Nutrition and Science

Nutrition and Science:

A Darwinian Perspective on Nutritional Medicine

By

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CONTENTS

PREFACE

When I had been an English general medical practitioner (GP) for 15 years, I became a little disillusioned with the emphasis on drug treatments. There was, indeed, a pill for every ill but sometimes they didn't work and they often had unacceptable side effects. So, in the 1980s I developed an interest in Nutritional Medicine and especially the role of micronutrients in fertility, pregnancy and general health. However, this was a controversial area of medical science and some practitioners of Nutritional Medicine were being accused of being substandard when their practice was put to scientific scrutiny. This always happens when a radically new approach is pioneered in the world of medicine but there was some truth in what critics of Nutritional Medicine had to say. At the same time the discipline of Nutrition Science was gaining ground in the academic world and in 1999 I grabbed the chance of doing a master's degree in Nutritional Medicine at the University of Surrey. The course was founded and directed by two highly respected nutrition scientists: Professor Joe Millward and Professor Margaret Rayman. Everything in the world of Nutritional Medicine was subjected to rigorous scientific scrutiny and I was able to carry these ideas back into the world of general medical practice – and try them out.

What I have learned from 42 years of being a GP, 30 years of studying Nutrition Science and doing research with colleagues at the University of Surrey has gone into this book. Throughout this period, I have found that my interest in evolution and Darwinian interpretations has stood me in good stead. Much of Nutrition Science makes better sense if you interpret health issues in terms of a mismatch between our natural environment (genetically we are still stone-agers) and our modern obesogenic environment. A good understanding of how natural selection delivers organisms (microbes, plants and animals) with features for survival but not for perfection helps to explain so much in the science of medicine and nutrition.

Much of the scepticism about Nutritional Medicine that I experienced in the 1980s has died away. However, doctors and the general public complain that they get mixed messages from the world of Nutrition Science. One week red wine is good for you and the next week there are

warnings that all alcohol increases the risk of cancer. One expert insists that omega-3 fish oil is good for your heart and the next week another expert presents evidence to the contrary. In this book I have looked at the evidence from both sides of such arguments and tried to arrive at a balanced opinion - often with the help of a Darwinian perspective.

One of my main conclusions about the role of Nutritional Medicine is that it has an important place in the medium to long term management of health and disease. In the first place, especially in acute illness, modern drugs are usually an essential rescue remedy and often save lives. Subsequently, however, there is a rebuilding job that involves lifestyle and nutrition strategies. Any acute inflammatory illness is best treated with effective drugs initially (i.e. salbutamol, antibiotics or prednisolone) but subsequently, the rebuilding job will often include a nutritional strategy along with other rebuilding strategies such as physiotherapy following an injury or counselling for mental illness.

I would like to pay tribute to all the members of the Department of Nutrition Science at the University of Surrey who have helped me with my writing and research but especially Joe Millward, Margaret Rayman, Susan Lanham-New, Michelle Dobrota Gibbs, Bruce Griffin and Barbara Engel. I have learned a lot about diet and the microbiome from Glenn Gibson at the University of Reading and about nutrition and the brain from David Smith at the University of Oxford. I would also like to thank the many GPs and practice managers in the Guildford area (too many to list) who have collaborated with me on research projects. I am very grateful to my wife, Tina Nichols (BSc Pharmacology) for reading through my manuscript and suggesting improvements and corrections. Lastly, I would like to thank the staff at Cambridge Scholars Publishing for helping me to get my ideas into print.

John A A Nichols, Guildford, Surrey, UK, June 2018.

CHAPTER ONE

THE CASE FOR NUTRITIONAL MEDICINE

1.1 The public, the health professional and nutritional medicine

A growth of interest in Nutritional Medicine, the growth of the over-the-counter (OTC) supplement industry and increasing awareness of the relationship between diet and health has put an extra burden on the busy GP and other members of the primary care team. More often than not, the patient will start an OTC supplement without giving a thought to discussing it with their GP, but when they ask a question like "Will taking lycopene capsules protect me from getting prostate cancer like my father had?" the GP or practice nurse may not know the answer. Nutritional Medicine was not on the syllabus when I was a medical student and there has been very little change since then. This book was originally designed to fill that gap by giving some practical advice that is suitable for use in everyday practice for members of the primary care team, but it is also written in a style that should make it easy reading for the interested lay person.

In the past, there have been two easy answers to patient's questions about nutritional supplements – too easy, unfortunately to be adequate:

1. *If it's a natural substance, it might not do you much good, but it can't do you any harm*. Although there is some truth in this when referring to a modest dose of a vitamin, for instance, we now have evidence that higher "pharmacological" doses of vitamins like vitamins E, A and B6 might be harmful in some circumstances, but the evidence is inconclusive. Since herbal remedies are sometimes referred to as supplements, every GP will realise that herbs like St John's Wort are more like drugs, with side effects and the potential for interaction with other drugs.
2. *You don't need to take extra vitamins and minerals if you eat a well balanced diet*. This is a gross oversimplification. We now know

that even the best, most varied, Western diet is not the same as the Stone Age diet that we are adapted to as a result of millions of years of evolution. This is especially true of the low vegetable fibre content of modern diets. Added to this, many of our patients have psychological and money problems that prevent them from eating well. A recent survey shows that 20-30% of people in the UK never eat fish,[1, 2] and some will tell you that they find the very thought of it disgusting – this is a major problem, as we will see in Chapters 3 and 4.

