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Nutrition Discussion Forum

Why do we not make more medical use of nutritional knowledge? How an inadvertent alliance between reductionist scientists, holistic dietitians and drug-oriented regulators and governments has blocked progress

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Many population subgroups that are at high risk of ill-health have multiple micronutrient deficits. These subgroups include the elderly, the socially and economically deprived, hospital patients and the mentally ill, among others. Placebo-controlled trials of simple micronutrient supplements have shown that they can improve immune function and reduce time suffering from infections in older people, reduce length of stay in hospital and improve clinical outcomes, improve pregnancy outcomes and reduce violent behaviour. If these findings could be transferred to the general population, the improvement in health and the reductions in cost of the service would be immense. Three main factors, however, are blocking both further research and the implementation of what we already know. These are: (1) reductionist attitudes among scientists who want to study only one micronutrient at a time; (2) holistic attitudes among dietitians and nutritionists who, with a lack of realism, want the relevant groups to change diet rather than take supplements; (3) governments who have created a regulatory framework that is commercially inimical to the development of multinutrients to treat disease. All of these attitudes need to change if we are going to apply what we already know about nutrition to the improvement of human health. But if attitudes do change we could see the fastest ever, and also the cheapest, improvement in human health.

Suppose we were to discover a new drug that we could be certain would never produce an important adverse reaction, would prevent and relieve a great deal of suffering due to depression, violence, cardiovascular disease, infections, inflammatory disease and a range of other conditions, and could be sold at a trivial cost when compared with most other medical interventions: would we rush to introduce such a drug into clinical medicine, would governments be keen to market it and promote its use, would doctors be keen to prescribe it? The answer to all these questions is probably no. For we have such a drug and it is hardly used by those who could most profit from it.

The drug is a combination of all known essential nutrients present at levels approximately equivalent to the official national recommended daily allowances. It is a drug which is widely used at their own expense by the affluent and relatively affluent middle classes who do not need it, and therefore benefit little from it, because they already consume most of the nutrients in adequate quantities in their diet. It is a drug that is rarely used, and rarely prescribed, for those who do need it: the socially and financially deprived, the elderly poor, the mentally ill, those in prisons, and those at high risk of obesity and cardiovascular disease. The evidence of its value is considerable, so why do we so rarely employ such a safe, low cost and effective remedy? The answer lies in a mix of scientific reductionism, holistic obscurantism, regulatory rigidity, the absence of commercial incentive, and a failure of the imagination on the part of government.

The value of nutrition

The first half of the last century was a golden age of nutritional biochemistry, when most of the essential nutrients were identified, their acute deficiencies understood and their value to humankind unequivocally demonstrated. But so lost has that hard-won knowledge become that most modern medical students and young doctors, who know much molecular biology of uncertain relevance, can no longer summarise even in broad outline the major metabolic pathways, cannot pinpoint the multiple locations at which essential nutrients work, and cannot describe with any clarity the consequences of gross deficiency.

Moreover, there is a lack of awareness of three lessons from that era which used to be well known. The three lost lessons are as follows.

(1) Even within an inbred strain of animals there are large variations in the minimum amount of an essential nutrient required for health. When a large group is fed on diets of progressively increasing deficit in a particular nutrient, some animals will become sick when dietary intake has been only slightly reduced, while others may not become ill until the nutrient has been largely depleted. Variations in daily nutritional requirements among non-inbred humans subjects are likely to be considerably greater, as is suggested by experiences of prisoners in Second World War camps where, despite similar conditions some succumbed rapidly to nutritional deficits while others remained healthy (Duncan, 1982; Venables *et al.* 1985; Roland & Shannon, 1991).

(2) Because most essential nutrients are required for the functioning of most tissues, a deficit of a single essential nutrient will cause loss of function of every tissue in the long run. But in the shorter term, the genetic

and environmental background of the individual will determine which organ breaks down first. Thus, in pellagra, some people will first develop dermatological symptoms, some gastrointestinal symptoms and some a psychiatric disorder. Alternatively, in scurvy, depression is commonly the first symptom, or it may be a thrombotic disorder, or a dermatological disorder, or a Sjogren's syndrome-like condition. The permutations and combinations and the variety of symptoms are almost infinite. But in each case complete cure follows the prescription of the single missing nutrient.

