Advanced industrial societies all over the world face a massive epidemic of chronic disease caused by insufficient vitamin D. Modern life keeps us indoors away from the sun which supplies 90 per cent of the vitamin D which we need.

A billion or more people in Europe obtain insufficient sunlight and vitamin D putting them at increased risk of diabetes, high blood pressure, arthritis, multiple sclerosis and the common cancers including cancer of the bowel, breast, prostate, ovary and lymph glands as well as diseases of bone.

This epidemic of chronic disease caused by insufficient vitamin D is probably as large as the epidemics caused by smoking and obesity, but the importance of vitamin D for health is still not properly recognised by governments.

This report of a meeting in London at the House of Commons, chaired by Ian Gibson MP, examines the evidence for the D-deficiency epidemic and considers how policy on fortification of food, sunbathing, and use of supplements might be changed to provide more vitamin D and better protection against chronic disease in the 21st century.

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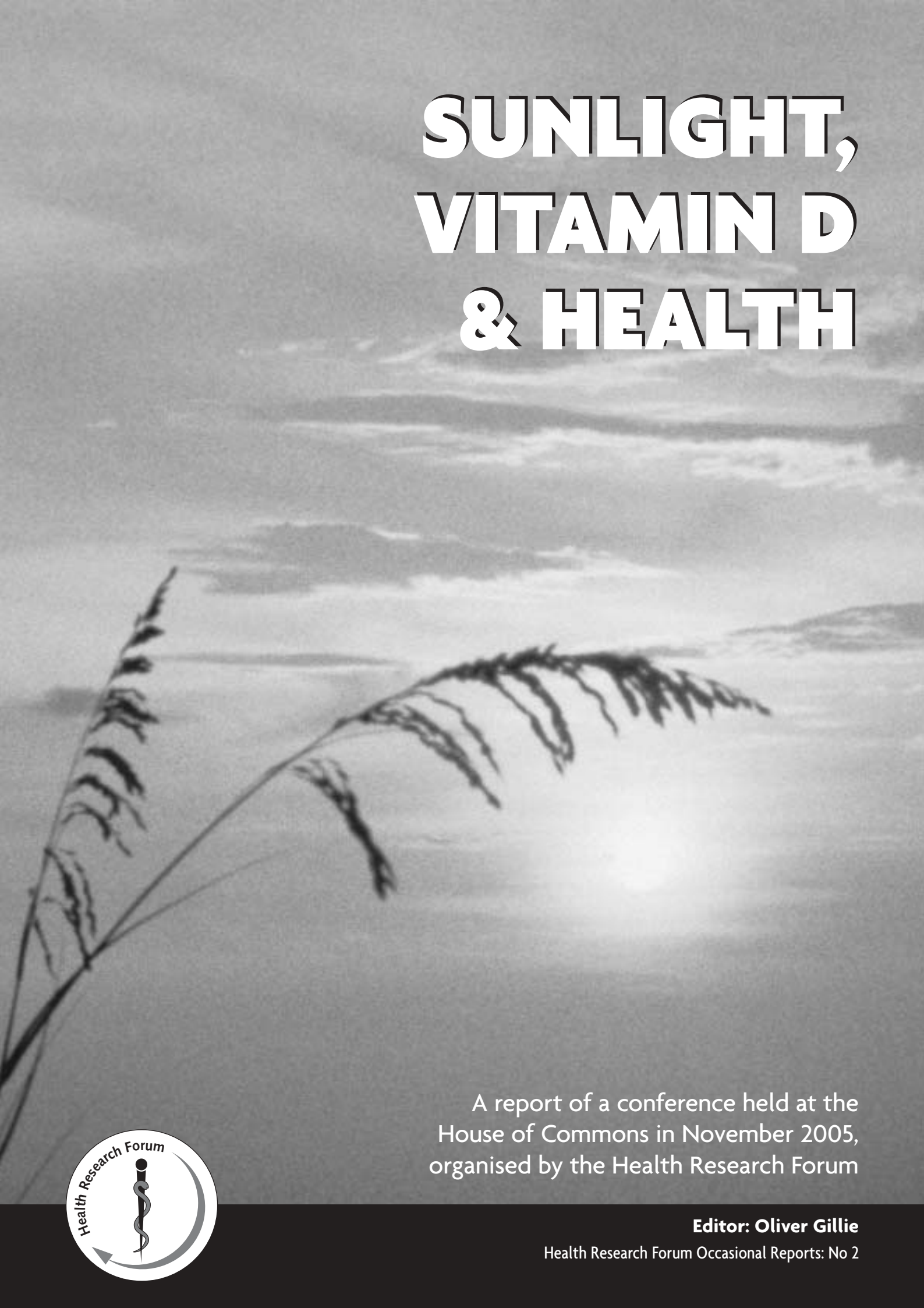
SUNLIGHT, VITAMIN D & HEALTH

A report of a conference held at the House of Commons in November 2005, organised by the Health Research Forum

Editor: Oliver Gillie

Health Research Forum Occasional Reports: No 2



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Oliver Gillie

Health Research Forum

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Contents

Preface

This is a fascinating collection of papers gleaned from the conference on Sunlight, Vitamin D and Health, held in the House of Commons in November 2005. This publication could not come at a more timely point. As the authors persuasively demonstrate, there is a great need for the government to revise its advice on vitamin D intake. There is growing evidence which suggests that most adults in the UK receive such low levels of vitamin D that they are at risk of all sorts of chronic diseases, including rickets, osteomalacia and osteoporosis.

