Serum creatinine concentration by time.

figure are transformed back into the original units serum creatinine concentrations change smoothly with time. A quadratic curve fits the data reasonably well, although a more appropriate model might be to fit separate exponential curves to the periods of improvement and deterioration. It is hard to see why they have chosen to use the artificial method of taking reciprocals rather than study the raw data. The authors rightly say that "a time when renal allograft rejection occurs can be determined only if there is a sudden event rather than slow changes from a non-rejecting to a rejecting state." I cannot accept that they have established this.

Lastly, their approach assumes that onset of rejection results in an immediate rise in serum creatinine. Is this really so?

D G ALTMAN

Division of Computing and Statistics,
Clinical Research Centre,
Northwick Park Hospital,
Harrow, Middx

*We sent a copy of this letter to the authors, whose reply is printed below.—Ed, *BMJ*.

SIR,—Mr Altman does not understand why we plotted the reciprocal rather than the untransformed, "raw" data, but to use the raw data is to overlook the biology of plasma creatinine concentration measurements when used as a guide to renal function.

It is logical to use the reciprocal because the relation between plasma creatinine concentration and glomerular filtration rate is hyperbolic and curvilinear whether studied in vivo or as a mathematical model.¹ It was a realisation of this that led physicians to plot sequential plasma creatinine measurements as the reciprocal, and so demonstrate the straight line relations, which can predict by extrapolation the subsequent course of some patients in renal failure.²⁻⁴ This suggested that in these patients nephron loss proceeded at a constant rate while in others, whose sequences of plasma creatinine measurements were best demonstrated on semilogarithmic plots, nephron loss proceeds at a rate which is a fixed percentage of the number remaining. In a disorder in which the loss of nephrons is sudden and total the subsequent increase in plasma creatinine should be demonstrated as a straight

line against time if raw data are used, as there will be no renal loss but continued production at a constant rate (as it is assumed to be whenever creatinine is used as a guide to change in renal function).

The loss of function with allograft rejection might follow any of these alternative courses and our choice of the reciprocal is based on comparisons between the three types of plot. We are now comparing the alternatives more carefully, having collected more samples each day than in our reported examples, and are hoping to obtain more information about the pathophysiology of rejection and to confirm our initial conclusion that the reciprocal is the transformation that most frequently demonstrates the changes in a way that is analysable by linear regression, and avoids the need for the multiple data points required when considering curves.

We have, as stated in our paper, subjected the data to analysis using a method developed by Smith⁵ and obtained further evidence for our hypothesis. This method was designed to select the most likely time for a change to have occurred, and does not make an arbitrary allocation of points to a phase of improvement or deterioration. It calculates the probability of there having been a change at any time during the sequence of results considered. This programme also gives more emphasis to points close to the time of change than to those distant from it, thus reducing any "magnification of error" introduced by transforming low creatinine values to the reciprocal. The objective was to determine the time of onset of deterioration, in contrast with the continuation of improvement or stability, and we have other facts which support our thesis that the point where our "line of improvement" and "line of deterioration" intercept represent moments of crisis for renal function. We frequently noted a sudden increase in weight on the date of intercept (not a few days before, when Mr Altman's method suggests that a decline in renal function may have started). Also, when studying circadian variations in electrolyte excretion after transplantation we identified isolated days when the reversed or absent circadian variations in sodium excretion (observed after transplantation) were distorted by a transient nocturnal drop in sodium output and a subsequent daytime natriuresis. These abnormal days were observed to coincide with the intercept of the lines of improvement and lines of deterioration.⁶ This provides support for our thesis that there is a sudden event at this time causing an alteration in one mathematically predictable course and heralding a change to another. There is considerable support for this view from experimental studies in renal transplantation, which show abrupt changes in renal perfusion associated with rejection.⁷

Our method of using the reciprocal identifies the onset of rejection several days earlier than methods used by many authors, who often use a rise in "non-transformed" plasma creatinine of 25% as their definition of rejection and do not use weight correction to remove the effects of water retention at the time of rejection. A "line of deterioration" has been observed to develop following periods of stable function, arguing against Mr Altman's suggestion that we have been observing the end of a sequential process—our "time of rejection" representing the minimum point in a continuous sequence of deterioration starting earlier than our "abrupt event."

