

## INVITED COMMENTARY

### Scientific opportunities... 'taken at the flood'

*"There is a tide in the affairs of men which,  
if taken at the flood, lead on to fortune;  
Omitted, all the voyage of their life  
Is bound in shallows and in miseries.  
On such a full sea are we now afloat,  
And we must take the current when it serves,  
Or lose our venture." – Brutus. (Shakespeare, 1564–1616)*

#### PROLOGUE

Over the past several decades it seems that only scientists working in the field of particle physics have been both politically correct and emotionally mature enough to leave 'the closet' and bare their souls to the point where their chosen scientific discipline is uniquely associated with the hijacking of complete subclasses of affectionate words from the English lexicon. Within the broad church that the general community of scientists inhabits, is it only particle physicists that are born bestowed with the gift for seeing 'the hand of nature' such that they feel themselves compelled to endow facets of their work with the poetry of such words as 'beauty', 'charm' and 'colour'?

In contrast, those of us in other scientific disciplines, such as the nutritional sciences, are rarely stimulated to such excesses; the term 'elegant' being the most effusive word of praise to pass our lips. However, even the most hardened of our ranks may occasionally fall upon a paper, either within, or close to, his or her field of expertise, which describes a piece of work that truly delights, captivates and elevates the spirit to a higher scientific plain.

Whilst conceding that what is 'meat' to one person, may be 'poison' to another, we would like to draw the attention of readers to the paper of Momčilović, Reeves and Blake (Momčilović *et al.* 1997) which appeared in the July issue of the *British Journal of Nutrition*. The authors argue that their experimental approach and results, though focusing on zinc, may have implications for all nutrients, and we urge readers, irrespective of their nutritional field, to set aside some time to find a quiet corner, a comfy chair, and to read this paper. We assure the reader that if they persevere through the first page or two, particularly the introduction to the idiorhythmic feeding regimen, the plot will unravel and the going will get easier.

#### OVERVIEW

The thrust of the authors' argument for their experimental approach of dietary modulation is that 'Our knowledge of essential nutrient requirements and metabolism is based primarily on experiments where animals are fed on a constant diet, although a constant diet is rarely, if ever, consumed in real life'. Of course, the manipulation of diet per se – in an attempt to gain greater insight into nutrient absorption and metabolism – is not new. Indeed, we ourselves have used insights gained from the partitioning of non-haem Fe intake in a model system to hypothesize that the effectiveness of less-frequent Fe-supplementation in the correction of iron-deficiency anaemia should be investigated in

humans (Wright & Southon, 1990). However, the authors seem to have elevated a particular type of dietary manipulation (one where nutrient dose is modulated in various ways in such a manner that the total dose over an experimental period is maintained as a constant) to the  $n$ th degree.

The Introduction, and Materials and Methods sections carry overtones of an Ancient Greek tale of some leviathan contest held over 24 days between, and within, four leagues (or divisions) of dose-time dietary zinc intake equivalents, with each league being composed of seven teams who each operate a slightly differing tactical approach; it is here that we are introduced to 'Epoch' – referee and timekeeper, and to the four 'Modulo' – each a hydra with seven heads. Superimposed, in the labyrinthine experimental design, are other overtones which remind one both of the depths of tactical Chess and the finesse of Bridge. At close quarters, within each Modulo of dose-time dietary zinc concentration, the experimental design appears stilted and skewed – like the heavy brush strokes of thick oil on canvass. However, when standing back to view the whole 'picture' one cannot help but be struck by its inherent elegance and beauty – which we can only define as a sort of 'symmetrical asymmetry'.

Essentially, the authors have assayed femur and incisor zinc accretion in weanling male rats after the feeding of experimental diets for 24 days. The experimental design is stratified around four dose-time equivalent zinc concentrations, each offering a different constant total dose. Each stratified layer has its own average dietary Zn concentration (modulo, M), the four modulus (M3, M6, M12 and M24) being related to diets that are regarded as Zn-deficient (M3; 3 mg Zn/kg), low Zn (M6; 6 mg Zn/kg), adequate Zn (M12; 12 mg Zn/kg) and ample Zn (M24; 24 mg Zn/kg). Each modulo has seven analogous dose-rate idiorrhhythms arranged in increasing order. The first is always the constant dose (i.e. 3, 6, 12 or 24 mg Zn/kg diet, depending on the modulo) which is fed daily ('conventionally-fed') for the duration of the experiment, i.e. in the manner in which, historically, most diets have been proffered. Another six idiorrhhythms involve offering the diet with  $n$  times the overall Zn concentration (M) only every  $n$ th day with Zn-deficient diet offered on other days; where  $n = 2, 3, 4, 5, 6$  and  $8$ .

In the authors' own words, 'The aim of the experiment was to observe the effects of idiorrhhythmic Zn dose-rate feeding on Zn accumulation in the femur and incisor and then compare the results with those of the conventional dose-response model'. Intestinal metallothionein was also assayed at the end of the experimental period since it was thought that an increased Zn load on dosing days may be large enough to evoke a biochemical defence response by inducing intestinal metallothionein. This protein is thought to function in Zn absorption homeostasis and provide protection from metal toxicity. Additionally, because there was concern that a strong environmental stress such as idiorrhhythmic dose-rate cycling of dietary Zn load may induce the expression of stress proteins, the restraint-stress-induced aortal heat shock protein HSP70mRNA was also measured in selected groups of animals.

The authors suggest that their results (which are both clearly presented and thoroughly discussed) could not have been predicted from conventional dose-response models but the question begs as to whether these results, although interesting, have any practical benefit. Would a similar response be observed across a broad range of other nutrients? Are there implications for efficient animal husbandry or, in humans, the treatment of acute clinical nutrient deficiencies, or general supplementation programmes aimed at combating suboptimal nutrient biochemical stores?

Though the results from this paper may have widespread implications, no blanket conclusions should be drawn. The authors have chosen to study a nutrient that has strong

homeostatic feedback control. Newly absorbed zinc can be re-cycled back into the intestine where it is re-absorbed or excreted and thus may be more susceptible to perturbation through idiorhythmic loading. Whilst the idiorhythmic loading of Fe may also produce interesting results in terms of liver iron stores, we have our doubts as to whether this will be bi-modal in nature. Once absorbed, iron can only be re-excreted via cell desquamation or blood loss. Following absorption, other nutrients such as vitamin C and folic acid (pteroyl monoglutamic acid; from fortified foods or supplements) are subject to renal thresholds and thus retention profiles following idiorhythmic loading may be different again. Each nutrient will therefore need to be examined separately.

We are sure that many readers will form their own opinions of the results and implications of Momčilović, Reeves and Blake's paper and, since the *BJN* currently hosts a 'Nutrition Discussion Forum' for readers' comments (see 'Directions to Contributors' which prefaces issue 1 of each volume), we would strongly encourage readers to take full advantage and have their critical comments set in print so that they can be shared with other readers.

#### EPILOGUE

In these days of short-term funding, with increasing demands for 'quick' results, it is heartening to see that sometimes the fates conspire to open a funding window of sufficient duration within which an interesting idea can be developed with the backing of an extensive, stable and competent support team. The authors seem to have taken full advantage of their chance, and have taken their scientific opportunity 'at the flood'. We congratulate both them and their team for their thought-provoking contribution.

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