important influence on the relation between blood pressure and mortality.

The value of antihypertensive treatment cannot be inferred from observational studies in the general population. In the very elderly people with hypertension seem to survive longer than those with lower levels of blood pressure, but this does not necessarily mean that no benefit would be obtained from antihypertensive treatment. Because of the survivorship phenomenon the proportionate benefit from treatment may be less than for younger patients. What matters more is the absolute benefit, and this is likely to be influenced by competing causes of death. We shall not know whether such treatment is worth while until clinical trials have been conducted in the very elderly.

P C WALLER

Glasgow Blood Pressure Clinic,
Western Infirmary,
Glasgow G11 6NT

- 1 Anonymous. *Build and blood pressure study*. Chicago: Society of the Actuaries, 1959.
- 2 Aromaa A. Blood pressure level, hypertension and five-year mortality in Finland. *Acta Med Scand [Suppl]* 1980;646:43-50.
- 3 Lindholm L, Lanke J, Bengtsson B, Ejlertsson G, Thulin T, Schersten B. Both high and low blood pressure risk indicators of death in middle-aged males. *Acta Med Scand* 1985;218:473-80.

Transplantation of fetal tissues

SIR,—Drs J M S Pearce (30 April, p 1211) and Dr R Gillon (30 April, p 1212) considered the lack of proved benefit and the ethical problems surrounding the use of fetal tissue transplanted into the brain. We would like to draw attention to a potential hazard of such procedures.

We have performed two transplantations in marmoset monkeys using neural tissue from the fetal ventral forebrain taken at an estimated 80 and 76 days of gestation. The recipient of the tissue from the 80 day fetus had previously had a unilateral ablation of the cholinergic input to the hippocampus using ibotenic acid.¹ Neural tissue was transplanted into the denervated hippocampus eight days later. After five months the animal had bilateral resection of the fornix and was killed three months later. Staining for acetylcholinesterase showed graft survival and moderate spread within the hippocampus.

The second animal had bilateral resection of the fornix followed one month later by bilateral transplantation of fetal ventral forebrain neurones taken at 76 days' gestation from two fetuses. Ten µl of dissociated cell suspension was injected into the hippocampus in each hemisphere. This animal was well for two months but then became ill and was killed three days later.

The brain was cut coronally into blocks and the transplanted tissue was clearly visible. It comprised two large masses, one in each hemisphere, occupying the space normally held by the hippocampus and lateral ventricles from the front of the temporal lobe to the back of the occipital lobe and extending in some places as far as the dorsal cortex. The mass stained positively for Nissl substance but negatively for glial fibrillary acidic protein. There were only a few acetylcholinesterase positive neurones in the mass. Most of the cells seemed to be primitive neuroectodermal cells with small axonal processes.

Under certain circumstances fetal neuronal tissue may continue to proliferate in a primitive form when transplanted into an adult host. Until the processes determining the relation between cell proliferation and differentiation are better understood it may not be possible to ensure that transplanted cells can be constrained appropriately. These cases involved cholinergic cells, but the same hazard may attend dopaminergic cell trans-

plants. In evaluating fetal neuronal transplantation as a treatment for neurodegenerative diseases the possibility of serious deleterious effects on the host should be considered.

R M RIDLEY
H F BAKER

Division of Psychiatry,
Clinical Research Centre,
Harrow,
Middlesex HA1 3UJ

A FINE

Department of Physiology and Biophysics,
Dalhousie University,
Halifax,
Nova Scotia,
Canada

- 1 Ridley RM, Samson NA, Baker HF, et al. Visuospatial learning impairment following lesion of the cholinergic projection to the hippocampus. *Brain Res* (in press).

SIR,—Dr J M S Pearce (30 April, p 1211) and Dr Raanan Gillon (30 April, p 1212) raise important issues which are timely and instructive. We feel, however, that it is equally important to emphasise the lack of understanding of the mechanisms underlying re-establishment of central nervous system function and, in particular, the possible role of neurotrophic agents in this process.

To consider the basic mechanism solely in terms of cell transplantation may be to overlook its fundamental principle. It is possible that the host response to chemicals released from grafted cells is of greater importance than the synthesis and release of pharmacologically active catecholamines. The neurotrophic effects of synthetic and naturally occurring neuropeptides have been reported.¹⁻³

Our current studies of the effect of neuropeptide fragments in countering experimental parkinsonism in rats encourage us to believe that grafted cells (including peripheral nerve cells⁴) may be serving merely as a vehicle for delivery of trophic agents or factors promoting their release. This concept has been proposed independently elsewhere⁵ and is substantiated by indirect evidence from animal studies.^{3,6,7} Investigation of the use of growth factors, even in the absence of grafted cells, may ultimately yield greater benefit than dopaminergic grafting.