It has become almost received wisdom that vitamin D insufficiency is not a serious health problem, and as such we don't have to worry about it too much. An extraordinary state of affairs if one thinks of the dearth of sunlight (a key source of vitamin D) available in the British Isles! Oliver Gillie, one of the authors in the collection, reveals that our current guidelines on sunlight intake are probably borrowed from those given by the Australian government to its public.

Whatever position one may take, it is important that the research gathered in these pages receives an objective if not a sympathetic ear. It seems ludicrous to me that we can be so dogmatic about this area and continue to foster an environment in which vitamin D is almost feared, as its main source – sunlight – is explicitly linked in the public (and professional) psyche to skin cancer. No other vitamin suffers as much indirect bad press as vitamin D, simply through association and often without hard evidence to justify the unease among officials when it is suggested that current levels should be increased by offering better supplements, changing diets and, most controversially, by increased sunbathing.

This publication is therefore, I hope, the beginning of a more proactive approach to public health advice. I, like many of the authors, would like to see the government instigate a national campaign to encourage the public to eat foods rich in vitamin D. I'd like it to revise its current guidelines, reintroduce vitamin D supplements for breast-fed babies and review its recommendations on the level and use of vitamin supplements.

A long list perhaps, but entirely achievable. If this goes too far for some, at the very least, good research projects must be sought to provide us with more information in this area. This report is the first step in a very right direction.

Ian Gibson, MP
House of Commons
Westminster
January 2006

Ian Gibson is member of Parliament for Norwich North. He is a member of the House of Commons Select Committee for Science and Technology, and a member of the All Party Group on Cancer.

Introduction

I would like to introduce this collection of papers with a tribute to Sir Richard Doll, who died in 2005 at the grand old age of 92. Julian Peto and I went to talk to him about vitamin D while he was still fit and well.

Sir Richard Doll

Doll had shown that a four-monthly oral dose of 100,000 IUs vitamin D3 reduced fractures in people over 65 [1]. The study, undertaken with Daksha Trivedi and Kay Tee Khaw, also showed a non-significant reduction in mortality in the subjects who took vitamin D. Impressed by these results, and believing that vitamin D probably had beneficial effects other than those on bone, Doll himself took a monthly vitamin D tablet equivalent to about 1,000 IUs per day. In fact the tablet he was taking was vitamin D2, which only has one-third the potency of D3. High-dose vitamin D preparations are only available on prescription in the UK and are all formulated with D2. Most clinicians are not aware of the important difference in potency between D2 and D3.

Doll had courageously changed his mind about the importance of vitamin D and the beneficial effects of exposure to the sun. As chairman of the UK Advisory Group on Non-ionising Radiation (AGNIR) he had signed off a report of the National Radiological Protection Board (NRPB) which states that casual exposure to the sun in the UK provides people with sufficient vitamin D [2]. That belief is still a foundation stone of official policy on sunlight in the UK, but when Doll looked further into the evidence he realised that it had little scientific support. However, he did not want his revised opinion to be made public until he had formally notified the NRPB, so he telephoned Professor Tony Swerdlow, the presiding chairman of AGNIR, to report his change of view.

In the months before his death Doll was reviewing the literature on vitamin D and sunlight. The study he had undertaken with Trivedi and Khaw was intended to be a pilot project, and Doll still hoped to obtain funding for a larger trial which would examine a wider range of possible benefits. He was also seeking support for a conference on vitamin D, and the meeting at the House of Commons at which this collection of papers was presented is a tribute to him and to his interest in vitamin D.

Doll believed in the utility of science and had seen at first hand what benefits can come from a clear understanding and exposition of the causes of disease. No doubt with this experience in mind, he left Julian and me with this thought-provoking comment as we departed: 'This isn't difficult science. We should have answers.'

He clearly felt that the subject of vitamin D had not had the attention it deserved from scientists and that a great deal could be achieved. There are still major disagreements among health researchers about the strength of the evidence that insufficient vitamin D or sunlight increases the risk of various diseases. But all are agreed that this is an important problem, and that these initiatives need to be supported by substantial funds and positive government action.

The meeting at the House of Commons was hosted and chaired by Dr Ian Gibson, MP. As well as being a member of Parliament Dr Gibson is a distinguished scientist with a long career in scientific research. He has been deservedly chosen on two occasions to be the ePolitix health champion, the member of Parliament who has done most for health causes during the course of a year. We are very grateful for his support.

After the morning meeting I met the speakers and other like-minded people to discuss what can be done to obtain the co-operation of the UK government, the European Union and others for further research and action to improve vitamin D levels in people everywhere. Several of those present said they would raise the issues with their professional bodies and would suggest that meetings and symposia be planned to discuss the subject. We also agreed to set up an organisation, which we have provisionally called the Vitamin D Forum, to keep all those interested in the subject of Vitamin D, Sunlight and Health in touch. Anyone reading this who would like to know more about the Vitamin D Forum should contact me.

I would also like to express my thanks to Ad Brand and the European Sunlight Association who provided financial support for this meeting. The ESA represents manufacturers of sunlamps and their associates. They have been enlightened sponsors and have not endeavoured to influence the choice of speakers or the programme of the meeting in any way. The ESA has paid travel and subsistence expenses to speakers but no honoraria have been paid to speakers for participating in this meeting. I myself have no commercial interests in this work and have received no payments of any kind in connection with it.

