Antidepressants and Barbiturates

SIR,—We were interested to read the paper by Dr. Marie Åsberg and others on the relationship between plasma level and therapeutic effect of nortriptyline (7 August, p. 331). However, the same authors in a previous paper¹ excluded patients receiving barbiturates from their study, yet failed to do so in this later paper. Some of their depressed patients received night sedation with pentobarbitone. As the authors of these papers have shown,² barbiturates lower plasma tricyclic levels. The Figure (from one of our patients studied over some months) shows the effects of 200 mg amylobarbitone nocte for 5 days (B) on the plasma level of nortriptyline. It can be seen that a marked lowering of this level occurred during this time. This effect is apparently due to the effect of barbiturates on stimulating liver microsomal activity.

As the evidence is that plasma tricyclic levels are related to clinical response, barbiturate hypnotics should not be prescribed for patients receiving tricyclic antidepressants.

Since Dr. Åsberg and others used pentobarbitone as the usual hypnotic, we wonder whether this accounts for some of the low plasma levels reported in their study compared with our own,³ and would recommend that no other drugs at all be given in studies of this kind. This is clinically possible if most of the daily tricyclic dose is given at night with advantage taken of the sedative action. We are studying the effects of other hypnotics and tranquillizers on plasma tricyclic levels.—We are, etc.,

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- 1 Åsberg, M., Price Evans, D. A., and Sjöqvist, F., *Journal of Medical Genetics*, 1971, 8, 129.
- 2 Sjöqvist, F., et al., *Proceedings of the European Society for the Study of Drug Toxicity, Excerpta Medica, International Congress Series*, 1967, 9, No. 145, 246.
- 3 Burrows, G. D., in press.

An Antidysrhythmic Agent

SIR,—The management of paroxysmal supraventricular tachycardia can be of great concern to the physician when treatment both by drugs and D.C. reversion has failed.

In 1969, during a series of animal experiments, we noted as a chance observation that capture of the dog's heart to allow atrial pacing was facilitated following intravenous verapamil (Cordilox). This had not been recorded previously and led us to consider whether this drug would be of value in the management of patients with resistant supraventricular tachycardia.

Our first really intractable patient did not appear for two years. She was a woman aged 45 years, who had experienced for many years symptoms due to a pre-excitation syndrome of the Wolff-Parkinson-White type. Three years previously a paroxysm had preceded an attack of acute myocardial infarction. Subsequently, she received treatment for paroxysms of tachycardia with drugs, including digoxin, quinidine, procainamide, propranolol, practolol, and sodium hydantoinate without long term benefit. On 26 March 1971 she had a further paroxysm

with a heart rate of 180 persisting for 12 hours. This did not revert to sinus rhythm after several attempts at D.C. reversion under diazepam sedation. She was then given verapamil 5 mg intravenously at a rate of 1 mg/minute and immediately reverted to sinus rhythm. Five days later she had a further acute episode of tachycardia with a heart rate of 180 which lasted for more than ten hours. Following further intravenous injection of 5 mg verapamil she reverted immediately to sinus rhythm. Subsequently, she was maintained on verapamil, 160 mg q.d.s. We have since found that her tachycardia is controlled by verapamil 40 mg q.d.s. and if this dosage is reduced further her paroxysms return. When seen on 9 September 1971 she was extremely well and had had no attacks for five months, whereas previously the attacks were recurring daily.

We have since treated another five patients who have had supraventricular tachycardia and each has reverted to sinus rhythm following a maximum of verapamil 10 mg intravenously. One of these patients had previously been treated unsuccessfully with

digoxin, quinidine, procainamide, and sodium hydantoinate over prolonged periods. Two patients with atrial fibrillation due to ischaemic heart disease had a considerable reduction in heart rate following intravenous verapamil, one with a rate of 180 which fell to 84, and the other fell from 140 to 80.

The exact mode of action of verapamil is unknown. It has been suggested¹ that the mechanism of action of this drug on the S.A.- and A.V.-nodes involves a direct cardiac effect as well as antagonism of vagal mechanism. However, in the dog we have shown (unpublished) that verapamil can not only reverse an isoprenaline-induced tachycardia but also reverse an atropine-induced tachycardia. Our experience in man indicates that its effects appear to be most beneficial in those patients whose heart rate can be temporarily slowed by vagal stimulation.