(3) Our knowledge base about daily requirements is seriously defective when it comes to requirements for time periods of ≥ 1 year in any population other than fit young males. Almost all our solid evidence-based knowledge relates to short-term experiments in healthy male volunteers. When it comes to life-long needs in broader population groups, our understanding is inevitably less secure, and our recommendations must be made cautiously.

The evidence for deficits

The evidence that many individuals from various forms of deprived backgrounds may suffer nutritional deficits is now strong (e.g. McWhirter & Pennington, 1994; Bailey *et al.* 1997; Ames & Wakimoto, 2002; Horrobin, 2002*a*). During the lifespan this is true of many otherwise normal young, middle-aged and elderly people as they fail for various reasons to eat a balanced diet. It is true of the mentally ill, especially of those with psychoses, whose diets may be very strange. It is true of large numbers of socially and economically deprived individuals who, by reason of education, preference, or financial deficit, may be unwilling or unable to eat foods that give the essential nutrients needed. It is true of many patients who are admitted to hospital. It may even be true of some of the affluent, whose hurried and stressful lifestyles prevent them giving due consideration to proper nutrition.

Whatever the reason, large numbers of individuals in any society are deficient in one or more essential nutrient. In particular individuals the nutrients affected differ, but deficits of folic acid, vitamin B_{12}, pyridoxine, Zn and Se are common, and those of many others not particularly rare (e.g. Ong *et al.* 1983; Black *et al.* 1986; Bunker & Clayton, 1989; Bates *et al.* 1999; Davies *et al.* 1999; Pentieva *et al.* 1999). In an affluent small European city, for example, about half of all patients with schizophrenia were found to be vitamin D-deficient (Fleischhacker *et al.* 2002).

Since normal biochemistry is essential if the human body is to respond effectively to disease and to its treatment, and since essential nutrients are required to ensure normal biochemistry, it follows that individuals who are nutritionally deprived will have reduced resistance to a range of diseases, and will also have impaired responses to whatever treatments are being offered. This is particularly true of psychiatric and neurological disorders since, while the brain makes up only 2 % body weight, it consumes 20 % total energy and therefore has a proportionately greater requirement for essential nutrients than other tissues (Horrobin, 2002*a*,*b*). These common nutritional deficits therefore have potentially serious effects on human health, and especially mental health.

Responses to the problem

If the problem is as I have suggested, then it is an issue that in theory could produce huge health returns for minimal expenditure. Why has this not happened? Multiple forces, coming from different directions have inadvertently conspired to ensure a near-complete failure to apply existing knowledge to generate an appropriate solution.

The reductionist scientist's position

This comes in various guises, but the most important arguments against doing anything are the following.

(1) We do not yet know enough about the health consequences of the nutritional deficits in the different populations. Provide the necessary support and we will collect the information.

(2) In order to understand clearly what is happening we must study one variable at a time. We must therefore set up a series of trials in which a single nutrient is compared with placebo, preferably in those who can be shown to be deficient in such a nutrient. Again, given the support, we will set up a trial programme that will last the lifetimes of many researchers.

The maternalist dietitian's and nutritionist's position

We know that these groups of people are deprived, and so what we must do is persuade them to eat proper meals without giving them the resources to do so. The faddish adolescents, the incapacitated elderly, the socially and educationally deprived and the mentally ill must all shop more intelligently, must eat four colour meals and must endeavour to consume a varied diet with twenty-three portions of fruits and vegetables each day.

The drug-oriented regulator's position

If it were possible to demonstrate that a nutrient combination had efficacy in a particular disease we would be happy to give that combination a pharmaceutical product licence. But because we know that many past drug combinations have contained inactive ingredients and because the public must be protected against inappropriate and poorly manufactured products, we will grant a licence to market a product only if it is possible to demonstrate by appropriate trials that every ingredient is necessary. Every ingredient must, of course, meet full pharmaceutical good manufacturing practice (GMP) standards and tolerance limits, if such a product is going to be used for therapeutic purposes and make medicinal claims.

The pharmaceutical company's position

We are not interested in developing such a product. It would have no patent protection and so anyone could

copy it. Moreover, with multiple ingredients, each of which would have to be subject to full GMP regulations, the cost of manufacture would be intolerable.

The Government's position

This is a free-market society where pharmaceutical and nutritional products are provided by private enterprise. Attempts by the state to do otherwise have been unsuccessful. We have no interest in aiming to address a need which private enterprise does not see as worthwhile.

What should have been the responses?

In a more rational world, the balanced and constructive responses might have been as follows.