Oliver Gillie, Health Research Forum, January 2006

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1. Trivedi, D., Doll, R. and Khaw, K., *Effect of four-monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial.* British Medical Journal 2003; **326**: 469-474.
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Summary: vitamin D, sunlight and health

Cancer risk reduced by vitamin D and sunbathing

Six out of 10 adults of working age in the UK, and probably in other European countries too, are at risk of chronic disease because they do not get enough vitamin D. The diseases caused, at least in part, by insufficient vitamin D or insufficient sunlight include not only bone conditions such as osteoporosis and rickets but diabetes, multiple sclerosis and several different kinds of cancer, as well as high blood pressure and probably heart disease.

Knowledge of the connection between vitamin D insufficiency and chronic disease other than diseases of bone has, until very recently, been minimal among doctors and others responsible for public health. So this meeting was organised at the House of Commons by Oliver Gillie, director of the Health Research Forum, a not-for-profit organisation, with the backing of Ian Gibson, MP, to review the scientific evidence linking insufficient vitamin D with chronic disease. Public health policy concerning vitamin D and sunlight was also reviewed at the meeting.

Exposure to summer sun improves survival from cancer according to Professor Johan Moan of the Institute for Cancer Research in Oslo, Norway, who has studied what happened to all the people diagnosed with cancer in Norway between 1964 and 2000 (page 33). He found that the risk of a person dying within three years of diagnosis with prostate, breast, colon, or lung cancer, or with Hodgkin's lymphoma, is up to 50% lower for those diagnosed during summer and autumn compared with winter.

'In Nordic countries, and in Britain, practically no vitamin D is generated in the skin during the winter months because solar radiation contains too little ultraviolet B,' said Professor Moan. 'In summer, calcidiol, a form of vitamin D that circulates in blood, is up to 100% greater than in winter. It seems likely that calcidiol protects against these cancers. We have also found that the risk of death from cancer varies in Norway from one part of the country to another, depending on the amount of solar radiation that is received.'

In the UK the risk of getting prostate cancer has also been found to vary with the amount of sun a man is exposed to, according to work by Professor Richard Strange of Keele University Medical School, Staffordshire (page 25). Men who sunbathe, or have holidays in sunny climates, and those who have suffered from sunburn, have a lower risk of prostate cancer. (In these observations sunburn is simply a sign of heavy sun exposure. Burning should be avoided because it carries a risk of skin cancer.)

'A lower level of exposure to UV light is linked to increased risk of prostate cancer in northern European men. Men with the lightest skin type, fair with freckles, have the least risk of prostate cancer, presumably because they are able to make use of the weakest sunlight to produce vitamin D,' said Professor Strange.

'I used to cover up and use sun cream when I went out walking in the hills but now I don't. I try to get as much sun as I safely can,' he said.

Multiple sclerosis linked to long winters

Insufficient exposure to the sun is also associated with a higher risk of multiple sclerosis. Evidence from Australia suggests that exposure to the sun during childhood and adolescence is particularly important for reducing the risk of MS (BMJ 2003; 327-316), and low exposure to the sun in winter was found to be associated with an increased risk of MS in Australia.

Above latitude 37°North the sun is not strong enough to provide any vitamin D in winter. The further north a country is the less sun it gets in summer and the shorter its summer season. This explains why Scotland, which also has a cloudy maritime climate that obscures the summer sun, has probably the highest incidence of MS in the world. Much other evidence shows a link between MS and latitude. In France, as explained by George Ebers on page 41, the incidence of MS in French farmers is significantly greater in the north than in the south of the country.

Extensive studies of twins, adopted children and half-siblings by George Ebers and colleagues have shown that MS is not caused primarily by risk factors within families such as diet or infection. Heredity influences a person's susceptibility to MS, but the place where a person is born and the time of year that they are born seems to be crucial in deciding whether or not they develop the disease. Risk of MS is greatest for those born in May, at the end of the winter when vitamin D levels are lowest.

The epidemiological findings on MS may be explained by insufficient sunlight causing low levels of vitamin D that prevent normal development of the nervous system early in life. The link with insufficient sun now seems beyond doubt. But it remains to be proved that lack of vitamin D is the actual cause of MS, although this seems likely.

The importance of this research on MS, which has taken many years to reach this stage, cannot be underestimated. The disease strikes people in the prime of life and after 15 years half of them are unable to walk without assistance. In Scotland as many as one in 400 people may be affected. The lifetime cost of caring for each person with MS comes to around £1.5m. So the annual cost of caring for the 70,000 people in the UK with MS comes to several billion pounds. If this disease can be prevented by more exposure to sunlight in the early years, as seems likely, it will be an astounding achievement for medical science to have shown the way.

Sunshine vitamin prevents early diabetes

Insufficient vitamin D in early life is associated with an increased risk of diabetes later on. Babies whose mothers take vitamin D during pregnancy and babies who are given vitamin D during the first year of life have a lower risk of developing diabetes type 1, according to Dr Elina Hyppönen of the Institute of Child Health, University College, London (page 50).

Breast-fed infants are most at risk of vitamin D deficiency and diabetes type 1 because milk from mothers living in northern Europe contains little vitamin D. Artificial baby milks are supplemented with vitamin D and so bottle-fed babies are not at risk of developing low vitamin D levels until after weaning.