Verapamil appears to be a drug of promise in the management of obstinate supraventricular tachycardia, and may certainly succeed when attempted D.C. reversion has failed.—We are, etc.,

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- 1 Garvey, H. L., *European Journal of Pharmacology*, 1969, 8, 159.

Transient Deafness from High Doses of Frusemide

SIR,—I should like to report a case of transient deafness during intravenous frusemide therapy in chronic renal failure. Reports of this complication of frusemide are few,^{1,2} although it is better known with ethacrynic acid.

A 49-year-old woman was admitted with oedema and chronic renal failure associated with pelvic malignant disease. In addition to peripheral oedema pericarditis and pulmonary oedema were noted.

There being no diuretic response to the oral administration, she was given frusemide intravenously, 500 mg as a single dose. The injection took approximately three minutes. Soon after completion she complained of an inability to hear anything spoken at her bedside. No deafness had been evident during routine neurological examination at the time of admission. About an hour later the hearing improved and was clinically normal within four hours. The next morning the same dose was repeated. The time taken for the injection was again about three minutes. Very soon after, the patient became distressed, saying she could hear nothing. No abnormality, apart from a profound loss of hearing, was noted during neurological examination. Loud speech was heard about an hour later and she had normal hearing by about four hours. Subsequently she was given 240 mg of frusemide intravenously very slowly, taking about five minutes for the injection. No deafness occurred then or over the next six hours of careful patient observation. The only other drug, nalidixic acid, the patient had been having for three days prior to the first dose of intravenous frusemide.

The use of large doses of frusemide in renal failure is now an established method of treatment. The dose of intravenous frusemide used in this department has ranged up to 1 g

and in chronic renal failure a satisfactory diuresis may be obtained.

That no deafness was evident with the smaller dose suggests that the effect is dose dependent, not a sensitivity phenomenon. In view of its inconstancy from person to person, however, there clearly are other variables, such as patient idiosyncrasy or possibly degree of renal failure to consider. The phenomenon appears to be of a benign prognosis.—I am, etc.,

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- ¹ Schwartz, G. H., David, D. S., Riggio, R. R., Stenzel, K. H., and Rublin, A. L., *New England Journal of Medicine*, 1970, **282**, 1413.
- ² Vargish, T., Benjamin, R., and Shinkman, L., *Annals of Internal Medicine*, 1970, **72**, 761.

Blood Flow in Ischaemic Feet

SIR,—We read with great interest the recent report (24 July, p. 220) by Mr. A. J. McEwan and Dr. I. McCa. Ledingham on the blood flow characteristics of apparently ischaemic feet. While we would agree that in cases of peripheral vascular disease there is a considerable dampening of the pulsatility of both the blood pressure and blood flow waveforms, our own measurements indicate that the total limb perfusion is higher in normal subjects.

Using a Nycotron electromagnetic flowmeter we have measured arterial blood volume flowrate in patients undergoing femoro-popliteal bypass grafting or profunda femoris angioplasty for atherosclerotic occlusions. Our measurements (taken from 17 subjects) have shown that the typical pre-reconstruction flow is 103 ml/min (S.D. $\pm$ 32) and that the post-reconstruction flow is typically 159 ml/min (S.D. $\pm$ 66).

Other work conducted by us on femoral vein flows has shown that in a total of 26 patients suffering from varicose veins the mean flow was 151 ml/min (S.D. $\pm$ 57). In those patients where measurements have been made simultaneously on the femoral artery and vein there has been no significant difference between the arterial and venous flow.¹ This would support our assertion that mean flow in an ischaemic limb is lower than in the normal limb.

We have found that examination of the flow traces, with respect of their pulsatility, is of value in picking up any thrombosis and dissection that may have occurred immediately following reconstruction. Without per-operative assessment of the flow such faults may only become apparent after the patient left the operating theatre.—We are, etc.

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¹ Sabri, S., Roberts, V. C., and Cotton, L. T., *Cardiovascular Research*, (in press).

Safety with Lasers

SIR,—After your leading article on "Safety with Lasers" (3 July, p. 3) we are surprised that your correspondent (7 August, p. 370) should quote a threshold level for human

eye damage using such inadequate information. In the case cited intraocular energy was not estimated because not only was the pupil diameter unknown but there were no details of beam geometry or the refractive state of the eye. The retinal energy density, which was the critical parameter, could not be calculated because the spot size was not determined.

