



# ASSOCIATE PARLIAMENTARY FOOD & HEALTH FORUM



## Links between vitamin D and chronic diseases

5-6.30pm, Tuesday 24 June 2008

Committee Room 2A, House of Lords

### Minutes

#### Introduction

Lord Rea welcomed members to the meeting and introduced Oliver Gillie, a distinguished journalist who has worked hard to raise the issue of the importance of the links between vitamin D status and chronic disease. Lord Rea said vitamin D is involved in a whole range of metabolic processes, so it would be odd if it were only significant for bone health.

Oliver Gillie is a scientist and freelance journalist with 25 years experience working for national newspapers in the UK. He has won 16 awards for his journalism and he has been awarded the Royal Jubilee medal by the Queen for his work in science and health journalism. He is deputy chairman of the Medical Journalists' Association and a trustee of the Caroline Walker Trust. Oliver is the Editor of "Sunlight Robbery", which argues that the Government's current advice on exposure to the sun is misguided.

#### Oliver Gillie – scientist and freelance journalist

Oliver said the links between vitamin D and chronic disease is an extraordinary story. He has been writing about health for 40 years and he thinks it is the most important issue he has come across in that time: it may be as important for health as the invention of penicillin or the discovery of the links between smoking, lung cancer and heart disease.

Scientific evidence now suggests that insufficient vitamin D and/or insufficient sunlight is likely to be an important contributory cause of many diseases, including heart disease, several cancers, raised blood pressure and a number of immune diseases, such as diabetes, multiple sclerosis (MS) and inflammatory bowel disease, as well as osteoporosis and fractures, which are a major cause of death in old people.

Some 90% of people in the UK have sub-optimal levels of vitamin D in the winter, so we are at risk of these diseases. Fortunately we can address this risk, with supplements or sunbathing, if the political will exists to improve the advice given to the public.

**Lord Rea** said that Oliver is a good example of the fact that political change is not achieved without persistence. He then introduced Dr Adrian Martineau of the Queen Mary, University of London. Adrian became a member of the Royal College of Physicians in 2001. He joined Queen Mary as a lecturer in Respiratory Medicine in 2002, where he co-ordinates a programme of research into the effects of vitamin D supplementation on respiratory health. He has recently published papers demonstrating that vitamin D supplementation enhances immunity to tuberculosis. Adrian's work is funded by the British Lung Foundation and the National Institute of Health Research.

Chairman: Lord Rea  
Vice-Chairmen: Dr Ian Gibson MP  
& Baroness Miller of Chilthorne Damer  
Secretary: The Earl Baldwin of Bewdley  
Treasurer: Baroness Gibson of Market Rasen

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## **Dr Adrian Martineau - Honorary Clinical Research Fellow, Queen Mary, University of London**

As early as 1849 Henry Chapman used cod liver oil - rich in vitamin D - to treat a range of diseases, including tuberculosis. He thought it “probably the only remedial agent by which the vital powers may be enabled to struggle successfully against that malady.” Vitamin D levels can be boosted both by taking fish liver oil and by sunbathing – and both were used to treat tuberculosis in the pre-antibiotic era, although neither practice was evaluated with clinical trials.

In 1930 vitamin D was isolated from cod liver oil to treat skin TB (lupus vulgaris). Treatment was so dramatically successful that it was never evaluated with clinical trials. Later antibiotics were developed and used to treat TB, and interest in vitamin D as a therapeutic agent in TB waned.

Since the late 1980s, there has been a steady increase in the incidence of TB in London. It has risen much more dramatically in certain areas of London, such as Newham and Brent (see slide 5).

Among Asian ethnic groups, those born in London have the same rate of disease as Londoners as a whole, but for those born in Asia who emigrated to London, the rate is ten times higher and it is also higher than in the population they leave behind. So, the highest rates are associated with those who leave sunny countries for the UK. This corresponds with falls in the vitamin D levels of people who move from Asian countries to the UK. This fall is not surprising because 80% of our vitamin D level is derived from sunlight and only 20% is derived from diet.

Adrian’s interest in vitamin D was stimulated by Robert Wilkinson’s research published in *The Lancet* in 2000 (see slide 11) which found a strong association between vitamin D deficiency and TB. The question we need to ask is, is TB causing vitamin D deficiency or is vitamin D deficiency a cause of TB? Adrian originally came to London with the idea of performing a randomised clinical trial to test whether vitamin D supplementation could prevent the development of active TB in those who had recently been exposed to an infectious patient (TB contacts) but to achieve a statistically significant result you would need to randomise 13,000 patients and this is very difficult in a mobile population such as London TB contacts.