ROBERT M REDFERN
JOHN B MILES

Department of Neurosciences,
Walton Hospital,
Liverpool L9 1AE

- 1 Morley JS, Ensor DM. Neurotrophic effects of β -endorphin C-terminal tetrapeptide (MPF). *Neuropeptides* 1986;8:45-9.
- 2 Strömberg I, Herrera-Marschitz M, Ungerstedt U, Ebendal T, Olson L. Chronic implants of chromaffin tissue into the dopamine-denervated striatum. Effects of NGF on graft survival, fiber growth and rotational behaviour. *Exp Brain Res* 1985;60:335-49.
- 3 Verhaagen J, Edwards PM, Jennekens FGI, Gispen WH. Pharmacological aspects of the influence of melanocortins on the formation of regenerative peripheral nerve sprouts. *Peptides* 1987;8:581-4.
- 4 Freed WJ, Cannon-Spoor HE, Krauthamer E. Intrastriatal adrenal medulla grafts in rats: long-term survival and behavioural effects. *J Neurosurg* 1986;65:664-70.
- 5 Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's Disease. *N Engl J Med* 1988;318:876-80.
- 6 Kesslak JP, Nieto-Sampedro M, Globus J, Cotman CW. Transplants of purified astrocytes promote behavioural recovery after frontal cortex ablation. *Exp Neurol* 1986;92:377-90.
- 7 Freed WJ, Cannon-Spoor HE. Cortical lesions increase re-innervation of the dorsal striatum by substantia nigra grafts. *Brain Res* 1988;446:133-43.

Risk factors for ischaemic brain infarction

SIR,—Dr Jaana Syrjänen and colleagues (23 April, p 1156) have shown that there is a strong association between recent infections and subsequent ischaemic brain infarctions. They offer some

speculations about the mechanism, but this is still uncertain.

Blood fluidity is altered after bacterial infections.¹ Our own unpublished data show that respiratory infections in particular induce a rise in plasma and blood viscosity. This is probably predominantly due to a rise in the concentrations of acute phase proteins.¹ Such a haemorheological consequence of infection might influence brain perfusion, and various experiments show that the flow properties of blood are among the determinants of brain perfusion.²

One possible mechanism by which infections lead to brain infarctions is the limitation of blood fluidity. This could predispose to strokes,³ and virtually all known risk factors for stroke (smoking, hypertension, hyperlipoproteinaemia, high fibrinogen levels, and diabetes) are also associated with abnormalities in the flow properties of blood.⁴

E ERNST

Haemorheology Research Laboratory,
Department of Physical Medicine,
University of Munich,
8000 Munich 2

- 1 Harkness J. The viscosity of human blood plasma: its measurement in health and disease. *Biorheology* 1971;8:171-93.
- 2 Thomas DJ. Blood viscosity and cerebral blood flow. In: Hartmann A, Kuschinsky W, eds. *Cerebral ischemia and hemorheology*. Heidelberg: Springer, 1987.
- 3 Ernst E, Matrai A, Marshall M. Blood rheology in patients with transient ischemic attacks. *Stroke* (in press).
- 4 Chien S, Dormandy J, Ernst E, Matrai A, eds. *Clinical hemorheology*. Dordrecht: M Nijhoff, 1987.

Insulin for the non-insulin dependent?

SIR,—Dr Roy Taylor (9 April, p 1015) assumes that improved blood glucose control is advantageous, although the most appropriate treatment for patients with non-insulin dependent diabetes will remain uncertain until the results of the United Kingdom prospective diabetes study are available. In younger patients with a long life expectancy blood glucose concentrations near to normal should be aimed for, whereas in older patients less tight control aiming merely to abolish symptoms may be more appropriate.

If an acceptable fasting blood glucose concentration cannot be achieved with diet and oral agents then a basal insulin supplement—for example, with once daily ultralente insulin—can be successful^{1,2} and does not carry the substantial risk of hypoglycaemia suggested by Dr Taylor. As this regimen aims primarily to reduce the fasting blood glucose concentration to normal there is no need to match individual meals to short acting insulin doses, and consequently there is less risk of hypoglycaemia should a meal be delayed or missed. Ultralente insulin is thus particularly useful in elderly patients living alone provided the dose is adjusted according to the fasting blood glucose concentration. Short and medium acting insulins, such as isophane and lente insulin, carry an increased risk of daytime hypoglycaemia in patients who still have a reasonable insulin secretory response to meals and are more useful in patients with a severely diminished secretory capacity who require additional insulin to cover meals.²

With failure of treatment with sulphonylureas it is a moot point whether they should be continued when insulin is started. Stimulation of endogenous insulin release by sulphonylurea allows a lower dose of insulin than would otherwise be needed.³ The gradual introduction of a long acting insulin to a patient who remains on maximum sulphonylurea treatment allows an easy transition even if one wishes eventually to withdraw the sulphonylurea. When a patient needs additional short acting

insulin to cover meals there is likely to be sufficient B cell failure for continuation of a sulphonylurea to be of marginal benefit, and it can be withdrawn. Simple guidelines on the use of tablets and insulin⁴ can cater for most patients until long term studies show a different regimen to be particularly beneficial.