Another easy answer is to tell patients with normal IgE (immune globulin E) and the related RAST allergy tests that "*…food allergy is all in the mind"*. We now know that this is not necessarily the case. For instance, some patients with IBS can tell you exactly which foods exacerbate their symptoms although they do not test positive on RAST testing. Double blind tests tend to support this interpretation. The balance of evidence suggests a rule of halves:

- *Half* the patients who think they have a "food allergy" but have normal IgE and RAST will have a genuine food intolerance and half will be imagining it.
- *Half* the patients with genuine food intolerance will have some idea what foods are problematic and, with minimal help and understanding, they will be able to control their symptoms.

The vigilant physician will always be looking out for more serious disease in these subjects and making appropriate referrals to rule this out.

As GPs and primary care practitioners, we have another problem that has developed over the last 20-30 years. Patients really would prefer a natural remedy to a drug if this was available and, increasingly, this is an option. However, balancing a natural remedy with dietary advice and a drug regimen may be time consuming and difficult. Sometimes, the doctor may need to carry out some sort of nutritional assessment, such as taking blood for homocysteine or serum zinc. These tests are either difficult or impossible to do on the NHS. Table I represents the arguments for and against the practice of Nutritional Medicine in primary care and Table II compares it with pharmaceutical drug-based medicine and the related disciplines of Herbology and Homeopathy.

Table I. Comparison between Orthodox Medicine and Nutritional Medicine

	Orthodox medicine	Nutritional medicine (NM)
Main emphasis	Involves understanding physical, social and psychological components of disease and usually a pharmaceutical solution but lifestyle advice is relevant	More emphasis on the physical component with an analysis of allergy, environmental and nutritional factors unique to the individual
Suitability to primary care environment	Usually fits into seven minute consultation and the computer software is designed for the orthodox approach	May take longer than seven minutes and NM repertoire (prescription items and tests) is seriously incomplete in the computer software
Patient preference	Many patients would prefer to avoid pharmaceuticals. They will often, however, opt for a "quick fix" if a pharmaceutical can do this	The NM approach with advice on diet and supplements may be preferred, as long as it is not too complex
Side effects	Common	Rare

Do not be put off by my references to complex and time-consuming aspects of Nutritional Medicine (Table 1). In this book, I am concentrating on the simple and the familiar, as far as possible. A patient with a complex NM problem might be better off with an expert opinion and I will point this out when appropriate. Unfortunately, nearly all these experts are private practitioners. Much of the most effective evidence based nutritional medicine for complex conditions is not available on the NHS and it is a matter for debate how this has come about, which is far beyond the scope of this book.

1.2 Confusion of Nutritional medicine with Homeopathy and other branches of alternative medicine

I will be concentrating on the use of dietary advice and prescription of minerals, vitamins, amino acids, essential fatty acids (EFAs) and probiotics. There may be passing references to herbal medicine and homeopathy, but these areas of medical practice are not really part of the discipline of Nutritional Medicine. Figure 1 shows how they overlap. Confusion between these three disciplines is common in both the public domain and the media. Recently, for instance, a feature on Chinese medicine in *The Guardian* newspaper included a photograph of a shop window in Hong Kong full of herbal and traditional remedies. The legend beneath it mistakenly described these as "Homeopathic remedies".

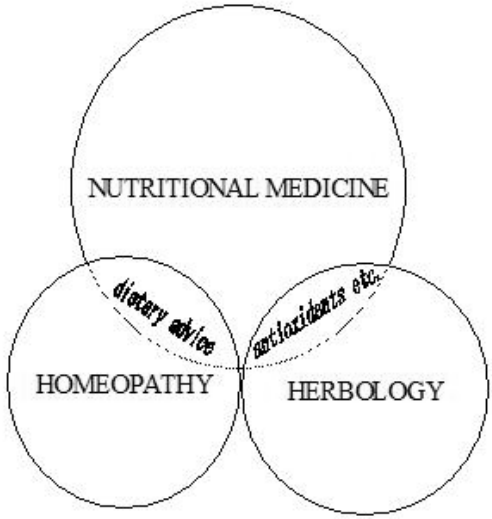

Figure 1.