In order to measure the immune response to TB, Adrian took a group of 202 patients of whom 107 were male. They varied in age from 18-100 (the median age was 34) and they came from various ethnic groups (see slide 16). Some 50% of the sample were profoundly deficient in vitamin D and only 15% had adequate levels of vitamin D. Those patients that were recruited in the summer and autumn, and patients of white European ethnic origin, had higher levels of vitamin D. Half of the patients received a single large dose of vitamin D (2.5 mg), while the other half received placebo. Six weeks later, a blood sample was taken from all participants, and incubated with TB-like bacteria (mycobacteria) in the laboratory. The blood of TB contacts who had received vitamin D supplementation controlled growth of the bacteria significantly better than the blood of those who had received placebo.

How does vitamin D work? Vitamin D binds to a receptor in the cells and stimulates production of a natural antibiotic substance found in white blood cells that protects against TB (see slides 23-28). This information provided the basis for Adrian’s current study in which he is trying to boost the immune systems of patients with taking antibiotic treatment for lung TB.

In summary research to date has demonstrated that Vitamin D deficiency is very common among TB contacts and TB patients in the UK. A single oral dose of 2.5 mg vitamin D corrects vitamin D deficiency in TB contacts and boosts immunity to mycobacteria. Thus, vitamin D supplementation may have a role in the prevention of TB, or as an adjunct to standard antibiotic treatment. Adrian referred to a book, *Sunlight, Vitamin D and Health*, edited by Oliver Gillie (see slide 31), which he said provides a concise summary of current knowledge of the subject.

Bones and muscles both contain vitamin D receptors for vitamin D, so it is not surprising that vitamin D is important for their health. Various studies have shown the significance of vitamin D for a variety of illnesses, including diabetes, heart failure and certain cancers. A meta-analysis of clinical

trials investigating various effects of vitamin D supplementation (see slide 33) found that vitamin D consumption is associated with a 10% reduction in all cause mortality.

Humans evolved in the equatorial region, which has higher levels of sunshine than northern Europe. If we compare the present levels of vitamin D in the UK population with our ancestors we can estimate what could be achieved in terms of public health benefits. A recent authoritative literature review, published in the *American Journal of Clinical Nutrition* by internationally recognized vitamin D experts (Hathcock et al) concluded that daily doses of up to 10,000 units/day of vitamin D can be taken safely (NB there are 40 units to one micrograms (mcg), that is 250mcg = 10,000 units); this intake is 10 times higher than that recommended as a 'guidance level' by the UK Expert Group on Vitamins and Minerals (1,000 IU/day). There is increasing evidence that a dose of 1,000 IU/day may be insufficient to achieve optimum vitamin D status in the population, and a strong case can be made for reviewing this guidance level with a view to revising it upwards.

Various strategies could be used in the UK to boost vitamin D levels, including supplementation, food fortification and encouraging sunbathing. Adrian is confident that improved vitamin D levels can be achieved in the UK, with appropriate public health messages, because health professionals would be encouraging people to do something cheap, painless and simple, that did not involve giving up any pleasurable activity. Adrian ended by thanking the funders of his research.

**Lord Rea** introduced Professor Ebers, the Action Research Professor of Neurology in the Department of Clinical Neurology at the University of Oxford. Before coming to Oxford, from 1980 to 1999, he was Director of the MS Clinic at the London Health Sciences Centre affiliated with the University of Western Ontario, Canada. His research interests have primarily been in the area of neurological genetics and MS. He initiated and led the Canadian Collaborative Study on Genetic Susceptibility to MS and his studies on the genetic epidemiology of this disorder have led to a much better understanding of both the environmental and genetic components. His main interest at present is studying the pathogenesis of MS and his lab has recently determined the inheritance pattern of MS and the site of the genetic region responsible for susceptibility.

**Professor George C. Ebers, Clinical Neurology Wellcome Trust Centre for Human Genetics, Oxford University.**

Professor Ebers said he would describe the genetic epidemiology of MS and show how vitamin D fits into that context.

As far back as 1787 Samuel Stanhope Smith (a vicar who became Principal of Princeton University) recognised that there was something special about the relationship between geography and skin colour. In fact skin colour is closely related to vitamin D levels. As our ancestors moved north from the equator into areas with less sunlight, those with darker skins died and their foetuses died, as people with paler skins survived.