Babies whose mothers come from ethnic minorities are at greater than average risk of diabetes type 1 because their mothers have lower than average vitamin D levels. Dark- skinned people have lower levels of vitamin D because dark skin exposed to the sun makes less vitamin D in a given time than white skin.

Dr Hyppönen, who is Finnish, has a baby of her own. She said: 'I have been unable to find any suitable products here in the UK, and so I am giving my baby vitamin drops that I obtained in Finland. There is a need to form appropriate vitamin D supplement recommendations for breast-fed babies in the UK, and to ensure that suitable products are available.'

Babies at risk because NHS vitamin drops withdrawn

Until 1975 infants in the UK were given free National Health Service vitamin drops containing vitamin D. But subsequently the vitamin drops, which were classified as a 'welfare food', were given only to mothers receiving state benefits. Mothers who were not entitled to free NHS infant vitamin drops could buy them, but the government never promoted them properly and so uptake gradually fell.

For the last two years or so NHS vitamin drops have not been available for mothers to buy because there was a problem with leakage from the bottles and all stock had to be withdrawn (page 63). Paediatricians in the UK have been pressing for government action to replace the defective product and after a two-year delay tenders have been put out for the products to be supplied. Meanwhile, doctors in Birmingham and Bristol, where there are large immigrant communities, have felt so frustrated by government inaction that they have launched their own scheme to provide a vitamin D supplement for babies under one year and for pregnant or lactating mothers. These schemes are paid for by the local Primary Care Trust.

Heart disease epidemic in sun-starved Britons

High levels of heart disease in Britain may also be caused by insufficient vitamin D. The higher incidence of heart disease in Scotland compared with England, or in England compared with southern European countries such as France, Italy or Spain may be explained by relatively weak sunlight and short summers in the north. In fact the good health associated with the Mediterranean diet may be accounted for as much by the Mediterranean sun as by the regional food.

Dr Armin Zitterman from the Heart and Diabetes Center, Ruhr University of Bochum, Germany, argued that insufficient vitamin D causes the calcification of arteries that commonly occurs in people with heart disease (page 18). Higher levels of vitamin D produced by supplements or sun exposure prevent heart disease by reducing inflammatory processes and disorganised cell proliferation in blood vessels and in the heart, he believes.

'Protection against chronic disease can be obtained in winter by taking 2,000 IUs (50 micrograms) vitamin D per day. In summer, enough vitamin D can be obtained by sunbathing for 10 minutes or so in the middle of the day, exposing the whole body. This will protect against bone disease and is likely to prevent heart disease too,' said Dr Zittermann.

But government advice in the UK is seriously out of date and misleads the public into thinking that adults ob-

tain sufficient vitamin D from casual exposure of only the hands and face to the sun. In fact, very little vitamin D is obtained from casual exposure to the sun in northern Europe. Most Europeans get little vitamin D from food, especially if they do not eat margarine or oily fish and choose a wholemeal breakfast cereal such as muesli that contains no vitamin D.

'Current dietary guidelines for vitamin D in the UK are incorrect in stating that adults below age 50 require no vitamin D and specify too little for older people,' said Reinhold Vieth, professor of nutritional sciences at the University of Toronto, Canada (page 47). 'Sun avoidance advice makes the vitamin D problem even worse in the UK. The result is an unacceptably high occurrence of what should be regarded as toxic vitamin D deficiency.'

This toxic deficiency of vitamin D is associated with a higher incidence of many chronic diseases: not only heart disease but several types of cancer including the commonest cancers – those of the breast, prostate and bowel. While there is evidence from clinical trials that high-dose vitamin D (1,000-2,000 IUs, or 25-50 mg vitamin D per day) can prevent rickets, osteoporosis, fractures, falls, arthritis and high blood pressure, the suggestion that vitamin D might prevent other disease comes from observational studies. The high-dose vitamin D supplement recommended by Dr Zittermann and others cannot at present be obtained over the counter in the UK but it can be bought from abroad through several suppliers, using the internet.

Inadequate levels of vitamin D in UK population

Vitamin D deficiency and insufficiency are very common in the UK as shown by figures compiled by Dr Barbara Boucher (page 53) from the Centre for Diabetes and Metabolic Medicine, Queen Mary School of Medicine and Dentistry, London, using a number of sources.

'The attendant risks from low vitamin D levels of rickets in children and of osteomalacia and increased fracture rates in adults are especially regrettable in the country that identified vitamin D almost a century ago,' said Dr Boucher. 'It has been known since the 1920s that these problems do not arise with adequate exposure to summer sunlight, even in this northern country, and that dietary supplementation (with, for example, cod liver oil) can both cure and prevent these problems.

'Furthermore, the continuing high prevalence rates of hypovitaminosis D is likely to be increasing the prevalence of the many non-bony disorders that are strongly associated with vitamin D inadequacy. These disorders include many common cancers (for example, breast, colon, prostate), type 2 diabetes, ischaemic heart disease, tuberculosis, rheumatoid arthritis, periodontal disease and autoimmune diseases such as type 1 diabetes of childhood and multiple sclerosis, as well as increased fracture rates in old age.'