The reductionist scientist

This situation requires some imagination. While normally I would want to change one factor at a time, I can see that in this situation this could be an inappropriate strategy. Biochemical pathways are as intimately interlinked as are the sections of a hosepipe. If a hosepipe is blocked in four places, I can understand that water will not flow if I unblock only one of them. All of the blocks must be dealt with simultaneously. Similarly, if an individual is deficient in two or three micronutrients that influence several different steps in biochemical pathways, then overall improvement in function will not occur if I correct one deficiency only. Moreover, if I propose that we proceed by identifying all the deficiencies present in each individual patient, and then we specifically correct only these deficiencies, I can foresee that the research programme would become impossible. The number of tests would become overwhelming, each patient's treatment would have to be individualised, and each patient would end up having to take multiple pills. Given the difficulties of compliance in any population, and particularly in these deprived populations, I suspect this would be impractical. Moreover we would end up with so many subgroups that outcome analysis would be impossible since no individual group would have enough patients to provide sufficient power.

Reluctantly I recognise that in these populations we must take a different approach. We should take the whole population to be investigated and recognise that each individual is likely to have their own pattern of multiple different micronutrient deficiencies. We are not going to do any harm if we decide to provide everyone with a multinutrient supplement containing roughly the national recommended dietary allowances or equivalent of all known essential nutrients. What we should do therefore is to choose our population to be studied, choose our outcome measures and then randomise everyone to the total micronutrient supplement or placebo. If there is a real effect then we can go back and dissect the main contributions to it in subsequent studies.

I have to admit that this field is beginning to interest me. This is because those old experiments showing individual variations in daily dose required, and in the different individual syndromes resulting from deficiencies in a particular nutrient, are beginning to have genomic and/or biochemical explanations to which I can relate. It is now apparent that genetic variations in enzymes and cofactors can produce much larger variations than we ever imagined in micronutrient requirements (Ames *et al.* 2002). I can therefore see that nutritional biochemistry could be about to become an enormously attractive and intellectually respectable field. It could lead to the use of human subjects to investigate disease in a sophisticated and highly relevant way. It could also lead to a range of safe and effective new therapies that would depend not on drugs but on does of micronutrients very different from those now recommended. But as a start, let's do these simple pragmatic trials and see if we can get a result.

The dietitian's and nutritionist's position

I must admit that we dietitians and nutritionists have not had much success in persuading many people to change their diet in a substantial way. When we are successful, it is usually with the affluent and educated who may be highly motivated and certainly have no trouble in finding the resources to buy what we recommend. But frankly the idea of getting the socially deprived or mentally ill or even the elderly to do this in a sustained way is living in a patronising fantasyland. We could never get enough of them to consume a diet containing all the known micronutrients. And, as we find so often, those who most need to change their diet would find it least easy to do so.

Of course I understand and sympathise with the idea that a truly balanced diet may contain micronutrients that even now we do not know about and is likely to be better than any micronutrient supplement. But I must admit that, for the great majority of the people we are concerned about, a good comprehensive multinutrient supplement would be much more effective. So I will back placebo-controlled trials of multinutrients.

The regulator

I admit that we might have got our regulations wrong. Frankly, when they were being drawn up no one seriously considered the possibility that nutrients might become drugs for specific diseases. Our rules about multiple ingredients, with each one having to justify its presence by clinical studies, were based on the need to control the industry making synthetic drugs. Companies were arbitrarily putting together different drugs and, while a few products had a genuine rationale, most were simply marketing ruses. We were becoming appropriately concerned about drug-related deaths, which are now running at $>100\,000$ per year in Europe and North America, and we realised that many of these deaths resulted from drug interactions. So we decided to get tough on combination products.

Many drugs are highly toxic or highly dose-dependent in their effects so that quantities administered must be absolutely precise. We therefore became increasingly tough about manufacturing to GMP standards and about the tolerance limits of active ingredients. We are now reluctant to approve any drugs where the concentration of each

active ingredient is not limited to a variation of less than ±1%. Of course this is unnecessary in most cases, but not in all and we felt we could not allow people to make judgements.

