

PAPERS AND SHORT REPORTS

Effects of sodium valproate in 100 children with special reference to weight

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Abstract

Excessive weight gain occurred in a patient who was taking sodium valproate and phenytoin. The sodium valproate was therefore withdrawn but the rapid weight loss that ensued led to phenytoin intoxication. Hence a retrospective analysis was conducted of 100 children with epilepsy treated with sodium valproate. Fit control improved in 77 and was best in children with generalised epilepsy. None of the reported severe side effects, such as acute liver disease and pancreatitis, were encountered. Milder but troublesome side effects, however, occurred in 65 patients. The commonest was increased weight gain, which occurred in 44 cases. Others were transient gastrointestinal disturbances (20), lassitude (nine), transient hair loss (six), transient enuresis (seven), and aggressive behaviour (four).

Introduction

Valproic acid, an eight-carbon-chain fatty acid, was found while being used as a solvent for derivatives of khellin to have an anticonvulsant action.¹ Its structure is quite different from that of other anticonvulsant drugs and it is thought to act by increasing presynaptic and synaptic gamma-aminobutyric acid² and conductance of postsynaptic K⁺ and Cl⁻³ and by a ketogenic diet-like action⁴ of its metabolites. The drug has many side effects, and those reported to date include weight gain,^{5, 6} gastrointestinal disturbances,^{5, 7} drug interactions,⁸ acute liver disease,⁹ pancreatitis,¹⁰ effects on coagulation,¹¹ hyperglycinaemia and

hyperglycinuria,¹² hyperammonaemia,¹³ sedation,⁵ alopecia,^{5, 7} and tremor.⁷

Though excessive weight gain is a recognised side effect of sodium valproate, it has not been studied in detail. In the recent data sheet on Epilim (January 1981) it is dismissed as "Increase in alertness, appetite and weight may occur." We analysed retrospectively 100 children whose epilepsy was treated with sodium valproate to determine the frequency and amount of weight gain and any association between excessive weight gain and the type of epilepsy or the degree of control of fits.

Patients and methods

The patients were an unselected group from the neurology clinics of two children's hospitals. There were 40 boys and 60 girls, and their ages ranged between 15 months and 18 years.

Treatment—The daily dosage of sodium valproate was 30-50 mg/kg body weight. The duration of treatment was between six months and five years, and altogether the drug had been taken for a total of 205 patient-years. Eighty-five of the patients had been taking other anticonvulsants before starting sodium valproate and served as their own controls; 45 required other anticonvulsants in addition to sodium valproate.

Type of epilepsy was classified according to the international classification (table). Patients who had several types of fit were classified according to the predominant type. For example, some children with secondary generalised epilepsy also had occasional partial seizures with elementary or complex symptoms, but not vice versa. Some others, classified as having myoclonic epilepsy, also had occasional tonic-clonic seizures, but the reverse was not seen.

Results

EFFECT ON SEIZURES

Twenty-four patients became fit free during treatment with sodium valproate, and the frequency of fits decreased by more than 50% in 28 patients and by less than 50% in 25. No improvement was obtained in 21 patients, and two had more fits when taking the drug. The response was better in generalised than in partial epilepsies (table). With better control of fits, behaviour and mental function often improved as well.

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SIDE EFFECTS

Increased appetite and excessive weight gain

Increased appetite and excessive weight gain were seen in 23 boys and 21 girls. Thirty-one of the 66 patients with generalised epilepsy and 13 of the 34 with partial epilepsy were affected in this way. The amount of weight gain was similar in both types of epilepsy. Weight-velocity charts of Tanner and Whitehouse¹⁴ showed that the yearly weight velocity, which had been within normal limits during the year before sodium valproate was introduced, exceeded or reached the 98th centile in 38 children during the year after the drug was started. (In a normal population only 3% of children are expected to reach or exceed the 98th centile.) In another six children the weight

