with moderate renal failure. With the authors we notice, however, that the difference in changes in plasma levels of PTH is small and present only in the subgroup of patients with a S-creatinine at baseline >3 mg/dl. Indeed at the end of the study the median of the plasma PTH was 30.6 (12.0-58.2) pmol/l in the placebo group and 24.4 (7.3-73.5) pmol/l in the calcitriol group. We are very keen to know whether this difference in the absolute outcome values of PTH is actually significant, because only the variations of the PTH during the study were statistically compared and found significant. The reason of the significant difference in the variation may, however, be the difference in baseline PTH values in the two subgroups with baseline S-creatinine >3 mg/dl. These latter are 12.6 (10.1-63.3) in the placebo group and 25.9 (6.9-81.8) in the calcitriol group and it would be interesting to know whether these are statistically different.

Another issue is to know whether a plasma intact PTH of 24.4 pmol/l (7.3-73.5) is an optimal plasma PTH range for patients with a median S-creatinine of 4 mg/dl, i.e. with a creatinine clearance of about 20 ml/min or an inulin clearance of about 15 ml/min.

In this range of renal failure simultaneous plasma intact PTH and bone histomorphometry data have been reported to our knowledge only by Lafage et al. [2], who showed in 19 patients that while their mean plasma intact PTH was 17±10 pmol/l their bone biopsy showed marked osteitis fibrosa in nine patients, mixed lesions in four, and normal bone in four. Therefore we doubt that the plasma intact PTH of 24 pmol/l obtained by systematic administration of 0.125 μg/day of calcitriol is appropriate, since they are very likely to be associated with marked osteitis fibrosa.

Ritz et al. think, nevertheless, that their data are clinically decisive for promoting systematic use of low doses of calcitriol in moderate renal insufficiency, since according to them there is a priori reason to assume that the effectiveness of calcitriol will wane with time, i.e. beyond the 12 months of their trial.

However, according to Hamdy et al. [3], suppression of PTH secretion by increasing plasma calcitriol in uraemic patients may wane after 18 months. Indeed in their placebo-controlled study of alfacalcidol given at 0.25 μg/day (i.e. a dose equivalent to 0.125 μg/day of calcitriol) for 2 years to 89 patients with mild to moderate renal failure (creatinine clearance 15–50 ml/min), the decrease of plasma intact PTH was present only during the first 18 months, the final levels at 2 years being comparable to the initial ones (10 pmol/l) in spite of a persistent increase of their plasma calcium. At difference of the Ritz’s study plasma phosphate increased however in this study, probably in relation to the well-known (but often forgotten) stimulatory effect of calcitriol on phosphate intestinal absorption, and may explain this escape of PTH suppression [4].

Since these two major controlled studies with 1α hydroxylated vitamin D derivatives show favourable effects only comparatively to a placebo but were unable to show long-term improvement of PTH hypersecretion, we would like to indicate that other approaches have been able to decrease PTH hypersecretion in the optimal range and to improve bone histology comparatively to the baseline data: in advanced renal failure, very restricted protein and phosphate diet with ketoanalogues, and physiological supplements of native vitamin D and calcium have corrected osteitis fibrosa and mixed lesion in all the 19 patients of Lafage et al. [2]. The exception of one who was non-compliant to the diet, normalizing bone histology in 10 patients.

In moderate renal failure, moderate protein diet (0.8 g/kg per day) supplemented with 3 g of oral CaCO₃ taken with the meal as phosphate binder associated with native vitamin D or 25OH vitamin D₃ in order to maintain a good vitamin D repletion (plasma 25 OHD at 75 nmol/l), suppressed PTH secretion in 21 patients without increasing plasma calcium, in spite of relentless 2-year progression of renal failure with increase of plasma phosphate. Furthermore sequential bone biopsies in 12 patients showed decreased osteoid volume on the second bone biopsy. The slope of the S-creatinine reciprocal versus time decreased during this period, suggesting that the rate of renal insufficiency progression was reduced. In two patients the same therapeutic approach has even been able to induce an adynamic pattern of their bone histology.

We suggest therefore that a comparative study of 1α OH vitamin D derivatives in renal insufficiency should now be made, not versus a placebo but versus CaCO₃.

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Reply by Editor
When analysing a study one very popular mistake is to make innumerable comparisons and attach P values to them. We carefully refrained from committing this error by defining at the beginning of the study that the data should be analysed by intention to treat analysis and that the difference in PTH values was the primary end-point. All other differences are clearly marked as post-hoc analyses for, which the attachment of a significance level is irrelevant. Therefore the question of whether subgroup analysis yields statistical differences is not appropriate.

Protestant theology postulates that the intentions of our Lord can best be recognized by sticking to the text of the gospel. In profane text as well it is rewarding to carefully read papers. Such perusal of the paper would reveal statement that (p. 2232) ‘There is increasing evidence that the bone response to PTH is altered in renal failure ... These informations had not been available in the planning stage of the study.’ The bone changes were not the aim of this study and any speculations of what had happened in bone, beyond what we can deduce from not-invasive measurements, are speculative.

