"arbitrary assumptions on model parameters like the glomerular transmembrane hydraulic pressure and the ultrafiltration coefficient" is uncorrect since the theoretical model depends only on one assumed parameter, the glomerular transmembrane pressure. Assuming this parameter, the value of the ultrafiltration coefficient is consequently derived. In addition, we and others have shown that the influence of the glomerular transmembrane pressure on the calculated shunt parameter omega is negligible [5, 6]. Thus, the criticism that no unique model can be identified is not appropriate.

Piero Ruggenenti, Roberto Pisoni, Andrea Remuzzi, and Giuseppe Remuzzi
*Bergamo, Italy*

*Correspondence to Piero Ruggenenti, M.D., Clinical Research Center for Rare Diseases, "Aldo e Cele Dacco," "Mario Negri" Institute for Pharmacological Research, Via Gavazzeni 11, 24125 Bergamo, Italy.*
*E-mail: ruggenenti@marionegri.it*

## REFERENCES

1. Pisoni R, Ruggenenti P, Sangalli F, *et al*: Effect of high dose ramipril with or without indomethacin on glomerular selectivity. *Kidney Int* 62:1010–1019, 2002
2. Ruggenenti P, Mosconi L, Sangalli F, *et al*: Glomerular size-selective dysfunction in NIDDM is not ameliorated by ACE inhibition or by calcium channel blockade. *Kidney Int* 55:984–994, 1999
3. Perico N, Amuchastegui CS, Colosio V, *et al*: Evidence that an angiotensin converting enzyme inhibitor has a different effect on glomerular injury according to the different phase of the disease at which the treatment is started. *J Am Soc Nephrol* 5:1139–1146, 1994
4. Remuzzi A, Puntorieri S, Battaglia C, *et al*: Angiotensin converting enzyme inhibition ameliorates glomerular filtration of macromolecules and water and lessens glomerular injury in the rat. *J Clin Invest* 85:541–549, 1990
5. Remuzzi A, Perico N, Sangalli F, *et al*: ACE inhibition and Ang II receptor blockade improve glomerular size-selectivity in IgA nephropathy. *Am J Physiol* 276:F457–F466, 1999
6. Edwards A, Deen WD: Error propagation in the estimation of glomerular pressure from macromolecule sieving data. *Am J Physiol* 37:F736–F745, 1995

# The statement that folate supraphysiological levels in uremic patients do not cause harm should not go unchallenged

**To the Editor:** The excellent paper by De Vriese et al in a recent issue of *Kidney International* on folate for cardiovascular disease in uremia largely underestimates the risk of folate overdose [1]. The suggestion that "high doses of folic acid are well tolerated and safe" takes root from four studies with 4 to 8 weeks and 12 to 17 months of follow-up. From one 10-year-old reference is the message that "routine measurement of vitamin $B_{12}$ concentrations and inclusion of vitamin $B_{12}$ in the supplements should completely eliminate . . . the risk of masking vitamin $B_{12}$ deficiency." Because close surveillance is suggested to look for adverse effects produced from folate fortification of food in the general population, which increases serum folate from 10.8 to 19.0 ng/mL [2], how can we forecast that in uremic people values as high as 200 to 400 ng/mL are safe over a long time? Treatment for hyperhomocysteinemia in uremic patients results in normal vitamin $B_{12}$ coupled with very high folate concentrations (Fig. 1). Could such an unbalance derange the biochemical basis of folate/vitamin $B_{12}$ interrelationship producing a "relative" vitamin $B_{12}$ deficiency?

Furthermore, no mention is made to other risks of folate overdose [3, 4], some potentially increased in renal disease, including tumor growth, hypersensitivity reactions, direct neurotoxicity, reduced zinc absorption, psychiatric changes, epilepsy, and renal damage (in pre-dialysis patients). Regarding vitamins, it has been clearly demonstrated that the task is not valid that if one that does good is increased that it will do even more good. The same was said about oxygen until it was shown that high doses caused blindness in preterm infants [5].