velocity increased but remained within normal limits. Boys and girls were similarly affected (fig 1). Using the growth and development charts of Tanner *et al*,¹⁵ we found that weight had increased by one centile in 25 patients, by two centiles in 13, by three centiles in four, and by four centiles in two. No increase in height velocity was seen. Because of continuing weight gain sodium valproate was withdrawn in three children. Figure 2 shows the patterns of increased weight gain. There was no obvious correlation between control of fits and excessive weight gain. Thirteen of all 24 patients who became fit free were affected, as were 15 of the 28 whose fit frequency decreased by more than 50%, nine of the 25 whose fit frequency decreased by less than 50%, six of the 21 who did not improve, and one patient whose epilepsy had deteriorated.

Types of epilepsy among 100 children and outcome of treatment with sodium valproate (percentages in parentheses)

Type of epilepsy	No of cases	Result of treatment				
		Fit free	Reduction		No change	Deterioration
			> 50 %	< 50 %		
Partial:						
With elementary symptoms	9		3	3	3	
With complex symptoms	13	1	3	3	6	
With secondary generalisation	12	2	5	3	2	
Total	34	3 (8.8)	11 (32.3)	9 (26.5)	11 (32.4)	
Generalised:						
Petit mal	5	3	2			
Grand mal	37	13	13	7	4	
Myoclonic epilepsy	24	5	2	9	6	2
Total	66	21 (31.8)	17 (25.8)	16 (24.2)	10 (15.2)	2 (3.0)