There is a range of opinion on Homeopathy and Herbology amongst academics and practitioners of Nutritional Medicine. This varies from hostility and distrust of non-scientific methods to moves to unite the three disciplines[a]

[a] Nutritional Medicine is a scientific discipline closely allied to Biochemistry whereas Homeopathy and Herbology are generally considered to be aspects of

Table II. Comparisons between Nutritional medicine and other disciplines

	Basic mechanism	Efficacy	Side effects
Pharmaceuticals	Usually achieves a favourable effect on body chemistry by blocking or "poisoning" an enzyme system	Rapid and reliable for short term effects and commonly life-saving	Common, usually reversible but occasionally lethal
Nutritional medicine	Optimum nutrition is rarely achieved and therefore nutritional status can be manipulated to cure or prevent disease	Longer interval from treatment to beneficial effect but a nutritional regimen may be more likely to offer a long-term solution	Side effects are rare at nutritional doses and most micronutrients and nutraceuticals are only toxic in much higher doses (c.f. vitamin A)
Herbology	Remedies based on hundreds of years of trial and error and usually contain a mixture of nutritional and pharmacological properties	May be very efficacious, but trial evidence is often poor or incomplete	Common, as with pharmaceuticals, and this is one reason for a UK directive in 2005 on registration of "Medicinal Herbals"
Homeopathy	Not scientifically established but current theory involves modification of water molecules by succussion and serial dilution	Unexpected evidence for efficacy from double blind RCTs, but this has been challenged on the basis of trial design	None. This is the main "selling point" in favour of homeopathy, but homeopathic practitioners will often also prescribe pharmaceuticals, herbs and NM

complementary therapy. There is no established basis for Homeopathic medicines within the discipline of science but Homeopathic doctors also draw upon scientifically validated disciplines including Nutritional Medicine and Psychology. Some GPs in the UK find that a visiting Homeopathic practitioner very popular with patients.

1.3 Changing attitudes of public and profession to Nutritional Medicine

Nutrition Science has had a low profile in primary care since the rapid rise of the pharmaceutical industry. I remember very well how this started in the 1950s. Every week there seemed to be a newspaper headline announcing another new "wonder drug". This was, undoubtedly, an important turning point in the practice of medicine, but the almost total abandonment of dietary treatments for common conditions is regrettable. I have asked myself for many years why we should dose a patient with drugs when manipulation of diet and other environmental factors gets to the root of the problem[b]. The answer is simple. Given seven minutes to make a diagnosis and decide on a treatment, it is so much easier to issue a prescription.

Several issues have influenced professional and public attitudes to Nutritional Medicine over the last ten years:

- Arguments for and against nutritional supplements
- The European Union (EU) food supplements directive
- Controversies on diet, food allergy and behaviour
- New evidence for probiotic advice in primary care
- Gene-nutrient interactions
- New developments in epidemiology and nutritional science

1.4 Arguments for and against nutritional supplements

1.4.1 Can supplements be dangerous?

The expert advice on the uses and abuses of nutritional supplements has become a confusing muddle. Leading nutritional experts have advised the profession and public against consumption of mineral and vitamin

[b] A young woman came to see me complaining of several weeks of chest pains, which could easily have been interpreted as cardiac chest pain in a middle-aged man. After a brief examination, I was able to reassure her that these pains were not cardiac but seemed to be musculoskeletal. I could easily have completed the consultation with a prescription for *ibuprofen*, but something made me ask about her diet and I found that although she had a generally healthy diet, she was consuming a whole bottle of fresh orange juice per day. Excessive consumption of citrus fruit is known to cause joint pains and migraine. After two weeks without citrus fruit, her symptoms had completely gone.

supplements[3, 4]. However, other investigators have pointed out the safety and value of carefully formulated supplements[5, 6, 7, 8]. According to a survey of GPs by *Norwich Union* in 2005, only 12% of GPs agree that: "Vitamin supplements are useful in helping many people maintain a good nutritional balance", and 41% of GPs agree that: "There is simply not enough information available about vitamins for people to make an informed decision on their own". There is little doubt, however, that when taken by the right subjects in the correct formulation, supplements can be beneficial.

Where adverse effects have been demonstrated, the risk is much lower than the 2.5-fold increased cardiac risk associated with Celebrex[9] or the 32% diabetogenic effect of bendroflumethiazide + atenolol reported from The ASCOT trial[10].

By comparison, some recent studies have shown that high dose vitamin E compared with placebo appeared to give a 1.4% higher risk of heart failure in a susceptible group of subjects[11] and 25,000 IU of retinol/day versus placebo gave a 12% increased risk of lung cancer in smokers which was not, however, seen in other studies[12] . The average primary care doctor writes hundreds of prescriptions a week. Most of these are for drugs that alter metabolic pathways by inhibiting (poisoning) an enzyme system. Some prescriptions are for nutritional supplements such as iron, calcium and vitamin D. Adverse reactions are almost entirely due to drugs and these can sometimes be bad enough to require hospital admission with 3-4% of all hospital admissions being due to drug side effects[13]. By comparison, nutritional supplements very rarely cause problems, let alone hospital admissions. In a one year survey of adverse reactions from so called "food supplements" that covered 17% of the USA population there were 26 severe adverse reactions. However, the term "food supplement" was used to describe a wide range of nutrients, nutraceuticals and herbal remedies and there is no effort to differentiate between relatively safe nutritional supplements and the hazardous borderline substances and herbals (Table II). This survey included the now banned borderline substance Gamma-hydroxybutyrate which was responsible for some of the 26 severe adverse reactions although the authors do not specify how many of the 26 were due to this substance[14]. This is a rather muddled report that tells us next to nothing about adverse reactions caused by genuine nutritional supplements.