Caterina Canavese, Daniela Bergamo, Giulio Mengozzi, Giuseppe Aimo, Luisa Sandri, and Antonio Marciello
*Torino, Italy*

*Correspondence to Caterina Canavese, M.D., Department of Nephrology, S. Giovanni Molinette Hospital, Corso Bramante 88, 10126 Torino, Italy.*
*E-mail: ccanavese@hotmail.com*

## REFERENCES

1. De Vriese AS, Verbeke F, Schrijvers BF, Lameire NH: Is folate a promising agent in the prevention and treatment of cardiovascular disease in patients with renal failure? *Kidney Int* 61:1199–1209, 2002
2. Lawrence JM, Chiu V, Petitti DB: Fortification of foods with folic acid. *N Engl J Med* 343:970–972, 2000
3. Campbell NR: How safe are folic acid supplements? *Arch Intern Med* 156:1638–1644, 1996
4. Kavlock RJ, Rehnberg BF, Rogers EH: Amphotericin B and folic acid-induced nephropathies in developing rats. *Toxicol Appl Pharmacol* 81:407–415, 1985
5. Mills JL: Fortification of foods with folic acid—How much is enough? *N Engl J Med* 342:1442–1445, 2000

### Reply from the Authors

Monitoring side effects in thousands of patients receiving 0.4 to 4,0 mg folate and in smaller numbers taking large doses for several years has revealed no evidence for toxicity [1, 2]. In renal failure patients, no side effects have been reported so far, the longest follow-up being 17 months.