In Canada we looked at plots of the sex ratio of MS cases against the year of birth in 30,000 patients. It showed that the frequency of MS has increased and it has particularly increased in females. The ratio for people born in Canada was the same as the ratio for people who emigrated to Canada from the UK (see slide 2), meaning that it is almost certain the same phenomenon would be seen if the UK were examined. In Scotland in particular the rise in sex ratio has been from 1/1 in the 1950s to now about 3.5/1. The increasing incidence of MS is so great in such a short time that it suggests it must be linked to environmental factors rather than genetics.

We have carried out a number of studies to investigate the relative significance of genetic and environmental risk factors (see slide 4). We started with the general population rate of 1/1000 cases as our baseline and worked back to look at the cumulative effect of adding a shared environment. We found that if you have MS the risk of your spouse getting MS is not increased. Being raised with a sibling who is destined to get MS does not increase your risk of MS. Birth order appears to have no effect on the risk of MS. If you are adopted at birth and are destined to get MS, it does not affect the risk of non-biologically related people living in the same house. Similarly there is no added risk for step-siblings sharing a house. Having conducted all these studies we could not

detect any effect on risk of sharing an environment with a person with MS. We concluded that factors determining geography exert huge effects but they must be acting at a broad population level and they do not discriminate among familial microenvironments. This left climate and diet as the possible key risk factors. Diet is usually shared within a family, so we focused on the influence of climate, although diet can also differ at a population level.

Slide 5 shows a 6 fold difference in the incidence of MS from south to north in different regions of Australia. The population is not distributed evenly and the map is drawn for present prevalence which is not necessarily when risk was acquired. It could be more relevant to do this by place of birth if risk is determined at an early stage. The best place for a study to investigate the influence of climate is a country with plenty of sunshine where the population does not move, such as France. We looked at French farmers and their families who have a separate health insurance system with excellent records. Conveniently for our purpose they are even less likely than their compatriots to move. The highest risk per/100,000 of the population by region is in the north-east of France, while the lowest rates are in Corsica and the south-east (the Cote D'Azur) (see slide 6).

France has a relatively homogenous population, but we found striking variations in risk by region. We used data collected by an EU satellite (Heliosat) to measure sunlight and ultraviolet light in France and there are clear relationships between degree of exposure to sunlight and incidence of MS. One anomaly climatologically viz. Poitou-Charentes is also anomalous for MS risk which seems improbable to be just coincidence.(see slides 7 and 8). This research provides circumstantial evidence, showing correlations between sunlight and MS rather than explaining causes but the visual characteristics are somewhat compelling.

Some people are chronically deficient in vitamin D through the year in the UK and some 50-70% of the population is deficient in the UK by the end of winter. It is not surprising that vitamin D is significant for various diseases because the vitamin D-responsive family is the largest in the genome with some 1000 members. The only rival in terms of scale are the odourant receptors. As a result, vitamin D surely must affect many processes, many yet to be determined. Among many known actions, Vitamin D acts as a cofactor for epigenetic modifications - these are factors in genes that affect the behaviour of genes.

There are few dietary sources of vitamin D. It is found in cod liver oil, shitake mushrooms and lichen (and thus in reindeer stomachs), this may be the reason for the conventional wisdom in many northern communities that cod liver oil is good for you and in northern Norway it is mother's wisdom that one must have a traditional meal of fish and fish liver once a week.

We have examined MS risk and early life events (see slide 10). These studies suggest that early life is important in determining the risk of MS. Half-sibling studies have been especially informative and are now quite feasible because of the high divorce rate. They can dissect 3 key questions. About half of  $\frac{1}{2}$  siblings are raised together and half are raised apart and among the latter many have never seen one another as the parents only communicate through lawyers. Among these we can ask whether  $\frac{1}{2}$  siblings raised together or apart had the same risk. Since  $\frac{1}{2}$  siblings share one parent not two we can ask whether sharing a mother is more important than sharing a father; and using the difference in risk between siblings and  $\frac{1}{2}$  siblings we can determine how many genes are involved in determining risk of MS. The answers to these 3 questions were clear. No difference in risk for raised together versus being raised apart, the mother is much more likely to be the common parent and the disease follows a pseudodominant pattern of inheritance. The highest risk is for female identical twins, where if one twin gets MS the other has a high (450/1000) risk of getting MS (see slide 12).

There is no simple inheritance pattern (see slide 13), but for two generations there is a near dominant risk, but between the second and subsequent generations the risk diminishes significantly. A remarkable family from Manitoba is especially informative. In this case the son of the Indian chief (with a typically low risk of MS) married a Caucasian mother (with a typically higher level of risk). Of their 18 children, 6 had MS but there was only 1 case of MS in the large, third generation, even though they were living in the same environment as their parents. We believe this change in risk between the second and subsequent generations shows that MS is the result of a manifestation of a

chemical modification in a gene and that this chemical modification decays after 2 or 3 generations. When we looked closely, we found that almost all the genetic cause of risk is in an area on chromosome 6.