1.4.2 In conclusion, although mineral and vitamin supplements are not totally free of side effects, they are relatively rare and significantly

less hazardous than commonly used drugs. There is no good data on the rate of severe adverse reactions from the correct dose of nutritional supplements. There certainly are isolated reports of minor side effects at normal doses and occasional severe adverse reactions from accidental overdoses (i.e. a child swallowing his mother's iron tablets after mistaking them for "sweeties" with fatal outcome) these are very rare.

1.5 EU food supplements directive

UK government regulations from 1996 made it difficult for shoppers to decide what OTC supplement is appropriate to their needs. Since these supplements are marketed as a food supplement and regulated in the same way as a food, the labels and inserts must not refer to any "medicinal claims" such as the evidence, accepted by many, that high dose vitamin C helps common cold symptoms. There are a few exceptions that mainly relate to common deficiency states. Therefore, an OTC product containing an iron salt can have a label or insert that claims that it is beneficial for iron deficient anaemia. For the vast majority of supplements, the shopper has to go by word of mouth, information from a magazine or internet search or just blind guesswork. In practice, the shopper is likely to ask a pharmacist or shop assistant for advice.

The European Parliament could have introduced legislation to improve the situation if they had followed the example of the USA. The Dietary Supplement Health and Education Act in 1994 made it possible for manufacturers of supplements in The USA to insert a "nutritional support statement". A new regulatory body was set up for dietary supplements under the Federal Drug Agency (FDA) to regulate the process. The nutritional support statement can explain the value of the supplement in terms of nutritional support in nutrient-deficiency disease, or state a description of the intended role, mechanism of action or effect on general health as a result of taking the product. However, the statement must also include the words: *This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*

The European Parliament was more concerned with legislation aimed at establishing a "European directive" that establishes the same standards of safety and efficacy for supplements, herbal remedies and functional foods as apply to the pharmaceutical industry throughout the EU. A policy of harmonisation; in particular, the supplements industry would be expected

to carry out large scale RCTs to prove efficacy, determine side effect profiles and establish a safe top dose or 'tolerable upper limit'. Many GPs favour this. In a survey I recently conducted, one GP commented on '… the uncertainty over the difference between regulated and unregulated treatment. Probiotics should go through the same channels that regulated medicines go through. We should not be expected to offer advice on unregulated products'. This is all very well, but patients who are currently stabilised on nutritional regimens, such as pyridoxine 50 mg three times daily may be forced to switch to a lower ineffective dose. Also, some relatively safe OTC nutrients, such as alpha lipoic acid and Selenium ACE may become prescription only medicines. However, more recently the EU policy of harmonisation of supplement regulation has ground to a halt. Tolerable upper limits have been challenged in courts in several countries and the uncertainly generated by Brexit is another factor. Prior to Brexit, if doubts were raised over scientific basis of a claim made for a nutritional supplement, The European Food Safety Agency (EFSA) would then be called on to make a decision. The future is unclear but some degree of harmonisation with the EU is a distinct possibility

In conclusion, the EU supplements directive may have done more harm than good and the USA model might be preferable. The future for standardisation of nutritional supplements and scientific review of health claims following Brexit is uncertain.

1.6 Controversies on diet, food allergy and behaviour: is "food allergy" just an excuse for bad behaviour?

There is a difference of opinion between orthodox immunologists, represented by The British Society for Allergy & Clinical Immunology and non-NHS practitioners represented by The British Society for Ecological Medicine (formally The British Society for Allergy Environmental and Nutritional Medicine). Although some unorthodox opinions on food allergy lack scientific backing, there is growing evidence that dietary treatment of conditions such as asthma, allergic rhinitis, irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are valid. The evidence for dietary treatment of IBS and IBD is particularly convincing[15, 16]. Most GPs and Gastroenterologists seem to be unaware of this evidence.

Recent publicity over school meals has re-ignited the issue of the effect of poor diet on behaviour problems in children and young offenders. This is

another area that has been largely ignored by the medical profession in the past. Good research has been done on these aspects of brain function.[7, 17, 18, 19]

A summary of the benefits of optimal nutrition on brain function "Changing Diets, Changing Minds: how food affects mental wellbeing and behaviour" was published in 2006 by the charity *Sustain* in collaboration with *The Mental Health Foundation* and is available for further reading at their web site[20]. This report includes a quotation from the late David Horrobin: "Schizophrenia is not caused by a nutritional deficiency… Nutrition is a way of putting the biochemistry of the brain in the best possible shape to allow other treatments to work. Nutrition is a partner in the therapeutic alliance, not the only player."