Concerns about large-scale folate administration gener-

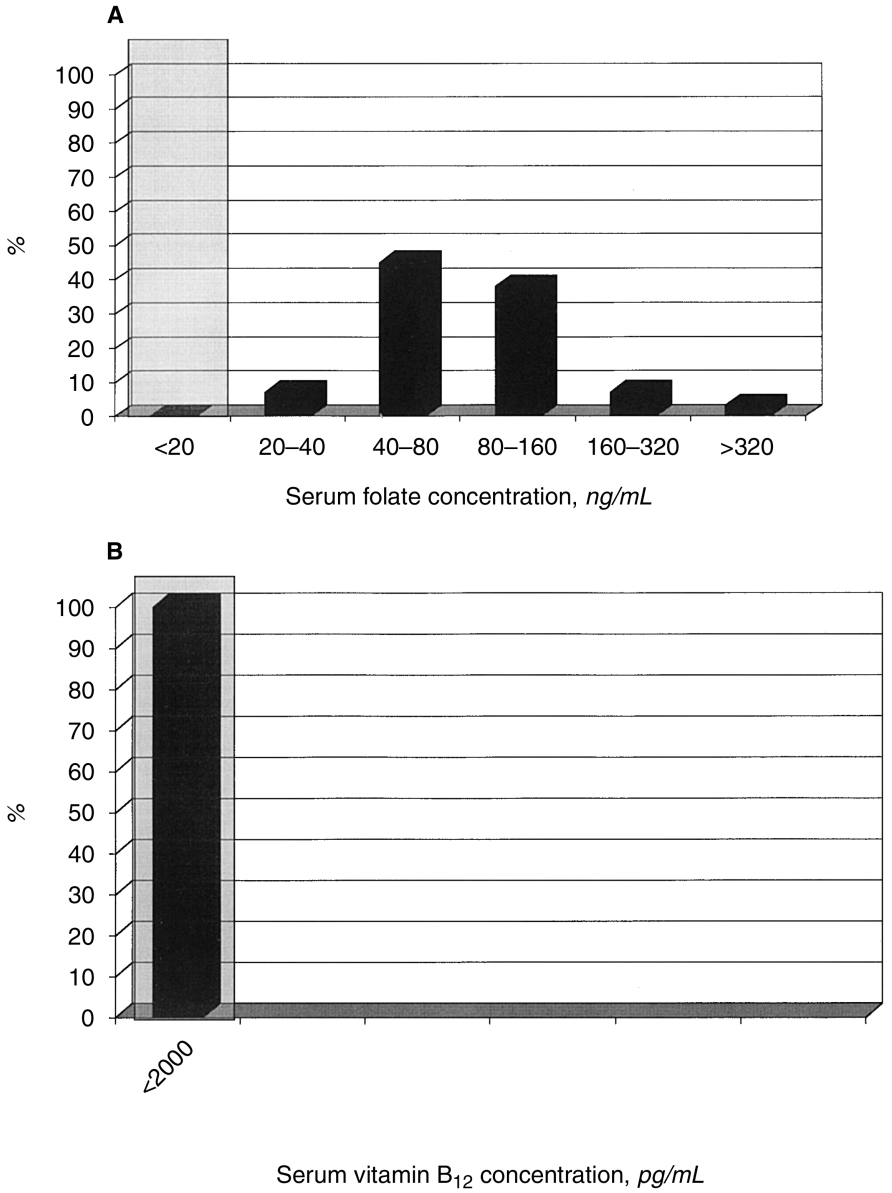


**Fig. 1. Distribution of serum folate (*A*) (normal value less than 20 ng/mL) and vitamin $B_{12}$ (*B*) (300 to 2000 pg/mL) concentrations in our 148 patients on chronic dialysis after 6-month continuous folate (15 mg/week) and vitamin $B_{12}$ (1000 μg/week) supplementation.** Shaded areas indicate normal ranges. The treatment-induced unbalance between the two vitamins is clearly shown. No patients have serum folate values within the normal range, while more than 50% of patients have serum folate values 5 to 15 times higher than the upper limits of safety. On the contrary, 100% of patients have serum vitamin $B_{12}$ values within the normal range.

ally focus on its potential risks in cobalamin deficiency. Folate does not lower cobalamin levels and no strong evidence supports the allegation that folate exacerbates the neurologic manifestations of cobalamin deficiency [1]. However, folate reverses the typical hematologic abnormalities of the disorder and may thus compromise its diagnosis. Patients with renal failure should therefore receive folate along with vitamin $B_{12}$, after exclusion of cobalamin deficiency [3]. Food fortification with folate is a quite different situation, as it affects the general population and systematic surveillance of cobalamin levels is impossible [4].

A carcinogenic effect of folate has been suggested, but not confirmed in subsequent studies. Rather, a protective effect regarding several malignancies has been found [1]. Hypersensitivity reactions have been reported, but it was unclear whether they were related to folate itself or to other components of the formulation [1]. Although small non-controlled studies suggested that folate reduced zinc absorption, subsequent larger randomized studies found no interference with zinc homeostasis [1].

The concerns about neurotoxicity are based on animal studies and one report of seizures in a patient with poorly controlled epilepsy after high intravenous doses [5]. Nephrotoxicity was observed in developing rats receiving megadoses of folate [6]. No reports of renal damage in humans have been found.

As stated in an excellent review on folate safety, "the data that suggest that folate supplements are unsafe are weak and consist predominantly of case series and reports" [1]. Although there is little evidence that folate causes important side effects at doses recommended in

renal failure patients, we fully agree with Dr. Canavese et al that the safety of long-term folate administration in the uremic population remains to be proved. Ongoing mortality studies will show whether the benefits of folate outweigh the potential harmful effects. As stated in our paper, "large-scale folate administration to patients with renal failure should be withheld pending results from these trials" [3].

An S. De Vriese, for the authors
*Ghent, Belgium*

*Correspondence to An S. De Vriese, M.D., Ph.D., Renal Unit, University Hospital, OK12, De Pintelaan 185, B-9000, Ghent, Belgium.*
*E-mail: an.devriese@rug.ac.be*

## REFERENCES

1. Campbell NRC: How safe are folic acid supplements? *Arch Intern Med* 156:1638–1644, 1996
2. Sheehy TW: Folic acid: Lack of toxicity. *Lancet* 1:37, 1973
3. De Vriese AS, Verbeke F, Schrijvers BF, Lameire NH: Is folate a promising agent in the prevention and treatment of cardiovascular disease in patients with renal failure? *Kidney Int* 61:1199–1209, 2002
4. Mills JL: Fortification of foods with folic acid – How much is enough? *N Engl J Med* 342:1442–1444, 2000
5. Ch'ien LT, Krumdieck CL, Scott CW, Jr, Butterworth CE, Jr: Harmful effect of megadoses of vitamins: Electroencephalogram abnormalities and seizures induced by intravenous folate in drug-treated epileptics. *Am J Clin Nutr* 28:51–58, 1975
6. Kavlock RJ, Rehnberg BF, Rogers EH: Amphotericin B- and folic acid-induced nephropathies in developing rats. *Toxicol Appl Pharmacol* 81:407–415, 1985