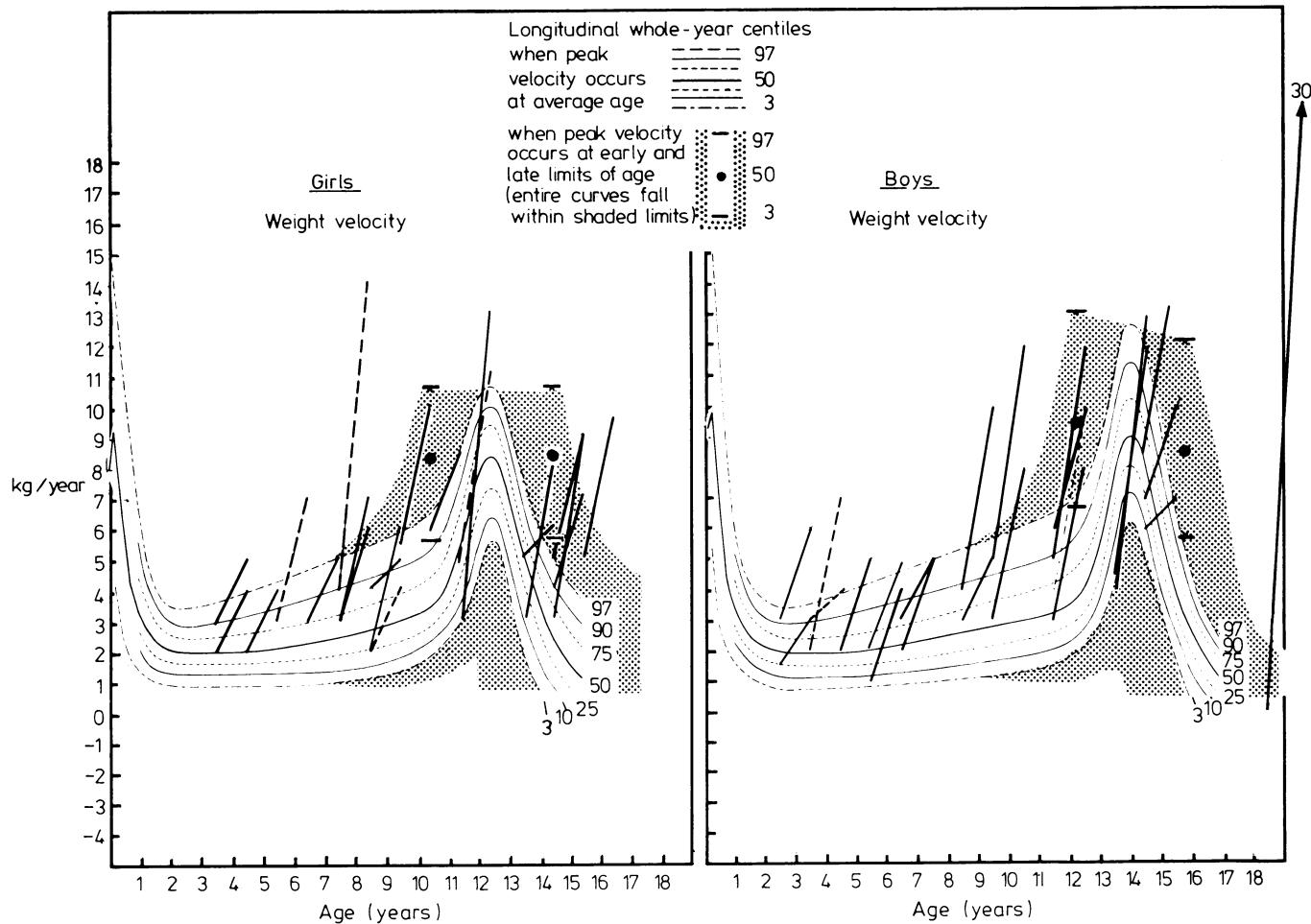


FIG 1—Yearly weight-velocity rates of children with weight gain during treatment with sodium valproate. Lines connect values in year before treatment was started and those for first year on treatment. Broken lines indicate cases in which yearly weight velocity before treatment was calculated from period of less than six months.