Increased numbers of samples at the time

when renal function changes are essential before our hypothesis can be fully proved. These are being collected in a prospective study.

MARTIN S KNAPP
R POWNALL

City Hospital, Nottingham

- ¹ Doolan, P D, Alpen, E L, and Theil, G B, *American Journal of Medicine*, 1962, **32**, 65.
- ² Mikh, W E, and Waker, M, *Clinical Research*, 1976, **24**, 407.
- ³ Rutherford, W E, et al, *Kidney International*, 1977, **11**, 62.
- ⁴ Knapp, M S, et al, *Lancet*, 1977, **2**, 1183.
- ⁵ Smith, A F M, and Cook, D G; submitted for publication.
- ⁶ Kountz, S, Lamb, D R, and Cohn, R, *Journal of the American Medical Association*, 1965, **191**, 12.
- ⁷ Knapp, M S, et al, *Kidney International*, 1978, **14**, 794.

Delayed haemorrhagic disease of the newborn

SIR,—The report by Drs N A Cooper and M A Lynch (20 January, p 164) of delayed haemorrhagic disease of the newborn complicated by extradural haematoma underlines a rare but definite problem. Recent similar experience¹ with a 6-week-old breast-fed baby admitted with apparent "viral" infection who developed an extensive haematoma at the lumbar puncture site and prolonged bleeding after venepuncture raised similar anxieties. Since breast milk contains 15 μg/l of vitamin K compared with the 60 μg/l of cows' milk, breast-fed babies are at greater risk from such a bleeding diathesis and even severe intracerebral bleeding, as reported. To prevent even a very occasional case the routine and safe administration of vitamin K to at least all babies who are breast-fed seems logical. Certainly in such babies administration of vitamin K or at least estimation of prothrombin time might be prudent when admission to hospital and invasive procedures are necessitated by infection or malaise.

A MINFORD
O B EDEN

Department of Child Life and Health,
Royal Hospital for Sick Children,
Edinburgh

¹ Minford, A, and Eden, O B, *Archives of Diseases of Childhood*. In press.

SIR,—Drs N A Cooper and M A Lynch have reported subdural haemorrhage, occurring at 6 weeks in a baby born at 37 weeks' gestation, who had vitamin K deficiency associated with breast-feeding (20 January, p 164). The incidence of significant bleeding from this cause after the neonatal period is unknown, but it is generally thought to be rare. We wish to record gastrointestinal bleeding due to vitamin K deficiency in a full-term, breast-fed baby aged 4 weeks.

The infant, who weighed 3.3 kg at birth, had not received vitamin K prophylaxis. He was fully breast-fed and had thrived until the age of 4 weeks, when he developed epistaxis and melena. On examination his general condition was good; he was mildly jaundiced and had two small recent bruises. His serum bilirubin concentration was 130 μmol/l (7.6 mg/100 ml); serum aspartate aminotransferase and alanine aminotransferase concentrations were normal. There were no bilirubin, urobilinogen-reducing substance, or abnormal amino-acids in the urine. The haemoglobin concentration was 14.2 g/dl, white blood cells $13.1 \times 10^9/l$, platelets normal, and serum fibrinogen 5.0 g/l (normal); but other tests of clotting function were grossly abnormal, indicating simple vitamin K deficiency. The prothrombin time was corrected to 17 seconds in vitro with normal plasma (50/50

mixture). The infant was given 1 mg of vitamin K intravenously and all clotting abnormalities were totally corrected within 15 hours; there was no further bleeding. Seven weeks later, at the age of 11 weeks, he was still fully breast-fed, was clinically healthy and no longer jaundiced, and had normal serum bilirubin and clotting tests.