RURY R HOLMAN

Diabetes Research Laboratories,
Radcliffe Infirmary,
Oxford OX2 6HE

- 1 UK prospective study of therapies of maturity-onset diabetes. Effect of diet, sulphonylurea, insulin or biguanide therapy on fasting plasma glucose and body weight over one year. *Diabetologia* 1983;24:404-11.
- 2 Holman RR, Turner RC. A practical guide to basal and prandial insulin therapy. *Diabetic Medicine* 1985;2:45-53.
- 3 Holman RR, Steenson J, Turner RC. Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement. *Diabetic Medicine* 1987;4:457-62.
- 4 Holman RR, Turner RC. Optimizing glycaemic control in type 2 diabetes: an approach based on fasting blood glucose measurements. *Diabetic Medicine* (in press).

In vitro fertilisation

SIR,—Mr David Barlow and others (12 March, p 751), Mr Peter Bromwich and others (12 March, p 759), and subsequent correspondents (9 April, p 1064) discussed means of improving oocyte collection and pregnancy rates and methods of cutting costs. The emphasis has been on various methods of oocyte collection and on the practicalities of sharing the cost between the public and private sectors. We have improved cost effectiveness at the Lister Fertility Centre by routinely using a luteinising hormone releasing hormone analogue before oocyte collection by either the laparoscopic or an ultrasound directed transvaginal route.

One hundred and twenty consecutive patients receiving in vitro fertilisation and gamete intrafallopian transfer were treated with intranasal luteinising hormone releasing hormone analogue four hourly from the first day of their cycle until ovulation was induced with 10 000 IU of human chorionic gonadotrophin. Ovarian stimulation was achieved using two ampoules of human menopausal gonadotrophins daily from the third day of the treatment cycle. The mean number of ampoules used in each cycle was 20.7 (SD 9.2). The follicular development was monitored by vaginal or abdominal ultrasound studies without hormonal monitoring.

The cancellation rate because of inadequate ovarian stimulation was 6%, but no cycles were cancelled because of spontaneous ovulation. The flexibility provided by the analogue enabled us to perform an average of 15 procedures in only four operating sessions each week, with no weekend service. The mean number of oocytes collected at each procedure was 8.5 (5.9). The clinical pregnancy rate for in vitro fertilisation was 39% (14 out of 36 cases) and the pregnancy rate for gamete intrafallopian transfer was 41% (35 out of 84 cases). The early miscarriage rate was 14%. These pregnancy rates are higher and the early miscarriage rate lower than those commonly reported.^{1,2} These improvements may be the result of reduced maternal serum concentrations of luteinising hormone at the time of conception after the use of luteinising hormone releasing hormone analogue.

Although using the analogue is associated with a small increase in the amount of human menopausal gonadotrophin needed in each cycle, it obviates the need for serial assays of serum oestradiol or luteinising hormone, reduces the number of cancelled cycles, and allows oocyte collections to be performed on planned lists during normal working hours. These factors, coupled with increased pregnancy rates and reduced miscarriage rates,

suggest that using the analogue will increase the cost effectiveness of in vitro fertilisation programmes.

H I ABDALLA A KIRKLAND
T LEONARD P A R STOCKER
R J BABER E C OWEN
J W W STUDD

Lister Hospital,
London SW1W 8RH

- 1 Seibel MM. A new era in reproductive technology. *N Engl J Med* 1988;318:828-34.
- 2 Lancaster PL. *In vitro fertilisation pregnancies. Australia 1980-1986.* Sydney: Commonwealth Institute of Health, 1987.

Induced ovulation in underweight women

SIR,—We were concerned by the recommendations of Mr Z M van der Spuy and others to withhold induction of ovulation and advocate weight gain in underweight anovulatory women (2 April, p 962).

We have compared their analysis of 41 singleton pregnancies resulting from induction of ovulation with our data from 71 singleton pregnancies, 12 induced with pulsatile gonadotrophin releasing hormone and the rest by human menopausal gonadotrophin. Our overall risk of delivering a baby with a birth weight below the 10th centile was 20% compared with 25% in their study, and our risk for underweight women was only 43% compared with theirs of 54%. The risk for women of normal weight was 13%, slightly above their figure of 11%. We found an overall abortion rate of 30%, with 27% in women of normal weight, 50% in the overweight, but only 22% in the underweight group.