We would take this opportunity of pointing out what must be a misprint in your leading article (3 July, p. 3). The second sentence of the second paragraph should read "A laser with a pulse duration of 50 nanoseconds could produce a miniature explosion within the retina . . ." Symbols can be easily misprinted and this may be a justification for writing such units in full.—We are, etc.,

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Fatal Complications of Central Venous Catheters

SIR,—Dr. R. Adar and Professor M. Mozes, (25 September, p. 746) report two fatal complications of central venous catheterization. It would be interesting to know the type of intravenous catheter involved, as the complications did not seem to be of technique of central venous catheterization but of catheter material. A stiff catheter could obviously perforate heart or vein tissue more easily than a soft catheter. At the moment there are three types commonly available—Nylon (Portex), Intracath (Bardic), and Venocath (Abbott). The Nylon catheter is quite stiff, Intracath is soft but stiffens slightly if left in place for more than three days, the Venocath is particularly soft, and although perforation could be caused by its stylet, it should not give rise to such complications once established.

The variability of physical characteristics of intravenous catheters should make it mandatory to report complications in relation to the type of material and make of catheter used.—I am, etc.,

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Psychogeriatric Care

SIR,—May I comment on a couple among the many important points raised in the correspondence which followed your leading article (24 July, p. 202) and my paper in the previous week (17 July, p. 166)?

Dr. M. Silverman (14 August, p. 435) argues that the psychiatry of old age is not a separate subspecialty. I agree with him, if by specialism he means "sapiential" specialism. But the present situation is such that there is surely an urgent need for a "functional" specialism—for some psychiatrists to take a special interest in tackling this urgent job of psychiatric work. There are analogies here with, say, drug dependence, which is not a subspecialty either. However, the issue he raises highlights an important practical point: at present the psychiatry of old age is an under-cultivated field and it does sometimes need to be considered separately from psychiatry as a whole in planning and in allocation of resources and staff. In particular, at a time

when extra money is said to be being channelled into services for the elderly, the special needs of psychiatric services for old people can be overlooked through being regarded merely as part of psychiatry as a whole.

I was characteristically kind of Dr. T. B. Dunn (31 July, p. 308) to write so generously about our unit at Goodmayes; the size of our continuing debt to him is obvious to anyone who knows the unit. I think his doubts about my view that the needs of most ambulant demented patients who are not able to be cared for at home would be better met by residential rather than hospital care may be based more on what he sees as the likely administrative consequences than on the objective appropriateness of such a shift. He feels that such a pattern of care, inasmuch as residential units would be the responsibility of local authorities, implies that the doctor would lose control over admissions, so that ultimately patients would reaccumulate in hospital blocking the acute beds. But this is to assume that there would be no expansion of residential facilities, while my argument implies the need for a great expansion. I was careful not to say that "residential" necessarily means local authority care—many hospital boards have long had such "hostels"—but no doubt such units would come mainly under the local authority.

Surely what is at issue is the need for a unified service, which for old people (and for any other people) means that the whole range of facilities should be planned and distributed according to need, rather than according to which side of an administrative fence a problem happens to crop up. This implies that collaborative deployment of hospital and local authority resources should no longer depend merely on local goodwill, vital as that is, but must be built into the new health service as a part of its structure. The "Consultative Document"¹ recognizes the problem but gives no indication of how it is proposed to remedy it, and one hopes that, along with expansion of the relevant facilities, this is high on the agenda of the working party which is now looking at the relationship between health and social services.—I am, etc.,

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¹ Department of Health and Social Security. *National Health Service Reorganization: Consultative Document*. 1971.

Neurofibromatosis with Leukaemia

SIR,—Dr. M. W. McEvoy and Dr. Jillian R. Mann (11 September, p. 641) report a 5-year-old boy with café-au-lait spots and acute myeloid leukaemia, whose mother has neurofibromatosis. Hardisty *et al.*¹ have recorded a 3-year-old boy with juvenile chronic myeloid leukaemia whose father and three siblings suffered from neurofibromatosis, though the patient himself had no signs of the disease. We have at present under our care a boy of 23 months who appears to have juvenile chronic myeloid leukaemia, having first presented at the age of 3 months. This patient has a large number of café-au-lait spots of varying size, as do his mother and older sister, though there is no family history of neurofibromatosis. As Drs. McEvoy and Mann have pointed out, both