We may have to rethink things with regard to medicines consisting of essential nutrients. I can see that, in contrast to drugs, there are excellent scientific arguments for including more than one substance. I can also see that, even if we combine all the micronutrients, we are rather unlikely to get any important toxicity, certainly nothing like the toxicity resulting from even single synthetic drugs. The manufacturing issue also might require some thought and relaxation. Paradoxically we put rather minimal efforts in to regulating excipients, many of which are used because they are traditional rather than because they have been thoroughly tested. We also have almost no regulations about food manufacturing except those relating to cleanliness and infectious agent contamination. Since foods provide so much higher volumes of chemicals than any drug, this does not make sense. Perhaps we need to think about an entirely different set of regulations for medicines composed of essential nutrients. These should certainly not be lumped in with herbal medicines, which present a quite different set of issues.

Although I am not involved with patents or intellectual property, I can see that this is a problem. We perhaps need to think about some quite different form of intellectual property that would protect unpatentable medicines of any sort that were shown in clinical trials to produce a major patient benefit. The USA protects orphan drugs for 7 years and the European Union for 10 years and so some new rules might be based on that concept. An unpatented product which provided a substantial advance, perhaps with substantial being defined objectively as something like an effect size, could be offered 10 or even 15 years protection from date of marketing. This would encourage companies to make really important advances in the interests of patients, irrespective of whether or not there were patent protections.

The pharmaceutical executive

My response depends entirely on whether or not there is any realistic expectation of anything of what the regulator said coming true. If he really means what he says, such attitudes could transform therapeutic development. The industry would cease to worry about patents to the same degree and enormous trials with tiny effect sizes, but a P value $< 0{\cdot}05$ would become a thing of the past. There would be a tremendous incentive to develop genuinely effective medicines for a much wider universe of possible sources.

The Government representative

Maybe we have been too *laissez-faire* in not deliberately encouraging the development of really effective medicines and in promoting those that work. We have perhaps left things too much to the industry. Our policies might be 10–15 years out of date because the industry then really did seem to be delivering a steady flow of genuinely important new products. Now the flow has fallen to a very uncertain trickle, with most products that are introduced producing only trivial clinical advances. Perhaps we need to do something more aggressive. Perhaps we might specify that if a new drug for an important problem achieves a substantial improvement in patient outcome when defined by effect size, it must be prescribed. That would really be a carrot.

Would it work?

The idea is that, by using multinutrient formulations, we might be able to generate large improvements in health at low cost and with near absolute safety. Building on that, by identifying genetic variants with increased nutrient requirements, we might be able to generate tailored supplements that for some nutrients might contain substantially higher levels than the usual recommended daily doses. This might be a rapid and effective way to bring the benefits of genomic medicine to a wide population.

Enormous amounts have been written about the impact of social deprivation on health. The phenomenon is undoubtedly real, but its basis is unknown. Is it due to deprivation *per se*, or due to low status even in the absence of deprivation, or due to poor education, or to lack of exercise, or due to poor lifestyle, or due to poor diet or due to a specific deficit in essential micronutrients? No one knows and none of the proposed solutions, with the possible exception of diet, is remotely feasible at realistic cost in a real world. Diet has been desperately disappointing in practice because the people concerned either do not want to change or cannot change. But most of those who find it difficult to change their diet could easily take a multinutrient pill or a placebo. At least we could then begin to answer one of the questions. Such trials would not be too difficult to do. For example, perhaps for 3 years we could randomise 2000 high healthcare users from deprived populations to a micronutrient supplement or placebo. If there were no differences between the two groups in healthcare utilisation we could certainly rule out micronutrients, and also go a long way to ruling out diet itself, as an explanation for the social status differences in health. But, if there were important outcome differences, just think of the enormous benefits that could be achieved with no health risk and a very low financial outlay!

Is this totally unrealistic or is there any reason to think it might work? There have in fact been a limited number of trials of this type. The results are startling but almost unknown. Here are some of the results.

Improving health and resistance to infections in old people

Chandra (1992, 2002) conducted two studies, one in subjects >65 and one in subjects aged 50–65 years old. In both studies normal healthy individuals, albeit living in relatively deprived communities, were randomised to receive a multinutrient supplement or placebo for 1 year. In both studies the supplemented group demonstrated objective improvements in immune function (e.g. T-lymphocyte counts and antibody response to influenza vaccines) as compared with controls. More importantly, the supplemented group

showed highly significant and clinically important reductions in numbers of days of recorded infection as compared with the placebo group (11 *v.* 24 d in the younger group and 23 *v.* 28 d in the older group). If substantiated, imagine the reduction in the burden on a health care system if these results were replicated nationally!