In conclusion, dieticians and hospital doctors tend to be out of date on food allergy and the relationship between brain function and nutrition. Members of the primary care team could achieve a lot with minimal education of patients.

1.7 New evidence for probiotic use in primary care: are probiotics a commercial scam or real science?

Since bacteria are present in many foods and play a major role in the digestive process and in maintaining normal health, the study of these "friendly bacteria" is a significant component of Nutritional Medicine. The well known scientific term for these bacteria is "probiotics" (see glossary, page 2) and the sale of probiotics has become big business. The commercial interests in the sale of probiotics have led to scepticism in some quarters and the need for adequate research to back up the claims of enthusiasts is certainly important. There is, in fact, a large body of evidence in favour of probiotics including some convincing RCTs. If Nutritional Medicine is interpreted as using natural remedies to attain optimal health, then the need for the presence of probiotics in our diet can certainly be defended. There is a body of evidence that suggests that excessive hygiene associated with modern living is a major factor in the aetiology of allergies and conditions such as eczema and asthma[21]. Perhaps, then, these disorders should be seen as nutritional deficiencies that can be corrected by taking a probiotic supplement.

The use of probiotics to counteract antibiotic-induced diarrhoea is a special case. This is standard advice in many European countries and, according to my own research, nearly 50% of UK GPs will give this

advice when they feel it is appropriate. Advice to take probiotics is especially likely to be given if the patient gives a history of antibiotic induced diarrhoea in the past. The best evidence of RCTs and meta-analysis seems to back up this advice (*Bandolier*, 2002[22]**.** Ongoing research into the use of probiotics for a wide range of conditions is starting to show promise (Chapter 2: 2.9). In particular, the discovery and testing of new probiotics and prebiotics (nutrients that are synergistic with probiotics) shows great promise and the next decade could see an impressive outpouring of useful new treatments.

In conclusion, probiotics are beginning to be accepted by both the general public and the medical profession. OTC use can be recommended for prevention of antibiotic diarrhoea and several other common conditions. Prescription of "magic bullet" probiotics for more serious medical conditions may be possible in the future.

1.8 Gene-nutrient interactions: one man's meat is another man's poison – genetic proof?

This is such an important topic that I am devoting a whole chapter to it (see Chapter 8). The enormous investment in genomic research by pharmaceutical and biomedical companies, mainly in the USA, bears witness to its potential importance. There are many sceptics, however, and it will be some time before genetic testing is accepted as reliable, safe and effective. There are too many unanswered questions at present, but more important, perhaps, is the cost of the tests. At present, it would cost you £100-200 to find out which genetic trait has caused a neural tube defect (NTD) conception and which combination of B vitamins would be most effective at preventing future NTD conceptions (see 3.3). In the future, when all the development costs have been recouped, the cost per test may be £10 or less. Gene-nutrient interactions may become increasingly important in the prevention and treatment of cancers, cardiovascular disease, osteoporosis, arthritis and mental illness.

In conclusion, at present we rely on family history to help us give good advice on prevention, lifestyle and best treatment. In the future (15-20 years), we may be able to use a battery of thousands of genetic tests that will allow us to diagnose and treat patients more accurately. The best treatment may well be a specific nutrient rather than a drug in many cases. A few of these tests are already available privately but the cost of a full set would be prohibitive for most patients.

1.9 New developments in epidemiology and nutritional science: how scientific is nutritional advice in primary care?

The RCT (randomised controlled trial) may be the gold standard for modern medicine, but at least 15% of the decisions doctors make in a consultation are based entirely on intuition and past experience and only 30-50% are based on RCTs[23, 24]. This is not just because they are unable to consult the latest evidence in the middle of a consultation. There is, very often, no evidence for the broad spectrum of issues that arise. Moreover, deficiencies in the RCT approach to research have been pointed out recently and alternative qualitative research techniques have been accepted as valid. Nutritional advice may seem to be a good example of an area where we are more likely to use our own past experience to give good advice. My grandmother always told me that "Fish is good for the brain" and I quoted her on this long before recent research confirmed her good advice. However, there is a wealth of good research that is relevant to nutritional issues in general practice. Whilst I was doing a masters degree in nutritional medicine (1999-2005), I found that the evidence that I came across in my studies proved to be relevant to general practice on an almost daily basis[c].

1.9.1 Scientific alternatives to the RCT

If evidence-based medicine requires that two large scale RCTs should come to the same conclusion, then this can certainly be done with, for instance, a trial of a supplement against a placebo. The classic example of this approach is the MRC trial of pre-conception folic acid 5 mg daily in women who had already had one NTD conception[25]. However, this type of

[c] The paper issued to MSc students for home study after a module on trace elements included a difficult essay, which I nearly passed over: *You have been asked to give dietary advice to a young woman who has recently become a vegetarian. What foods would you recommend and what pitfalls does she need to be aware of in optimising her trace element needs?* Two days later a young woman came to see me and said, "I have just decided to become a vegetarian, but friends tell me I might miss out on important trace elements. Can you advise me what foods I should include to prevent this?" I asked her to return to see me in two weeks. With my essay completed, I was able to advise her how to avoid deficiencies of iron, zinc, selenium, iodine, cobalt and chromium. Advising the value of Brazil nuts (selenium) coated in dark chocolate (chromium) was particularly satisfying!

