membrane-stabilising activity, and acebutolol, a cardioselective drug with membrane-stabilising activity, on circulating thyroid hormones in