New foods and better sun advice could curb cancer and other chronic disease

Government action could overcome the problems caused by insufficient vitamin D in the UK. Oliver Gillie said: 'The solution is simple compared with persuading people to give up smoking or lose weight, and could have a dramatic effect in reducing chronic disease. More foods need to be fortified with vitamin D so the public can, if it wants, choose foods such as bread, milk, butter and cooking oil that contain the vitamin.

'Official advice on sun exposure needs to be changed in most European countries. The SunSmart programme run by Cancer Research UK, and similar programmes in other European countries, aims only to prevent skin cancer. It is based on a mistaken calculation of the amount of sunlight and vitamin D that is needed for prevention of chronic disease. The vitamin D requirement factored into the calculation is far too low.

'As a result, Cancer Research UK's SunSmart programme has probably caused many more deaths from cancer than it has prevented. The SunSmart policy may also be partly responsible for apparent increases in chronic diseases such as multiple sclerosis and diabetes. Sadly, Cancer Research UK has not seen fit to alter its advice substantially, despite many warnings.

'In the British Isles or other parts of northern Europe we should not avoid sunlight in the middle of the day as instructed by Cancer Research UK because it prevents us from getting enough vitamin D. We should follow the SunSafe advice, presented here for the first time. The SunSafe advice aims to encourage people to expose themselves to the sun safely and raise their vitamin D levels, without burning and with minimum risk of skin cancer. A tan is entirely natural and a sign of good health.'

The SunSafe advice (see box over, and page 66) has been specially designed for northern Europe. In contrast, Cancer Research UK's SunSmart advice, which is endorsed by the UK government and promoted at government expense, was designed originally for the sun-drenched Australian climate and is totally unsuited to our climate here.

The SunSafe Advice – Safe and Smart

1. Sunbathe safely without burning – every day if you can.
2. The middle of the day is a good time for sunbathing in the UK.
3. Start by sunbathing for 2-3 minutes each side. Gradually increase from day to day.
4. Don't use sun screen while sunbathing.
5. If feeling hot or uncomfortable expose a different area, cover up, move into the shade – or use sun screen.
6. When abroad, where the sun is generally stronger, expose yourself for shorter times until you find out how much is safe.
7. Children benefit from sun exposure, but need guidance.
8. A tan is natural and is generally associated with good health.

Box: The SunSafe advice is based on up-to-date scientific evidence and on the common-sense approach to sun exposure that was taken in the UK before advice such as SunSmart was promoted. It encourages safe exposure to the sun, which is our major source of vitamin D, and so can be expected to contribute to prevention of disease caused by vitamin D insufficiency.

Caution urged on sun exposure

A sceptical view (page 57) was presented to the meeting by Brian Diffey, professor of medical physics at Newcastle University, who is an adviser to Cancer Research UK. He believes that evidence remains insufficient to advocate a public health policy of deliberate sun exposure as a means of reducing chronic disease, especially cancer.

'We receive more than enough sun exposure during recreational activities,' he said. 'Public health messages that make patients feel blameworthy that their cancer may be self-imposed, for example by not getting enough sunlight, need a strong evidence base. Any compromise on the key messages in the UK SunSmart programme could lead to more cavalier behaviour, resulting in an even greater adverse impact on skin cancer incidence and mortality with no resulting benefit seen in other cancers.'

The miracle of vitamin D: importance for bone health and prevention of common cancers, autoimmune diseases and cardiovascular heart disease

More than 90% of most people's vitamin D requirement comes from casual exposure to sunlight. 'Aggressive sun protection will result in vitamin D deficiency if there is inadequate vitamin D intake from the diet and supplemental sources,' Michael Holick, professor of medicine, physiology and biophysics at Boston University Medical Center, Boston, USA, told the meeting (page 8). 'Very few foods naturally contain vitamin D and so it is not possible to get more than a fraction of the vitamin D required for good health from the diet.

'It has been assumed that young and middle-aged adults are not at risk for vitamin D deficiency. However, their lifestyle is such that they are constantly working indoors and when outdoors they wear a sunscreen because of their concern over sun exposure and the risk of skin cancer. As a result they often obtain insufficient vitamin D.'

The body has a huge capacity to produce vitamin D (page 8). A person in a bathing suit exposed to sunlight or ultraviolet B radiation for sufficient time to cause a light pinkness to the skin will raise the blood levels of vitamin D to the same degree as if the individual took between 10,000 and 25,000 IUs of vitamin D. But anything that alters the amount of ultraviolet B radiation that penetrates into the skin will have a dramatic influence on the production of vitamin D. Increase in skin pigmentation, use of sunscreens, increase in latitude, increase in the angle of the sun due to seasonal changes, and age all dramatically influence the production of vitamin D. The application of a sunscreen with an SPF (specific protection factor) of 8 to the skin will reduce the production of vitamin D by 97.5%.

Dr Holick believes there needs to be a re-evaluation of the beneficial effects of sunlight. 'There is no question that chronic excessive exposure to sunlight increases the risk of squamous and basal cell carcinoma of the skin. However, by contrast, lifetime moderate sun exposure appears to be associated with a lower risk of malignant melanoma which is the major cause of deaths from skin cancer. Most melanoma occurs on the least sun-exposed areas of the body. Recently it has been reported that those with the most sun exposure were less likely to die of malignant melanoma once they developed the disease. And high frequency of sunbathing by age 20 has been found to reduce the risk of non-Hodgkin's lymphoma by 30 to 40%.'