The vitamin K deficiency in this baby could be attributed solely to inadequate intake, as breast milk is known to be relatively deficient in the vitamin. The prolonged neonatal jaundice was considered to be due to the inhibitory effects of breast milk on liver enzymes, which occur in 2-3% of breast-fed babies.¹ It is not known if changes in the bile occur in breast-milk jaundice which could materially affect intestinal absorption of vitamin K, but if present these would have been a contributory factor.

Administration of vitamin K at birth would clearly have prevented the haemorrhagic disease in this patient. Now that increasing numbers of babies are breast-fed during the first month of life a case could be made for the routine administration of intramuscular vitamin K at birth. Intramuscular injections are, however, not without their disadvantages and before we consider such a policy the risks of haemorrhagic disease in fully breast-fed babies born at term need careful scientific appraisal.

We thank Professor J K Lloyd for permission to report this case under her care.

I F ROBERTS
P J MCHUGH

St James's Hospital,
London SW12

¹ Winfield, C R, and MacFaul, R, *Archives of Disease in Childhood*, 1978, **53**, 506.

Caring for babies of very low birth weight

SIR,—I would like to add support to Dr R R Gordon's reply (25 November, p 1492) to your leading article (21 October, p 1105) on caring for babies of very low birth weight.

A register of all cases of cerebral palsy diagnosed in children born in Western Australia since 1956 provides an annual incidence of cerebral palsy around 2 per 1000 live births. The incidence fell from 3 to 1.5 per 1000 from 1966 to 1975, during which time neonatal intensive care was introduced (in 1970-1).

However, as shown in tables I and II, the total rate of cerebral palsy and the rate of spastic cerebral palsy in low-birth weight infants have remained high and the improve-

ment in the cerebral palsy rate has been in those over 2500 g. Thus the low-birth weight infants who have received neonatal intensive care have recently contributed more to the cerebral palsy rate than previously.

F J STANLEY

Community and Child Health Services,
Perth, Western Australia

Induction of labour and postpartum haemorrhage

SIR,—The observations reported by Mr P R S Brinsden and Mr A D Clark (23 September, p 855) showing an increased incidence of postpartum haemorrhage following induced labour compared with spontaneous labour has prompted a similar analysis for the Oxford obstetric unit.

A total of 7295 consecutive vaginal deliveries during 1976-8 have been analysed; patients with a history of significant antepartum haemorrhage were excluded. Primigravidae and multigravidae were analysed separately, and grouped according to labour onset and management; during the period covered the intravaginal administration of prostaglandin E₂ gel before formal induction of labour was introduced¹ and patients thus treated have been analysed as a separate group (see table). Postpartum haemorrhage was defined as blood loss exceeding 500 ml at delivery as recorded in the patient's notes. Almost invariably patients were given intramuscular syntometrine with delivery of the anterior fetal shoulder.

Induced labour resulted in a significantly increased rate of postpartum haemorrhage compared with spontaneous labour; mode of delivery (spontaneous, forceps, breech, ventouse), did not appear to influence the incidence, and there was a similar negative association in relation to the use of epidural analgesia in labour. Postpartum haemorrhage occurring in the group of patients given vaginal PGE₂ gel the evening before planned formal induction was comparable with the augmented labour group. However, some patients treated this way established labour without any further oxytocic being given and postpartum haemorrhage rates of 6.3% and 3.2% for primiparae and multiparae respectively were observed, similar to those in the spontaneous labour group; while those requiring subsequent formal induction had postpartum haemorrhage rates of 9.8% and 8.2% respectively, equivalent to those in the routine induction group.