research is unlikely to produce answers to all our questions, even if funding was available. In practice, nutritional science depends on a variety of other approaches[26] as well as the RCT:

1) **Observational Epidemiology**

This depends on studies of "exposure" of populations (to nutritional deficiencies and other adverse nutritional factors such as anti-nutrients) and outcome in terms of health and disease statistics. However, this approach does not necessarily prove a cause and effect relationship. Thus, the epidemiological studies that link low B vitamin intake and subsequent raised serum homocysteine with ischaemic heart disease have not been validated by interventional studies (chapter 4: 4.6.2(3)). Perhaps only interventional studies can establish a clear-cut relationship between cause and effect. A possible exception is the cohort study. This is an epidemiological approach involving a prospective study of a large group of subjects in which nutritional status is carefully monitored over a number of years. Outcome, in terms of health and disease measurements is recorded and compared with exposure. There have been several important prospective cohort studies on ischaemic heart disease, The Framingham Study being the best known. Case-control studies can be a good starting point in researching a new idea. This usually involves comparing patients with an established disease or disorder (cases) with normal subjects (controls). Selecting controls to minimise confounding factors is crucial. Thus individual cases and controls may be matched in pairs for age, gender, smoking history, race, social class etc. This can be a useful way of narrowing down the key nutritional factors causing a common condition such as diverticulitis.

Another good example of observational epidemiology is the National Diet and Nutrition Survey (2003)[2]. This is a very thorough survey including data on lifestyle and blood tests for nutritional status. A representative sample of 2,660 individuals from the UK population recorded a weighed seven-day diet diary. The survey revealed low dietary intake of various key nutrients. For example, 42% of women aged 19-24, had a daily intake of iron below the recommended minimum level (LRNI).

2) **Laboratory studies**

Although many observational epidemiological studies involve laboratory tests, this does not come under my definition of a laboratory study as the subjects are "free living" in the external environment. Laboratory studies of nutritional status often involve human volunteers being confined to a controlled laboratory environment in the same way as experimental animals and tend to involve small numbers due to expense. These studies are particularly important as they are used to establish the scientific validity (see glossary, pages 1-2) of field measurements. The doubly labelled water technique, for instance, involves giving subjects a dose of $^{2}H_{2}{}^{18}O$ and monitoring urinary output and weight change. True energy intake can be accurately estimated from this data and compared with field-study tools such as the 7-day diet diary. This has consistently shown a tendency to under-report calorie intake, especially in overweight subjects (Margetts B, Nelson M *Design Concepts in Nutritional Epidemiology:* Chapter 7)[24].

3) **Experimental epidemiology**

This approach involves some sort of manipulation of "exposure" by changing nutritional intake or some other aspect of nutritional status such as intake of an anti-nutrient. The model proposed in *Design Concepts in Nutritional epidemiology* is generally relevant to nutritional science (see figure 2). The RCT using a single agent comes under this heading (i.e. MRC trial of pre-conception folic acid 5 mg daily in women who had already had one NTD conception, 1991) conforms to this design, but so do educational interventions. However, many RCTs of single nutrients have been disappointing, producing either no apparent benefit or even a small adverse effect, despite epidemiological evidence of benefits. This is certainly partly due to the synergistic combinations of nutrients that are required for normal physiological function. For instance, vitamin E cannot function as an antioxidant without an equivalent increased supply of ascorbic acid[27]. Interactions between nutrients, anti-nutrients, other dietary factors, genetic differences and ethnic and lifestyle factors are so complicated that apparently contradictory results from nutritional research are hardly surprising.

4) **Nested case-control studies**
This is a very useful and effective way of combining cohort studies with case-control studies - see (1) above. If nutritional status is established at the commencement of a large cohort study, a case-control study can be built into the cohort study at a later date. However, unlike most case-control studies, this will have the advantage of being a prospective study. See chapter 8 for a good example: a large cohort (n=63257) in which nutritional intakes (including green tea) of all participants had been established and from whom DNA samples had already been taken. 297subjects who developed breast cancer ten years after the start of the cohort study were compared with a control group for intake of green tea and genetic variants for cancer susceptibility. Further analysis showed that green tea intake was protective in subjects with a specific genetic variant for cancer suceptibility (8.5.2). Thus a trial of green tea efficacy in relation to breast cancer prevention was 'nested' within a larger cohort study. A well-conducted nested case-control study may be more effective than an RCT in researching this type of nutritional scenario.