Dr Holick welcomed the recent recommendation by medical bodies in Australia and New Zealand advising a bal-

ance between avoiding an increased risk of skin cancer and achieving enough UV radiation to maintain adequate vitamin D levels. 'Hopefully this recommendation will be embraced by the regulatory agencies and the dermatology societies in Europe and the United States,' he said. 'It's time to stop demonising the sun and appreciate the wealth of benefits that sunlight has for human health and for the prevention of many serious chronic diseases.'

The vitamin D epidemic: truth and consequences

Michael F. Holick, PhD, MD, Professor of Medicine, Physiology and Biophysics, Program Director of General Clinical Research Center, Director of Bone Health Care Clinic, Boston University Medical Center, Boston, USA

Most humans depend on sun exposure to satisfy their requirement for vitamin D3. During exposure to sunlight, ultraviolet B radiation (290-315 nm) is responsible for converting 7-dehydrocholesterol, the precursor of vitamin D3, to previtamin D3 which, in turn, is rapidly converted to vitamin D3. Season, latitude, time of day, skin pigmentation, obesity, ageing, sunscreen use and glass all influence the cutaneous synthesis of vitamin D3. Vitamin D3 is biologically inert and requires metabolism in the liver to 25-hydroxyvitamin D3 (25[OH]D).

Once formed, this major circulating form of vitamin D3, which is used to determine the vitamin D status, is converted in the kidney to its active form, 1,25-dihydroxyvitamin D3. 1,25-dihydroxyvitamin D3 interacts with its vitamin D receptor in the intestine to enhance intestinal calcium absorption, and interacts with the vitamin D receptor in the osteoblast, which results in the formation of osteoclasts to remove calcium from the skeleton.

In addition to its role in regulating calcium homeostasis, vitamin D3 is very important for a wide variety of physiological and metabolic functions. The vitamin D receptor exists in most tissues and cells in the body, and most tissues and cells in the body also have the enzymatic machinery to produce 1,25-dihydroxyvitamin D3. It is believed that the local production of 1,25-dihydroxyvitamin D3 is important for helping to prevent many common cancers, including colon, prostate, breast, ovary and oesophageal cancers.

1,25-dihydroxyvitamin D3 is also recognised by the immune cells and modulates immune function, which may be important in the prevention of many common autoimmune disorders including type 1 diabetes, multiple sclerosis, rheumatoid arthritis and Crohn's disease. In addition, 1,25-dihydroxyvitamin D3 is a potent regulator of renin production and therefore may be important in the prevention of hypertension and cardiovascular heart disease.

Monitoring serum 25-hydroxyvitamin D concentrations yearly is important to guarantee that both children and adults are vitamin D sufficient, which will help prevent many serious chronic diseases and maximise bone health. Sensible sun exposure without sun protection, usually five to 10 minutes of exposure of arms and legs or hands, face and arms, two to three times a week between the hours of 10 a.m. and 3 p.m. in the spring, summer and autumn is adequate to satisfy the body's vitamin D requirement. In the absence of sunlight, 1,000 IUs of vitamin D3 are necessary to maintain a healthy level of 25-hydroxyvitamin D above 30 ng/ml (75 nmol/l).

Photoproduction of vitamin D and factors that alter its production

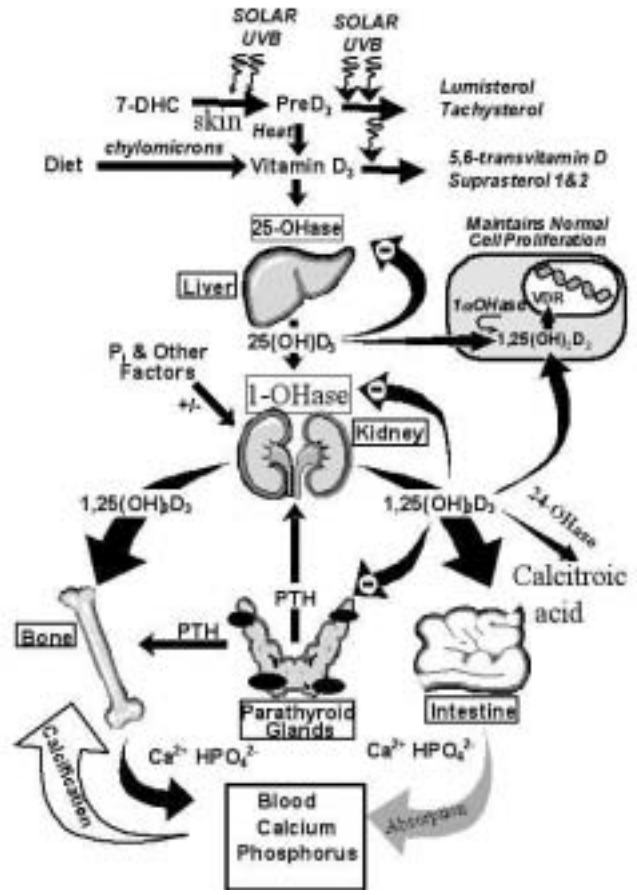
When solar ultraviolet B radiation (UVB; 290-315 nm) penetrates the skin, the 7-dehydrocholesterol in the plasma membrane of the skin cells absorbs it. This results in the ring opening of 7-dehydrocholesterol to form previtamin D3. Previtamin D3 is thermodynamically unstable and is rapidly converted to vitamin D3. Once formed, it is ejected out of the plasma membrane into the extracellular space where it finds its way into the dermal capillary bed, and is bound to the vitamin D binding protein (see Figure 1) [1].