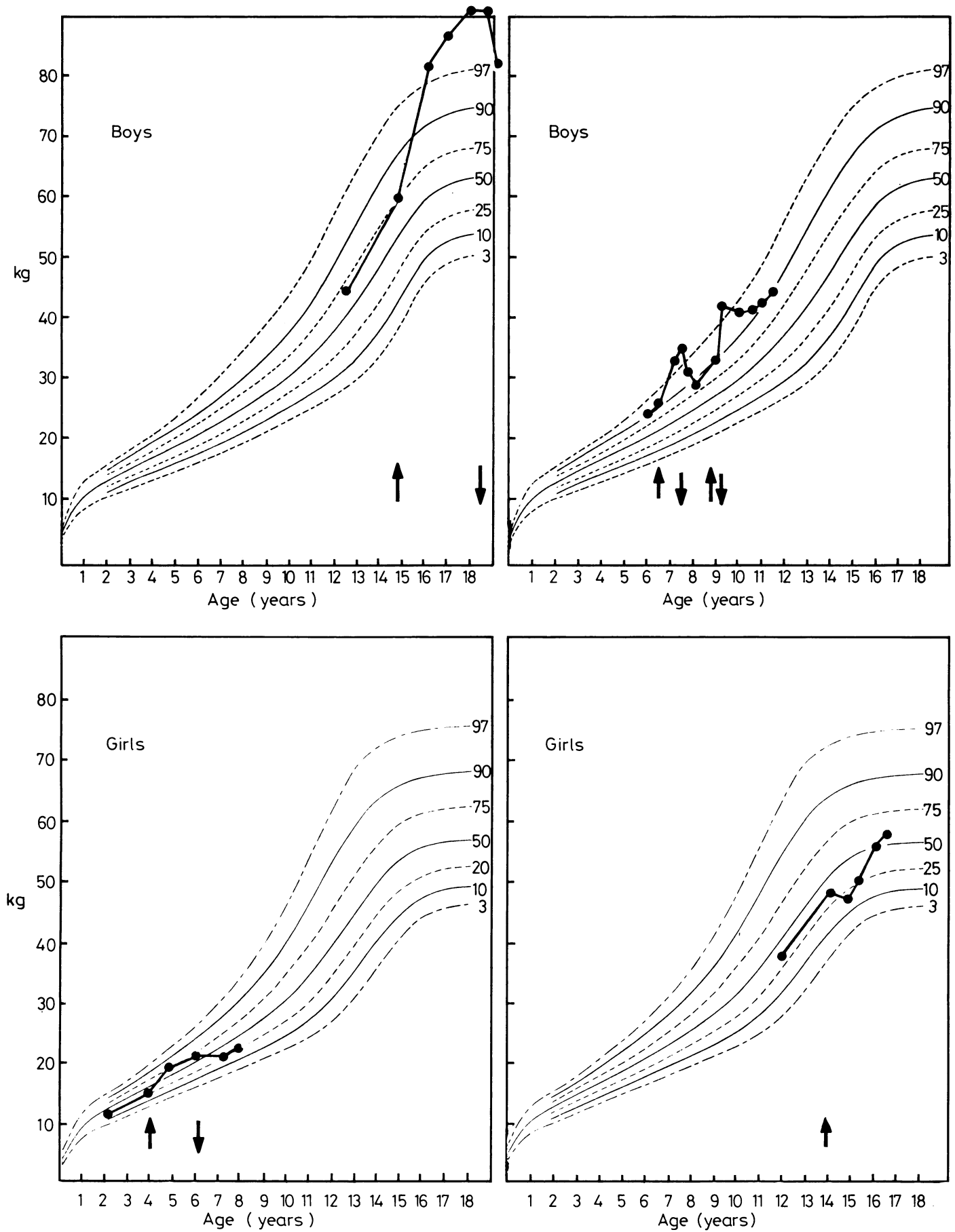


FIG 2—Some patterns of weight gain. Arrows indicate starting and phasing out sodium valproate.

Of the 85 patients who had been taking other drugs before starting sodium valproate, none showed a comparable increase in weight related to introducing or stopping drugs. Smaller changes in appetite and weight were related to alterations in phenytoin-induced gum swelling.

Gastrointestinal disturbances

Nausea, vomiting, diarrhoea, or abdominal pain occurred in 20 patients. Such disturbances were transient when treatment was started in a low dose and increased gradually, but in some patients given a high dose initially it was necessary to reduce the dose and increase it slowly, after which it was usually tolerated. Abdominal pain was, however, severe in four patients and necessitated stopping the drug in three.

Gastrointestinal disturbances led to loss of weight in 11 children. Five of these gained excessive weight after the gastrointestinal symptoms disappeared. In three others weight returned to the original channel after improvement in the gastrointestinal symptoms; and in the remaining three, in whom these symptoms required stopping sodium valproate, weight returned to normal.

Nocturnal enuresis

This occurred in seven patients and stopped without treatment after a few months.

Effect on hair

Transient hair loss was seen in six patients; and in three the hair became noticeably curly, especially in the frontal region. Microscopical examination of hair from two of these patients showed no abnormality.

Other side effects

Severe lassitude was reported in nine children and aggressive behaviour in four others. Since there was no apparent improvement in their epilepsy the drug was withdrawn. Poor appetite was noted in the patients who suffered severe lassitude during treatment, and four of them also lost weight. After stopping the drug all these symptoms disappeared.

There were no signs or symptoms of hepatic, pancreatic, or haematological disorder, and laboratory tests for these were therefore not performed.

Discussion

Apart from hormones no other drugs are known to cause increased appetite and weight gain. The mechanism(s) by which sodium valproate does this and the reason why some patients do gain weight while others do not are not understood.

A partially controlled limbic or temporal lobe phenomenon seems unlikely, since all types of epilepsy were affected in our series, and the degree to which fits were controlled had no influence. A direct effect of sodium valproate or a metabolite on the hypothalamus is more likely since small doses of the drug did not affect weight, whereas doses higher than 25-30 mg/kg did. Other workers (P M Jeavons, personal communication, 1981) believe that weight gain is unrelated to dose.

