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?

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*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.

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- 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.

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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