dissatisfaction with other doctors, thereby causing us to *under*estimate the problem.

Clearly our study approached only one facet of the complex interrelationship between parent and GP, but the Department of Health and Social Security's multicentre post-neonatal study with which we are now involved looks at the interrelationship from many sides, including an interview with the GP. The reports from this study should provide more insight into the patient-doctor inter-relationship.

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Haemoperfusion in treatment of drug intoxication

SIR,—We read with interest the report by Dr J A P Trafford and others (3 December, p 1453) describing the application of XAD-4 resin haemoperfusion in the treatment of drug intoxication. We are at present engaged in the clinical evaluation of not only this resin column but also of three charcoal-based devices, B-D Hemodetoxifier (Becton, Dickinson and Co); Adsorba 300 C (Gambro Ltd); and Haemocol (Smith and Nephew Ltd), and feel that some of the claims made by Dr Trafford and his co-workers for the superiority of the resin device may be a little premature.

Firstly, the anticoagulation regimen required for all four columns is, in principle, identical.

Secondly, so far as we can see, there are no significant differences in the extent of platelet damage encountered with any of these devices.

Thirdly, we know of no comparative data which support the contention that the clearance of tricyclic antidepressants is better than may be achieved by charcoal haemoperfusion. This notwithstanding, the claim that this technique is beneficial in the management of tricyclic antidepressant poisoning is, to say the least, highly questionable. Without exception the tricyclic antidepressants are extremely lipid-soluble compounds such that the proportion of the dose available for clearance from the blood is minute compared with that which is sequestered in the tissues. This is borne out by calculating the total quantities of amitriptyline and nortriptyline removed from their patient 9 using the plasma level data, which were supplied by this laboratory (see table).

A good approximation of the total amount of the parent drug (amitriptyline) and its active metabolite (nortriptyline) removed can be derived from the formula: $Q = \text{mean } (A-V) \times F \times t \times 10^{-6}$ where Q = total drug removed (mg), A = column inlet (arterial) drug concentration, V = column outlet (venous) drug concentration, F = blood flow rate (ml/min), and t = duration of haemoperfusion (min). Thus the quantity of amitriptyline removed from patient 9 (flow rate 300 ml/min; duration of haemoperfusion, 150 min) was 16·8 mg and of nortriptyline 14·5 mg, making a total removal of 31·3 mg of active drug. This contrasts with the values of 200 mg (amitriptyline) and 155 mg (nortriptyline) quoted by Dr Trafford and his colleagues. It is hard to comprehend, therefore, that the removal of less than the equivalent of two tablets of amitriptyline from a severely intoxicated patient could in itself have resulted in the marked clinical improvement described.

In our own published work[1 2] we have repeatedly stressed that the selection of poisoned patients for haemoperfusion therapy should be based not only on clinical criteria but also on the feasibility of eliminating a significant proportion of the ingested drug by efficient clearance of the blood. A useful guideline is the pharmacokinetic concept of volume of distribution, which takes account of the relative propensities of drugs to be deposited in the tissues. Thus whereas the volumes of distribution of the barbiturate drugs are of the order 0·5-2·0 l/kg, those for the tricyclic antidepressants lie between 20 and 60 l/kg.[3] Our experience suggests that for those drugs with volumes of distribution greater than 5 l/kg haemoperfusion is unlikely to achieve a significant reduction in the total body load.

We also question the clinical indications for haemoperfusion in this case. The patient was described as deeply unconscious, but no mention is made of other complications. Noble and Matthew[4] found that the average length of coma in a series of 100 cases of tricyclic antidepressant poisoning was only 6·4 h, the longest period of coma being 18 h. We would suggest, therefore, that it is generally unnecessary to shorten coma in poisoning with these drugs. In cases with other complications where it is felt necessary to reverse coma it is much simpler to administer an intravenous injection of physostigmine salicylate.[5]

Failure to consider these basic clinical and pharmacological principles may lead to the widespread misuse of a technique which, used intelligently, can prove an invaluable aid in the management of severe intoxication.

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[2] Widdop, B, *et al*, *Archives of Toxicology*, 1975, **34**, 27.
[3] Avery, G S, in *Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics*, ed G S Avery. Edinburgh, Churchill Livingstone, 1976.
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SIR,—Referring to the report of Dr J A P Trafford and others (3 December, p 1453) on the apparent efficacy of haemoperfusion with R-004 Amberlite resin in the treatment of poisoning with tricyclic antidepressants, we would like to comment on the quantitative aspect of drug removal.

Since the tricyclic antidepressants are all extensively bound to the tissues their volumes of distribution to pseudoequilibrium are high (10-20 l/kg)[1] and the blood concentration of these drugs is low even when taken in overdose. Braithwaite[2] found plasma or whole-blood concentrations of 0·56-1·31 mg/l in a group of patients with grades III and IV coma and of 0·98-1·9 mg/l in fatal cases of poisoning with nortriptyline or amitriptyline.

The perfusion method of Dr Trafford and his colleagues uses a flow rate of up to 300 ml/min (18 l/h) and the duration of the procedure was 3 and 2·5 h in the patients with clomipramine and amitriptyline poisoning respectively. Since the clearance values reported are close to the flow rate there is little doubt that the resin removes amitriptyline and its metabolite nortriptyline from the perfused blood. Reinfusion of blood cleared of drug could result in a transient decrease in plasma concentration until redistribution takes place and a state of pseudoequilibrium is again established.[3]

The total amount of blood perfused during 2·5 h (45 l) is small compared with the apparent volume of distribution of the tricyclic antidepressants (approximately 700-1400 l in a patient of 70 kg body weight). An efficient extracorporeal device for drug absorption or haemodialysis could therefore at most remove 3-6% of the total amount of drug contained in the body at pseudoequilibrium. Also, with a mean concentration of 1 mg/l in venous blood, the most optimistic calculation of drug removal would be 45 mg. Removal of large amounts of tricyclic antidepressants as reported by Dr Trafford and his colleagues (200 mg of amitriptyline and 155 mg of nortriptyline) could be possible only if the concentration in blood was very high. This could conceivably be the case early after the overdose, when distribution equilibrium is not yet attained. However, most intoxicated patients are not likely to be admitted to hospital until this initial phase is over.

Drug analysis was carried out in only one of the reported cases (No 9) and the efficacy of haemoperfusion in clomipramine poisoning (No 7) was inferred only from the clinical improvement that occurred during the procedure. In view of the published data on blood levels of antidepressant drugs in overdose cases,[2] and as long as the flow rate is limited, we feel that there is little hope that haemoperfusion techniques, whatever adsorbent or resin is used, will be of much help in the management of this difficult clinical condition. Identification in the emergency room of the exceptional patient with very high blood concentration who could conceivably benefit from haemoperfusion would require rapid quantitative determination of tricyclic antidepressants.

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Plasma concentrations of amitriptyline and nortriptyline in patient 9

Time from onset of haemoperfusion (min)	Amitriptyline (μg/l)		Nortriptyline (μg/l)	
	Inlet level	Outlet level	Inlet level	Outlet level
15	559	100	382	21
45	559	93	450	46
75	585	160	379	92
135	300	153	339	103

Dr Ruth Clayton

SIR,—It has been brought to the attention of the editors of volume 23 of *Biographical Memoirs of Fellows of the Royal Society* that certain sentences in the memoir on Professor C H Waddington may be read as derogatory of the work of Dr Ruth Clayton and her colleagues. This was in no way the intention of the author but arose from an unfortunate