Some neurons in which gamma-aminobutyric acid is the transmitter substance and which inhibit pacemaker neurons are themselves inhibited by neurons activated by that agent, resulting in disinhibition.¹⁶ In some patients sodium valproate may disturb the balance between inhibiting and disinhibiting neurons activated by gamma-aminobutyric acid by increasing disinhibition, so causing deterioration in epilepsy or nocturnal enuresis or increased appetite.

Obese patients have decreased activity of Na⁺ and K⁺

adenosine triphosphatase in red blood cells.¹⁷ A similar defect is thought to occur in all cell types in man as in the ob ob mouse.¹⁸ Bondy¹⁹ speculated that the resulting decreased cellular thermogenesis could be the cause of the increased appetite. Sodium valproate increases the membrane stability by increasing K⁺ and Cl⁻ conductance,³ and it may be postulated that less adenosine triphosphatase is needed for repolarisation, causing reduced thermogenesis. The resulting minor temperature changes in the hypothalamus may also explain increased appetite during treatment with sodium valproate.

Gastrointestinal side effects may be due to a direct effect on the gut. They are rarer with the enteric-coated preparation. That they appear to be commoner in the USA may be due to the wider use there of valproic acid rather than sodium valproate.

There are important clinical implications of the excessive weight gain and increased appetite caused by sodium valproate. Two of our patients were diabetics; fortunately their weight and appetite were not affected. One girl, aged 13, who became obese while taking sodium valproate developed meralgia paraesthetica, which is very rare in childhood.²⁰ Another patient taking sodium valproate and phenytoin developed phenytoin intoxication after the sodium valproate was stopped because of a gain of 30 kg over six months. He lost 15 kg within a few weeks, and phenytoin, which had been adjusted for his increased weight, caused intoxication. With other drugs, such as digoxin, a similar sequence of events could cause serious problems.

In some children, particularly adolescent girls, the excessive weight gain has a serious psychological effect; their morale and self-confidence are undermined and they may become withdrawn and depressed. This problem, when added to those of adolescence itself and epilepsy, may be catastrophic. Loss of hair is also very disturbing, especially for girls; it is helpful to be able to reassure them and their parents that this will not persist.

Nocturnal enuresis does not seem to have been reported as a side effect; again it is helpful to be able to give an optimistic prognosis for this problem.

There could be positive therapeutic implications for the effect of sodium valproate on appetite and weight gain in, for example, anorexia nervosa if it were possible to recognise in advance the 44% of patients who show this side effect.

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SHORT REPORTS

Why request reprints?

It is common practice for original articles in medical journals to give an address for reprint requests. Often authors receive many requests, usually from abroad. Since photocopiers are now freely available in most parts of the world we were interested in the true relevance of reprint requests and canvassed the views of other doctors.

Methods and results

We sent a questionnaire to 280 doctors of grade senior registrar or lecturer and above working in all specialties in the teaching hospitals in Nottingham; 161 replies were received and analysed. The doctors replying included 46 senior registrars and lecturers (31%), 89 consultants and senior lecturers (60%), and 13 professors and readers (9%); 13 did not specify rank. Of these respondents, 57 (35%) published one or no medical papers each year, 87 (54%) published two to five papers, and 17 (11%) published more than five each year. Taking each doctor's estimate together it appeared that nearly 10 800 reprint requests had been received by them in the past year.

The table shows the origin of reprint requests in order of frequency.