There may be a connection between this gene region, the chemical modification and a maternal parent of origin effect. The latter incidentally is confirmed in aunts, uncles, nieces and nephews (AUNN). This evidence suggests that something happens in the parental generation that affects the risk of MS in subsequent generations.

The maternal parent of origin effect is confirmed in aunts, uncles, nieces and nephews (AUNN) and the evidence suggests that something happens in the parental generation that affects the risk of MS in subsequent generations.

We used identical twins where one had MS and the other did not and looked to see if there were chemical differences in the genes that are known to be important and we found there are a number of these which we are currently studying. (see slide 21).

In summary, MS incidence is increasing. A modifiable environment determines some 80% of cases and it acts at a broad population level by interacting with a susceptible genotype. It is good to live in an area with sunlight and vitamin D is a strong candidate to explain why this is the case. The environment interacts with genes to alter their function and this is likely the way in which it affects the risk of getting MS, but this interaction is volatile and it decays over time. We now can unite the genes involved with vitamin D, the best environmental candidate. We did a search of the genome and found that the best genetic candidate for MS risk, the major histocompatibility complex in particular a section called class II containing key genes for the immune system has a vitamin D response element. This is a stretch on the DNA which is regulated or controlled by the binding to it of the vitamin D complex. This is unlikely to be coincidental. I believe the evidence is now sufficiently clear to justify public health policy changes to protect against the risk of MS at least and many other diseases may come into play.

## Questions

**Dr Susan Lanham-New of Surrey University** asked what the speakers regard as optimum levels of vitamin D given that there does not appear to be consensus on this issue. **George Ebers** said the same level is not likely to be applicable to vitamin D's interaction with all of the 1000 different genes it controls and we lack trial evidence to categorically pick one level. All we can do is to consider our evolution and surmise that black people in Africa may have the optimum level (some 100 -140 ng/L). Regardless, the experts are unanimous in agreeing that the level should be higher than it is. **Adrian Martineau** said the current modest recommendations are based on historical evidence that 400 units (or 10 mcg) a day were sufficient to protect against rickets. More recent evidence has shown that the risk of diseases such as cancer and diabetes is lowest among people with serum 25-hydroxyvitamin D of 75 nmol/l and above.

**Alan Long of Vega Research** agreed with George Ebers about the significance of epigenetics and referred to evidence comparing Sephardic and Ashkenazi Jews among other examples.

**David Godfrey of the Food Additives and Ingredients Association** asked whether the higher incidence of TB among Asians who had emigrated to the UK, in comparison with the UK population, might be related to the fact that they use ghee rather than margarine, which is fortified with vitamin D, in their cooking. **Adrian** said that the risk of getting TB is higher shortly after exposure to TB, so it may be that these immigrants were exposed to TB before arriving in the UK, but it could also be affected by other factors associated with emigration. Although margarine is fortified with vitamin D, several recent studies in the UK suggest that this is not sufficient to achieve adequate vitamin D levels even in those who consume it regularly.

**Peter Clough of Efamol Ltd** asked Adrian what dose of vitamin D he is using in his latest research. **Adrian** said they use doses of 100,000 IU (2500 mcg) fortnightly over an 8 week period, and the current recommended safe upper limit is 1,000 IU (25 mcg/day). Adrian and his colleagues monitor

their patients at fortnightly intervals and they have found no evidence of raised blood calcium as a result of using this high dose.

**Jane Landon of the National Heart Forum** asked if people are equally able to assimilate and store vitamin D. **George Ebers** said their studies of twins shown that twins without and with MS had the same levels of vitamin D, so having MS does not appear to lower one's vitamin D level. However, if you look at the genes that are involved in metabolising vitamin D, it does seem to have an effect on vitamin D levels. It is less than 10,000 years since we came out of Africa and every gene will be under selective pressure to adapt to increase our chance of surviving, so it is likely that there are genetic factors that could affect vitamin D status.

**Dr Susan Lanham-New** of Surrey University said a large study published last year which looked at 1000 people had found no difference in vitamin D levels between people eating and not eating margarine. She said that Surrey University is conducting a study, funded by the FSA, which is looking at the effect of exposure to sunlight on vitamin D levels and she asked whether the speakers believe a recommended daily intake (RDI) should be set for vitamin D. **Adrian** said that the zero RDI for vitamin D in healthy adults at present may be inappropriate, and that on-going clinical trials may demonstrate this in the next 5 years; he himself takes 2000 IU (50 mcg/day) during the winter. **George** said the EU and USA authorities had considered this and both thought higher levels were needed but neither made specific recommendations in the absence of research evidence. However, experts in this field typically take 4000 mg/day or more. A systematic review in the *American Journal of Clinical Nutrition* (Hathcock et al) suggested that 10,000mg/day is safe and promoting this evidence should increase confidence that people can safely take lower doses.