Anything that influences the number of UVB photons penetrating into the skin will affect the synthesis of vitamin D3 [2, 3]. An increase in the zenith angle of the sun results in more of the UVB photons being absorbed by the stratospheric ozone layer. Very few, if any, UVB photons strike the earth's surface at higher latitudes, especially during the early morning and late afternoon and in the winter and, therefore, vitamin D synthesis is limited if not completely absent [1, 4, 5]. Thus during late autumn and into early spring very little, if any, vitamin D3 is produced in the skin of people living above 37° latitude (see Figure 2) [1-6].

At the latitude of London little, if any, vitamin D3 is made from sun exposure between the middle of October and the middle of April. Increased skin pigmentation and the topical application of sunscreen can reduce the number of UVB photons penetrating into the skin by as much as 99% and, therefore, reduces vitamin D3 synthesis by the same degree (see Figure 3) [2, 3, 6, 7, 8]. This is typically seen with a sunscreen with an SPF (sun protection factor) of 15 or a darkly pigmented individual, typically of African origin, with skin type 5.

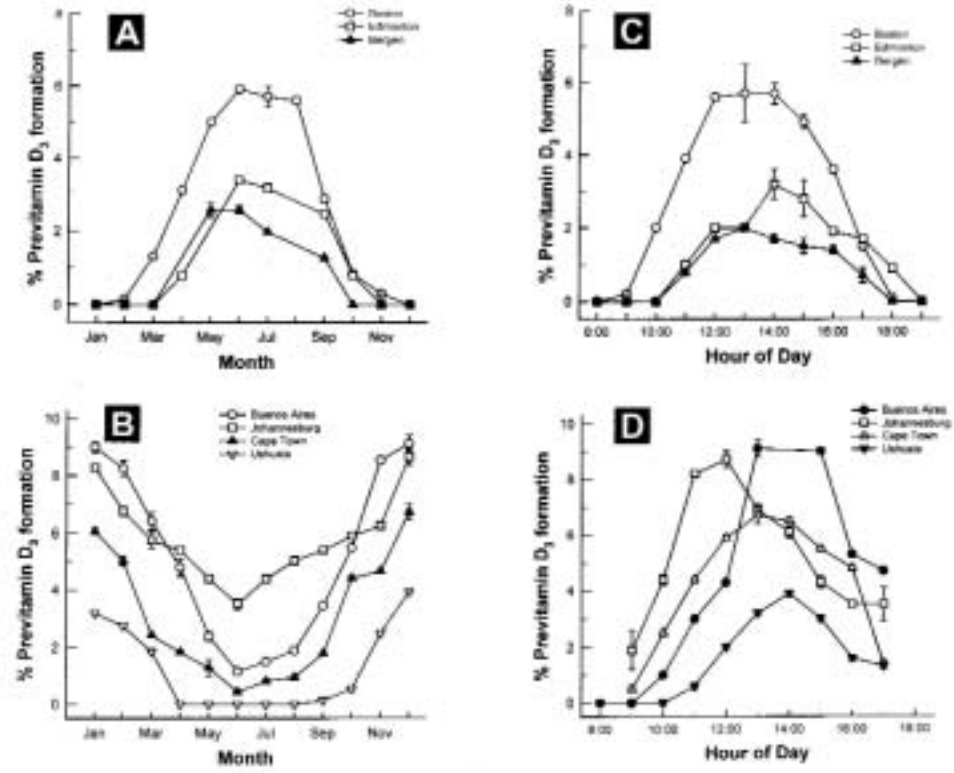
Peoples of the Middle East, who have skin type 4, typically have a 95 to 98% reduction in cutaneous vitamin D3 production compared to a fair-skinned person of Celtic origin (skin type 2). In black Africans, this reaches 99%. Ageing diminishes 7-dehydrocholesterol levels in the skin, and there is a four-fold decline in vitamin D synthesis by the

Figure 1



Schematic representation for cutaneous production of vitamin D and its metabolism and regulation for calcium homeostasis and cellular growth. During exposure to sunlight, 7-dehydrocholesterol (7-DHC) in the skin absorbs solar ultraviolet (UVB) radiation and is converted to previtamin D3 (preD3). Once formed, D3 undergoes thermally-induced transformation to vitamin D3. Further exposure to sunlight converts preD3 and vitamin D3 to biologically inert photoproducts. Vitamin D coming from the diet or from the skin enters the circulation and is metabolised in the liver by the vitamin D-25-hydroxylase (25-OHase) to 25-hydroxyvitamin D3 (25(OH)D3). 25(OH)D3 re-enters the circulation and is converted in the kidney by the 25-hydroxyvitamin D3-1α hydroxylase (1-OHase) to 1,25-dihydroxyvitamin D3 [1,25(OH)2D3]. A variety of factors, including serum phosphorus (Pi) and parathyroid hormone (PTH) regulate the renal production of 1,25(OH)2D. 1,25(OH)2D regulates calcium metabolism through its interaction with its major target tissues, the bone and the intestine. 1,25(OH)2D3 also induces its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-hydroxylase (24-OHase). 25(OH)D is metabolised in other tissues for the purpose of regulation of cellular growth.