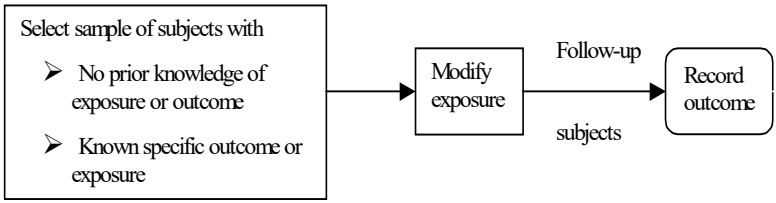

Figure 2. Experimental design in nutritional science (after Margetts and Nelson in *Design Concepts In Nutritional Epidemiology*[26])

The RCT may be the gold standard for drug trials, but nutritional science has to have a broader frame of reference to answer the questions that we, as medical professionals and scientists, ask of it. Confounding factors, especially lifestyle factors, have to be taken into account and all this has to be funded without the benefits of drug company support. Non-RCT research and the accumulated wisdom of an experienced practitoner will always be relevant to the decisions we make in this area of primary care.

1.9.2 Mother nature knows best? A unifying theory of nature and health should be useful to fill in the gaps in scientific knowledge and help the health professional to give the best possible advice. Bias is usually cited as an adverse factor in medical research. When it refers to confounding

factors (such as trying to measure the effect of diet on the incidence of cancer when the results are skewed by smoking habits and other unidentified environmental factors) bias is certainly a negative influence. However, the idea that a medical researcher or practitioner should approach a topic without any bias whatsoever is ridiculous. Our bias is determined by our previous experience. Without a "bias" of some sort, a medical researcher would be unable to formulate an hypothesis and could, therfore, never even make a start. A medical practitoner, likewise, depends on past experience and discussions with patients and colleagues to formulate a "healthy bias"[28]. A bias that acts as a useful yardstick for judging the best way of managing many simple problems is to to assume that "mother nature knows best" most of the time (i.e. breast is best). A philosophy that goes back to Aristotle suggests that there is a law of nature that is independent of man-made laws. The modern equivalent is, perhaps, the argument in favour of Darwinian Medicine.

1.10 How Darwinism helps us to interpret Nutritional Medicine

The proponents of Darwinian Medicine (Nesse & Williams 1996, Book: *Evolution And Healing - The New Science Of Darwinian Medicine*[29]) argue that nearly six million years of human history were spent adapting to a hunter-gatherer lifestyle and we still have the genetic make up of those Paleolithic Stone Age ancestors. Our modern diet, lack of exercise, and psychological stresses of modern life are bound to give rise to problems. Whereas our ancestors scavenged a diet that was rich in soluble fibre, mineral, vitamins, plant flavanoids and essential fatty acids, we are forced by circumstances beyond our control to eat an inferior diet. Worse still, we have the problem of junk food (see Chapter 4: 4.9), which is mainly "empty calories" and explains why so many people have an intake of fibre and micronutrients below the recommended daily allowances. For our Paleolithic ancestors, there were times of starvation but in times of plenty, the diet was loaded with vitamins and other micronutrients. The ancestral adaptions to starvation are thought to be the root cause of some of the health problems that arise in middle age. Ironically, genes that were a "survival ticket" for our ancestors at times of drought and starvation tend to cause the metabolism to "unravel" later in life. (Chapter 4: Causes of the Metabolic Syndrome, 4.4.2).

1.10.2 Stoneagers in the fast lane

We are "Stone agers in the fast lane" and our failure to recognise this can lead to diseases associated with inappropriate diet (i.e dental caries) lack of exercise (i.e. obesity and back problems) and a contaminated environment (i.e. lung cancer). I find this paradigm quite helpful when explaining to patients why an apparently harmless activity or food may be a health hazard. For instance, a patient who gets migraine when they eat cheese may find it easier to understand and accept it when you explain that although cheese is full of nutrients, it is not really a natural food for our species. Our Stone Age ancestors never drank milk, nor did they ferment it to cheese. There is actually quite good evidence that hunter gatherers are, in many ways, healthier than agricultural communities and city dwellers[30, 31, 32].

Sometimes this way of explaining things to patients does not work. Not everyone believes in evolution[d]. I have, however, only rarely encountered problems when using this frame of reference to explain health matters to my patients.

1.10.3 Apparent errors and imperfections of evolution that put health and life at risk

We are used to praising the beauty and wonder of nature but it is not always beautiful and Darwin was one of the first to emphasise that nature produced both beauty and grandeur but, at the same time, ugliness and suffering. *The Origin of Species* is full of examples of these contrasts and contradictions. Although he was careful not to make more than passing references to the human species in 1856 (he wanted to avoid a clash with religious views of man as being above the animals) he made it clear that

[d] A young man I had treated for a manic depressive disorder with schizoid features came to see me with his new wife. They wanted to know if he would have to stay on lithium for the rest of his life. I explained that recent evidence suggested that he might be able to reduce the dose if he took a balanced Omega 3&6 preparation, but I could not guarantee that it could ever be stopped. I went on to explain how the seashore ape theory of our pre-human ancestors helps to explain our need for extra omega 3 & 6 to build and maintain a human brain, to which he replied: "Sorry doctor, but we are Christians, we don't believe in evolution". I suggested an alternative explanation was "We eat the wrong foods because we have strayed too far from the Garden of Eden" and he told me that this was acceptable! Subsequent blood tests confirmed that his omega 3:6 ratio was well outside the acceptable range and he seemed to benefit from a supplement to correct this.