**Lord Rea** asked if the Scientific Advisory Council on Nutrition (SACN) had recommended a RDI. **Oliver Gillie** said it had not and that their recent update on vitamin D had been very conservative and very disappointing. **Adrian** said there is no high dose preparation of vitamin D3 available for prescription in the British National Formulary; these doses can be given intermittently to prevent vitamin D deficiency during winter and spring. He would like to see a 50,000 unit (1250 mcg) tablet included in the British National Formulary.

**Lord Rea** said that Governments will not usually act unless their scientific advisory committees advise them to do so and the committees are usually very cautious and require unanimity among the scientific community. So, if the Government is to be persuaded to act on vitamin D, more evidence is required to make the case for change. **George** commented that charities can help because their credibility as the champions of patients can help influence public opinion. He thinks we are too cautious in the advice we give, for example to pregnant women. We will not, for example, recommend that they take a high dose vitamin D tablet, which would be the equivalent of sunbathing for 15 minutes. In France there was ready acceptance of giving pregnant women 100,000 units early in pregnancy and they have been doing this now for several years.

**Lisa Miles of the British Nutrition Foundation** asked if adequate vitamin D levels could be achieved through diet rather than by taking vitamin D supplements. **Adrian** said a person would need to eat more than one portion of oily fish per day to achieve this. This is achieved in some countries, but not in the UK. He added that supplementation is attempting to replace a climatic deficit and it is difficult to achieve that through diet. **Oliver Gillie** said that nutritionists' reluctance to recommend supplements is a challenge for those trying to boost vitamin D levels in the UK and food fortification could help.

**Dr Jayne Spink of the MS Society** asked whether, given contracting MS is largely unpredictable, there are other practical steps which people can take to reduce their risk of MS because the whole UK population is unlikely to take vitamin D supplements. **George** suggested that individuals at high risk of MS are likely to take and/or give their children vitamin D supplements because they are highly motivated. He added he would like to test the effect of a whole population in a small country such as Tasmania or Scotland taking vitamin D supplements.

**Peter Clough** asked what possible adverse effects had led to the official advice on safe upper limits for vitamin D supplements. **Adrian** said hypercalcaemia (high calcium levels in the blood) leading

to renal failure had been identified as a possible risk, but this was only likely to occur with food fortification if a major error were made in fortification. **George** said that early fears about high vitamin D levels have not been substantiated by more recent evidence and there is no one in the vitamin D field who thinks these early fears were justified.

**Jane Landon** asked the speakers what they would recommend in terms of exposure to sunlight given well known concerns about skin cancer risk. **George** said that taking supplements circumvents opposition to recommendations to increase exposure to sunlight. **Oliver** Gillie said that we have been given poor advice by Cancer Research UK which had not clearly said that the highest risk of melanoma is for people who are not habitually exposed to sunlight who then get sunburnt. Evidence shows that people habitually exposed to sunlight – for example those working outside – are less likely to get skin cancer. **Oliver** suggested there should be a review of the health costs and benefits of exposure to sunlight that involved a wide range of experts and not just dermatologists. **Adrian** agreed that increased sun exposure could not solve the problem alone, because UK sunlight from October to April in the UK is too weak to make vitamin D in the skin, and we cannot store vitamin D long enough to sustain our vitamin D levels through the winter months.

**Lord Rea** commented that some of the health benefits associated with increasing exercise may be derived from greater exposure to sunlight and **Adrian** agreed.

**Jenny Lisle of the Royal College of Physicians Faculty of Public Health** (RCP FPH) suggested that a position statement to clarify the consensus view on vitamin D levels might be helpful in informing the public and influencing opinion. **Adrian** agreed, saying it was a wonderful idea and it would be very helpful if the RCP FPH would undertake it. **Oliver** agreed it would be a fantastic initiative and said it would be very helpful if they looked at the significance of vitamin D disease by disease, so that the full weight of the evidence now available could be fully appreciated.

**Lord Rea** thanked the guests for their excellent presentations and announced the date of the Forum's next meeting: a discussion on the progress of the work of the School Food Trust at 4pm on Tuesday 8 July.

*CLC, July 2008*