The increased postpartum haemorrhage rates associated with induced labour are thus similar to those reported by Brinsden and Clark, while the postpartum haemorrhage rates in augmented labour, not analysed by them, were between those for spontaneous and induced labour. There are two possible explanations for these findings. There is evidence that the dosage of intravenous oxytocin given to induce labour is greater than necessary,² causing the uterus to contract more than required or desirable and so reducing myometrial efficiency following delivery. PGE₂ possibly acts primarily on the cervix and lower uterine segment when

used as above, and provokes uterine contractions which are more frequent but of much lower pressures than with oxytocin; thus it does not overstimulate the contractile upper segment so results in postpartum haemorrhage rates similar to those in spontaneous labour. Alternatively, when labour results from PGE₂ gel treatment alone, high levels of PGE₂ persist in the myometrium throughout labour, enhancing the normal contraction-retraction processes following delivery; our finding of higher cord plasma levels of PGE at delivery following labour induced in this way than at formally induced labour provides indirect evidence to support this hypothesis.

These observations on postpartum haemorrhage rates are important if a change in the attitude towards the management of induction of labour is advocated. It has previously been shown³ that there are advantages to the outcome of induced labour initially treated with vaginal prostaglandin gel, to which the reduced frequency of postpartum haemorrhage can now be added.

I thank Sister Sue Bradley in helping with the data collection and Ms Pat Yudkin for help with the statistical analyses.

I Z MACKENZIE

Nuffield Department of Obstetrics and
Gynaecology,
John Radcliffe Hospital,
Headington, Oxford

¹ MacKenzie, I Z, and Embrey, M P, *British Medical Journal*, 1977, **2**, 1381.

² Woolfson, J, et al, *British Journal of Obstetrics and Gynaecology*, 1976, **83**, 934.

³ MacKenzie, I Z, and Embrey, M P, *British Journal of Obstetrics and Gynaecology*, 1978, **85**, 657.

Variations in number of births and perinatal mortality by day of week

SIR,—In his letter (24 February, p 549) Dr M J V Bull compared his estimate of the proportion of births taking place in general practitioner maternity units based on claims made by GPs for care during confinement with the lower figures given in my paper (16 December, p 1670). My data were based on births in hospitals classified in the Registrar General's statistical review as "NHS hospitals A."¹ These are hospitals with GP maternity beds but without specialist obstetric beds. Thus I did not take into account hospitals with both specialist obstetric and general practitioner maternity beds.

There is a third source of data which can shed further light on this question. This is the Hospital In-patient Enquiry (HIPE), which gives an estimate of the total number of women delivered in general practitioner beds regardless of whether the hospitals concerned have specialist obstetric beds. In the accompanying table I have combined data from HIPE and birth registrations to derive estimates of the proportion of women delivered in each type of

TABLE I—Total cerebral palsy rates

Birth weight (g)	1968-71 Rate*		1972-75 Rate*		% of 1968-71 rate
	No	per 1000	No	per 1000	
≤ 2000	32	17.5	21	14.1	81
2000-2499	24	7.3	21	7.2	99
≥ 2500	137	1.8	65	0.9	50

*Excluding all under 500 g.

TABLE II—Spastic cerebral palsy rates

Birth weight (g)	1968-70 Rate*		1971-75 Rate*		NS
	No	per 1000	No	per 1000	
≤ 2000	13	11.1	20	10.6	NS
2000-2499	14	5.7	20	5.3	NS
≥ 2500	86	1.5	55	0.6	P<0.01

*Excluding all under 500 g.

Postpartum haemorrhage (PPH) and onset of labour in Oxford 1976-8

	Primigravidae		Multigravidae		Total
	Total	No (%) with PPH	Total	No (%) with PPH	
Spontaneous labour	1495	77 (5.1)	2209	56 (2.5)	3704
Augmented labour	547	41 (7.5)	346	20 (5.8)	893
PGE ₂ gel before induced labour	657	54 (8.2)	426	24 (5.6)	1083
Induced labour	638	66 (10.3)	977	71 (7.3)	1615
Total	3337		3958		7295

χ² test, 3 DF: primigravidae P<0.001; multigravidae P<0.001.