It is not clear to me why the failure of PTH suppression with concomitant hyperphosphataemia in the Hamdy study is relevant to our protocol, which was designed to carefully avoid any hyperphosphataemia.
Simplified approaches to calculate Kt/V

Sir, Movilli [1] recently highlighted the range of Kt/V values obtained with various simplified equations which approximate to a full 3-sample (3S) solution and called for standardization. These equations are based on either the natural logarithm of pre-/post-dialysis serum urea (Ln(Co/Ct)) or the percentage urea reduction ratio (URR), and the latter perform badly at extreme Kt/V values. Apart from this qualification the author did not recommend a ‘best’ equation.

Even without consideration of 2-pool kinetics, there are other aspects to be considered if an informed judgement is to be made. If urea generation rate (G) and fluid volume removed (Uf) from the urea distribution volume (V) during dialysis are zero, then for a constant set of dialysis conditions, Ln(Co/Ct) but not URR is independent of the value of Co and Ln(Co/Ct) = Kt/V. These effects (G, Uf) are not negligible and must be corrected for in any simplified equation and should apply to the full range of possible dialysis conditions.

Equations derived by regression of URR or Ln(Co/Ct) against a rigorous solution [2-4] do not allow for variation in G, K or Uf/V and the constants may only ‘best fit’ the range of dialysis conditions (clearance, ultrafiltration, duration, frequency, nutrition) of the patients studied. Those derived by simplifying the relationship between Kt/V and Co, Ct, G, K and Uf/V [5-6] allow the use of factors to account, to some degree, for individual or patient group conditions. Smye et al. [5] used the equation: (1) Kt/V = Ln(Co/Ct) + G/K (1/Ct-1/Co) + Uf/V.

An equation used in this department is: (2) Kt/V = (1+Uf/V) * (Ln((Co-G/K)/(Ct-G/K)) + Uf/V).

Applying these equations to data from 140 3S analyses (range: Kt/V 0.7-2.55; nPCR 0.43-1.40; dialysis 2 and 3 per week) with the approximations: G = 0.180 mmol/min, K = 0.180 mL/min, V = 0.6 (dry weight) and Uf = measured weight loss, G/K becomes 1 (for SI units only) and the errors (method difference; equation—3S: mean, SD, upper, lower range limits) for equations 1 and 2 were -0.03, 0.05, 0.11, -0.19 and 0.00, 0.04, 0.15, -0.07 respectively. With Smye’s approximations: Uf/V = 0.042, G/K = 0.92 the errors were slightly greater (F test; P < 0.05). Errors from empirical equations based on URR were: Jindal et al. [2] (0.01, 0.06, 0.16, -0.16) and Daugirdas and Depner [6] (0.06, 0.05, 0.29, -0.04). The main contributory factors to the errors were analysed by multiple stepwise regression. The URR equations cited by Movilli gave gross errors in some cases, all gave some absolute errors >0.2 and the main source of error was the non-linear relationship between URR and Kt/V. Equations 1 and 2 and that of Keshaviah gave no errors greater than 0.2, confirming the analysis of Smye. Keshaviah’s equation, Kt/V = 1.16 Ln(Co/Ct), is the most simple with main errors related to Uf, but it may not perform as well with other patient populations. Equations 1 and 2 allow adaptation to extreme values of G, their principal source of error, which may be estimated if necessary [6]. Although not necessary clinically, the use of algorithms (unpublished data) to estimate G from the predialysis interval significantly reduced errors with equation 2 (F test, P < 0.05).

Basile claimed that his equation performed better than that of Jindal because it was derived from the narrow Kt/V range of target values which were of ‘clinical interest’. I suggest that the values of greatest clinical interest are those outside the target range because they suggest a change of prescription. If a standard equation for Kt/V is adopted it should not be based on URR because of the inherent non-linearity, I recommend that the equation should allow for (1) individual volume changes during dialysis, and (2) the use of specific factors which may be estimated as a representative patient-group mean or, if necessary, a patient-specific value. The need to consider, and reassess, such factors may serve to emphasise that patients should be considered individually for deviations from the general rule and that the equations are only as good as the data, so that care must be taken to ensure the validity of all measurements.

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Protein intake does not depend on the Kt/V

Sir, We are very interested in the recent paper by Panzetta [1]. Protein intake does not depend on the dose of dialysis delivered—provided Kt/V is adequate.

The author demonstrates that if the dialysis dose is adequate, protein intake is a dialysis-independent or patient-dependent variable. These data contradict those by Lindsay [2]. In 1989 Lindsay showed that low levels of Kt/V corresponded with low levels of nPCR and found a direct correlation between the two parameters.

Our data agree with those by Panzetta [1] and Movilli [3]. In fact from June 1988 to May 1994 we studied 134 uraemic