Improving hospital outcomes

Several studies (Katakity *et al.* 1983; McWhirter & Pennington, 1994; Azad *et al.* 1999; Covinsky *et al.* 1999; Hall *et al.* 2000; Cunha *et al.* 2001; Kyle *et al.* 2002) have shown that many patients admitted to hospital have multiple micronutrient and macronutrient deficiencies. Moreover, while in hospital, either because of poor appetite and unattractive food, or a mixture of both, many patients have inadequate micronutrient and macronutrient intakes. Randomised controlled trials have looked at the effects of administration of multinutrients in hospital. In one study, multinutrient administration resulted in a mean reduction of 0·4 d in hospital stay in all patients and 2·3 d in patients who stayed >10 d (Vlaming *et al.* 2001). In another study in gastrointestinal surgery patients, supplemented patients lost less weight, did not develop fatigue, maintained handgrip strength and developed fewer complications (Keele *et al.* 1997). In both studies the supplements did not contain a fully comprehensive list of known micronutrients, so results might have been even better with a more comprehensive supplement. Again, the economic implications for a national hospital service are potentially enormous with shorter stays and better outcomes being achieved at trivial cost.

Improving pregnancy outcomes

In a controlled study in Tanzania of a very limited multivitamin product, the supplemented group showed a significantly greater gain of weight, a key marker of successful pregnancy outcome in less developed countries (Villamor *et al.* 2002).

Reducing violence in a UK prison population

In a randomised study in a UK prison, inmates were randomised to receive a placebo or a multinutrient preparation each day (Gesch *et al.* 2002). There were no other interventions and violent events were recorded as usual by the prison officers. Violent events were reduced by a remarkable 35 % in the supplemented as compared with the placebo group ($P<0{\cdot}001$). The prisoners' nutrient status was not different from that of similar social groups out of prison. Imagine the consequences, not just for prisons but for the whole of society, if similar results could be achieved in the general population. That this may be possible is indicated by a randomised trial in borderline personality disorder of just one of the micronutrients given to the prisoners, eicosapentaenoic acid. Borderline personality disorder patients frequently commit verbal and physical violence and they make up a high proportion of the prison community. Active treatment as compared with placebo significantly reduced the incidence of both verbal and physical violence (Zanarini & Frankenburg, 2003).

If results like these had been achieved by patent-protected single chemical entities, product licences would have been obtained and industry would have ensured a steady stream of comment and follow-up stories in both the medical and general media. Everyone would know that drug X had a major impact on health of the elderly, or on improving outcome in hospitalised patients, or on reducing prison violence. But although all the studies were published in major journals and achieved a brief burst of publicity, there has been little or no follow-up and the work is sinking without trace. Low-cost, effective and safe interventions are being lost.

Taking the example of the prison study, the attitude of the UK Government to this is strange. Violence in prison and violence in society are clearly major preoccupations of both the public and the Government. The record of interventions based on social, employment, family or other measures is almost universally dismal. Occasional projects led by charismatic and energetic leaders have produced some success, but implementation on a wider scale has usually failed at astronomical expense. More and more, and more and more expensive, unproven and complex interventions are being proposed.

In complete contrast, a simple nutrient supplement is something that is reported to work more effectively than any other known intervention. It has been shown to do so in a randomised, placebo-controlled study with a design far more rigorous than most of what passes for research on violence. The technique could be immediately and widely implemented, not just in prisons, but in the wider society by people with no special training in any technique. The cost-effectiveness would be remarkable. One would have thought that the UK Government would wish to explore the approach, or at least evaluate it, on a much wider basis. Other major policy changes have been made on the basis of much more limited evidence. But surprisingly, the Government has turned down requests for any support for replication. It is difficult to find out why, but it seems that the sociologists and criminologists who dominate Government advice on this issue simply do not understand the methodology or the results.

Conclusion

So let's be imaginative and give multinutrient supplementation a chance. We may already have most of the knowledge required to produce huge improvements in human health. To test the proposition, we may have to abandon two failed notions, the holistic one that we need to change diets, and the reductionist one that we should initially study single nutrients. If we do that, and if we incorporate the new findings on genetic variations in nutrient requirements, we could truly be at the beginning of one of the biggest and safest healthcare revolutions.

The Editors report with regret the recent passing of Dr David Horrobin. Correspondence arising from this Nutrition Discussion Forum should be addressed to Dr Crispin Bennett, Laxdale Ltd, Kings Park House,

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