natural selection applied to all forms of life. Natural selection, working over millions of years, may produce awesome results such as the mammalian eye and the beauty of flowers but, by its very nature, all this grandeur, beauty, ugliness and suffering is the outcome of a utilitarian mechanism. Natural selection is entirely geared to adaptations that increase the chances that an organism will reproduce successfully and is not geared to human comfort and welfare except insofar as it helps to achieve this objective. There are, therefore, apparent 'design faults' that make life difficult for us and most prominent of these is human ageing. More than half the time and effort of the medical profession is geared to treating various aspects of human ageing. I explain in further detail how various aspects of human ageing can be understood in an evolutionary context in Chapter 6 (6.2.1).

To quote Darwin himself on the imperfections of nature (*Origin of Species*, Chapter VI): "Natural selection tends only to make each organic being as perfect as, or slightly more perfect than, the other inhabitants of the same country with which it comes into competition. And we see this as the standard of perfection under nature. Natural selection will not produce absolute perfection, nor do we always meet, so far as we can judge, with this high standard under nature." He goes on to describe imperfections of the human eye – one of his very occasional references to humans. It is interesting to note that deterioration in the structure and function of the human eye begins about the time that the job of reproduction and child rearing is complete (6.10.12). When the young of any species is independent, and this takes a long time for humans, the mechanism of natural selection becomes redundant in the parent and cannot affect future health either beneficially or adversely[e]. However medical science comes to the rescue and the role of Nutritional Medicine in these circumstances is detailed in Chapter 6.

[e] A possible human exception is the theory that the human female menopause is an adaption that is not seen in other female mammals. The exceptionally prolonged human childhood and high level of family group co-operation make the grandparenting role a significant factor in childhood survival and the menopause allows the grandmother to concentrate on grandchildren. Without any babies of her own, she can still help to ensure the survival of her genes by being a good grandparent.

1.10.4 Imperfection of natural selection explains a range health problems

If natural selection is primarily geared to survival of the species by successful reproduction, that clearly explains why women have to suffer the discomfort and pain associated with pregnancy and birth. Natural selection does not and cannot select for an easy painless birth – a safe and successful birth, perhaps, but that is not quite the same thing. In Chapter 3 (3.5.1), I explain how pregnancy sickness, an apparent contradiction of nutritional priorities, could be an example of natural selection. If nausea at this stage of pregnancy protects the fetus from items of diet that could be damaging (damaging to the fetus but not harmful to the mother) then natural selection will select for nausea. In these circumstances, natural selection is blind to the misery of pregnancy sickness for the mother and works only to improve the chances of the fetus surviving. This is an example of the smoke detector principle described by the Williams and Nesse[33]. They explain that a biological phenomenon that seems counterproductive must serve a very useful (probably life saving) function, even if this only happens occasionally. Thus, the many false alarms that trigger a smoke detector will be worthwhile if it only once warns you that a fire has just started and saves your life. Nesse and Williams use the smoke detector principle to explain why allergies (including food allergies) are on the increase. Most allergies are mediated by the IgE antibody system and this includes hay fever, asthma and the oral allergy syndrome (2.8.1: footnote f). In modern humans the IgE antibody system seems to serve no useful purpose but only causes the misery of allergy symptoms. An exception is the apparent ability of IgE antibodies to attack the sort of parasitic worms that probably infested our Stone Age ancestors. This is the basis of the 'hygiene hypothesis' of allergies. However, Nesse and Williams question whether the hygiene hypothesis is adequate. Perhaps, they suggest, the IgE system also offers protection against inhaled and dietary toxins. There is some evidence for this but also for the possibility that, like the smoke detector, the IgE system is a last ditch immune response against microorganisms and parasites when all else has failed. In this instance, the 'smoke alarm' blares out a very high blood level of IgE that causes a level of inflammation that could be damaging to the host but is certainly damaging to the enemy it is targeted at. Veterinary scientists describe cattle that are heavily infested with tics that seem to exhibit this sort of response. The tics suddenly either die or else drop off by the score. The theme of food allergy and intolerance keeps recurring in the following chapter and should be understood in terms of our

evolutionary origins, the changes from a Stone Age diet to modern foods and an appreciation of Nesse and Williams' smoke detector hypothesis.

1.10.5 In conclusion, giving nutritional advice is especially likely to be influenced by past experience. The medical practitioner can, however, use a biological approach which is a mixture of the scientific evidence available, common sense and an appreciation that many aspects of modern lifestyle and diet are harmful because we are still genetically adapted to the Palaeolithic Stone Age diet and lifestyle. Apparent design faults in human structure and function can be understood as inevitable consequences of how humans have evolved. These problems increase with age but Nutritional Medicine can play a key role in dealing with them at all ages.

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