Countries of origin of reprint requests (figures are numbers (%) of doctors answering each question)

Answer	North America	Eutope	Iron Curtain	Japan, New Zealand, Australia	Third World
<i>Where do your reprint requests come from?</i>					
Most frequently	106 (66)	40 (25)	12 (8)	2 (1)	0
Next most frequently	31 (25)	63 (50)	21 (17)	4 (3)	6 (5)
<i>Do you return reprints on request?</i>					
Occasionally or never	85 (63)	78 (59)	54 (46)	67 (66)	45 (43)
Usually or always	51 (37)	55 (41)	64 (54)	35 (34)	59 (57)

Doctors returned reprints (when available) most often to Iron Curtain and Third World countries, but the response was not high to anywhere. Indeed, only two of the 17 doctors who published more than five papers a year usually returned reprints to North America. Seventy-four doctors (56%) said that any reprints that they had were handed to colleagues locally or remained in a drawer. Reprint requests were regarded as a waste of time and money by 105 doctors (72%), and only 25 (17%) thought that they were a valuable way of keeping in touch with other investigators and knowing who was interested in their work. Nearly a third of doctors thought that reprint requests were a good way of collecting foreign stamps.

When doctors were asked whether they themselves requested reprints from authors 125 (83%) said rarely or never, 19 (13%) said occasionally, and six (4%) said often. When a copy was required 141 (97%) arranged a photocopy locally. Five doctors commented that they requested reprints only when high-quality reproductions of photographs or radiographs were required.

Comment

The large majority of doctors regarded reprint requests as a waste of time and money. Although our questionnaire covered only a small number of doctors, they represented a cross-section from all hospital specialties.

North American and European countries were by far the most common sources of reprint requests, although only a third of doctors usually returned reprints to these countries. It is hard to see any value in requests from these countries, where photocopiers are freely

available. Photocopy laws generally allow copies for personal use. The commonly used printed reprint-request postcards (for example, Request a Print), often filled out and signed by secretaries,¹ suggest that requests are accepted practice, especially in North America. The belief that access to library or photocopier facilities may be more difficult in Iron Curtain or Third World countries probably explains the higher return rate of reprints to these areas. It would be interesting to hear how important reprints are to doctors working in these areas.

The estimate of 10 800 reprint requests received by our 161 respondents in the past year suggests that the cost of replying to all requests would be considerable. Assuming return by air mail, postage costs alone would be over £3000. Countrywide, the cost to the National Health Service (which in the end actually pays for the stationery, postage, and time) would be alarming if all doctors replied to every request. Doctors in our area rarely requested reprints themselves from authors, and almost all relied on arranging photocopies of interesting articles locally. Efficient library facilities are a feature of medical centres in most countries.

We do not deny that it is sometimes useful to be able to write to authors about some point of interest or debate, but we believe that reprint requests are largely outdated and a waste of time and money.

We thank our colleagues for completing the questionnaires.

¹ Dirckx JH. Reprints. *N Engl J Med* 1981;304:738-9.

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Warfarin poisoning in patients with prosthetic heart valves

Massive warfarin overdose in patients with prosthetic heart valves requires a prolonged period of carefully controlled partial reversal of anticoagulation. We report two cases where partial reversal was maintained with repeated infusions of fresh frozen plasma. The frequency of treatment was monitored by the prothrombin time ratio (PTR), and serial plasma warfarin concentration estimations predicted the required duration of treatment.

Case reports

Case 1—A 64-year-old man, on long-term warfarin for a Björk-Shiley prosthetic valve, took an overdose of an uncertain quantity of warfarin, digoxin, frusemide, and sedatives. Specific treatment was required only for warfarin. The initial PTR, 18 hours after the overdose, was 5.2 (British comparative thromplastin). The patient was given factor II, IX, and X concentrate (Defix: Scottish National Blood Transfusion Service). When 40 ml of the concentrate had failed to reduce the PTR to within the accepted therapeutic range¹ of 2.0-4.0, he was given repeated infusions of 300 ml of fresh frozen plasma over a period of five days (see figure). This maintained the PTR at or near the therapeutic range. At no time did he bleed. The initial plasma concentration of warfarin and metabolites, measured by fluorimetry,² was raised at 44 µmol/l (13.5 µg/ml) (figure) but subsequently