It must be emphasised that having a baby whose weight falls below the 10th centile does not necessarily imply intrauterine growth retardation and the dire problems cited by Dr van der Spuy and others. Few of the small babies in our study even required neonatal intensive care.

We have been impressed by the beneficial effects of a successful pregnancy in underweight women on their subsequent weight gain, with the restoration of menses and spontaneous conception. Some of these women respond better to the responsibilities of motherhood than to exhortation to gain weight alone.

What concerns us particularly, however, about the insistence on weight gain and the withholding of stimulant treatment is the well documented evidence of the decline in natural fertility with age and the impairment of response to ovarian stimulants in women aged over 31.¹ By withholding treatment we could be denying them any possibility of fertility. Women requiring ovarian stimulant treatment for conception have a greater risk of a small baby even when they are of normal weight. Rather than denying treatment to the underweight we should be monitoring all such pregnancies closely.

VICKY OSGOOD
JEAN GINSBURG

Department of Endocrinology,
Royal Free Hospital,
London NW3 2QG

- 1 Ginsburg J, Bowes L, Osgood VM. Pregnancy in infertile couples. *N Engl J Med* 1984;310:1334-5.

Imaging of the urinary tract

SIR,—We endorse the conclusion by Dr G de Lacey and others (2 April, p 965) that routine urography is unnecessary in the assessment of patients with prostatism, but we are concerned that they make no mention of urine flow rates or

ultrasound measurement of residual urine. They imply that symptoms and, if necessary, cystoscopy are reliable guides to the severity of prostatic obstruction. This is not the case.

The assessment of prostatic size at endoscopy is often inaccurate.¹ The size of the prostate may be misleading as anatomical enlargement is only part of the pathophysiology of bladder outflow obstruction: dynamic and functional mechanisms are also important. The classical prostatic symptoms are a poor guide to the presence of severity of obstruction.^{2,3}

Multiple measures of the rate of urine flow and ultrasound studies of residual urine can differentiate the obstructed from the non-obstructed bladder and identify patients at risk from urinary retention or upper tract dilatation. Patients presenting with prostatic symptoms who do not have significant bladder outflow obstruction will not benefit from surgery, and others, with mild or moderate obstruction but little residual urine, can be managed conservatively.⁴ Objective assessment of patients tends to produce a low operation rate and improves the results of surgery.⁵ A urine flow rate clinic (incorporating a small real time ultrasound machine) is easily incorporated into a urology outpatient department and may be run by a nurse.

M A STOTT
P H ABRAMS
F C L FENELEY

Urodynamic Unit,
Ham Green Hospital, Pill,
Bristol BS20 0HW

- 1 Mitchell JP. *The principles of trans-urethral resection and haemostasis.* Bristol: J Wright, 1972.
- 2 Abrams PH, Feneley RCL. The significance of symptoms associated with bladder outflow obstruction. *Urol Int* 1978;33:171-4.
- 3 Andersen JT, Nordling J, Walker S. Prostatism I. The correlation between symptoms, cystometric and urodynamic findings. *Scand J Urol Nephrol* 1979;13:229-36.
- 4 Ball AJ, Feneley RCL, Abrams PH. The natural history of untreated prostatism. *Br J Urol* 1981;53:613-6.
- 5 Abrams PH. Prostatism and prostatectomy: the value of urine flow rate measurement in the pre-operative assessment for operation. *J Urol* 1977;177:70-1.

Drug addicts and the GP

SIR,—Dr Tessa Richards (16 April, p 1082) is too optimistic. Few general psychiatrists have much time for addicts, and it is unreasonable to expect general practitioners to be any more enthusiastic, especially when they will not be paid extra for their trouble. This is a pity because they could undoubtedly do a lot for drug addicts, including those addicted to "our favourite drug," alcohol.¹ In Denmark general practitioners routinely give supervised disulfiram.²

General practitioners could easily prescribe methadone for maintenance or withdrawal, and anxiety about diversion of supplies would be reduced if it were swallowed under the pharmacist's supervision. Most pharmacists are willing to supervise. However, general practitioners would need to understand that the success of a methadone programme is judged not only by how many addicts withdraw from opiates but also by how many are able, while taking methadone, to avoid lives of crime, degradation, and infection with the human immunodeficiency virus.

General practitioners should see their local drug dependency units as centres of excellence and expertise. Regrettably, the users say that the standard of service is frequently poor. Time consuming and repeated assessments of dubious value are often required, and clinic hours rarely cater for the many addicts working hard to rebuild their lives and finances. The lack of medical research in many such units is a disgrace.