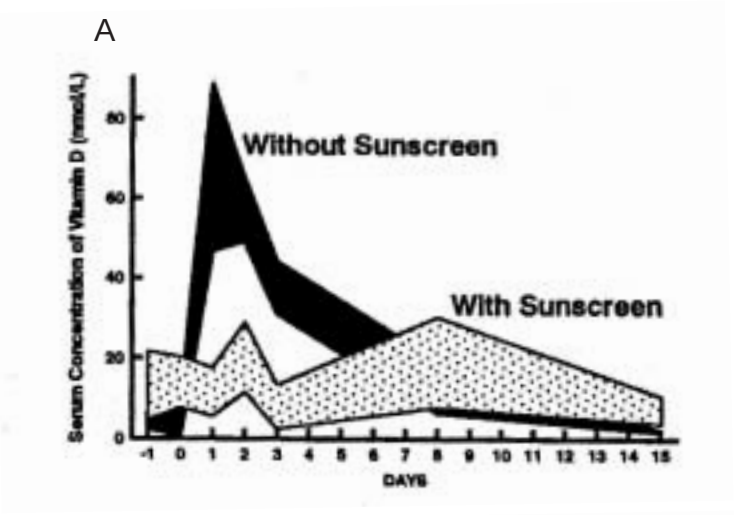
Figure 2



Influence of season, time of day in July, and latitude on the synthesis of previtamin D3 in Northern (A and C: Boston, Edmonton, Bergen) and Southern hemispheres (B: Buenos Aires, Johannesburg, Cape Town, Ushuaia and D: Buenos Aires, Johannesburg, Cape Town, Ushuaia). The hour indicated in C and D is the end of the one-hour exposure time in July.

Adapted from and reproduced with permission [5].

Figure 3

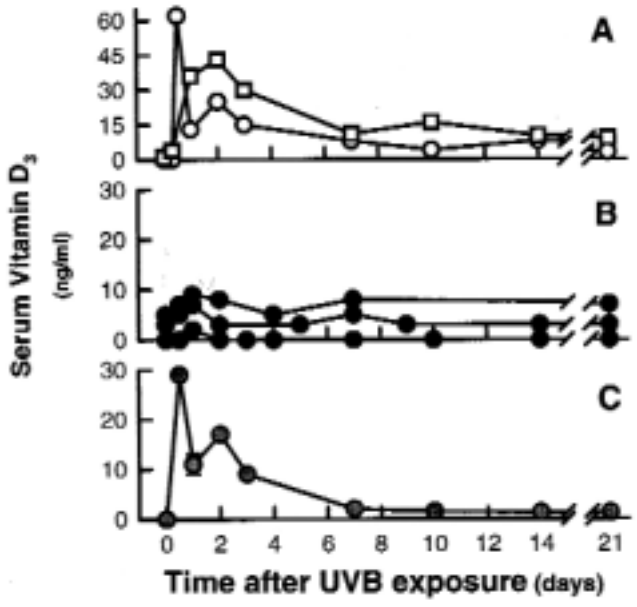


(A) Circulating concentrations of vitamin D3 after a single exposure to 1 minimal erythemal dose (MED) of simulated sunlight either with a sunscreen, with a sun protection factor of 8 (SPF-8), or a topical placebo cream.

(B) Circulating concentrations of vitamin D in response to a whole-body exposure to 1 minimal erythemal dose in healthy young and elderly subjects.

Reproduced with permission [3].

Figure 4

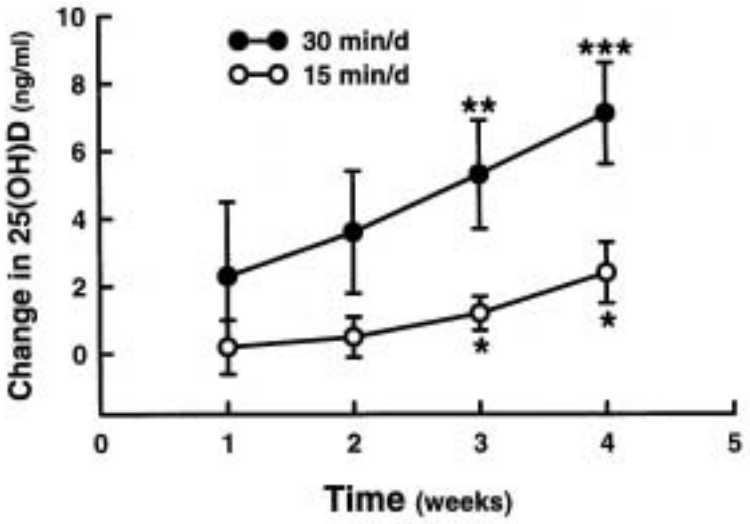


Change in serum concentrations of vitamin D in:
(A) two lightly pigmented white (skin type 2); (B) three heavily pigmented black subjects (skin type 5) after total-body exposure to 54mJ/cm2 of UVB radiation; (C) Serial change in circulation vitamin D after re-exposure of one black subject in panel B to a 320mJ/cm2 dose of UVB radiation.

Reproduced with permission.7

age of 70 years (see Figure 4) [9,10]. Obese individuals sequester the vitamin D3 produced in the skin and, therefore, require larger body surface exposure or longer exposures to satisfy their body's requirement [11]. Glass absorbs all UVB and thus exposure through glass is not effective in producing vitamin D3 in the skin [3].

Figure 5



Changes in serum 25(OH)D levels from baseline in subjects spending 15 or 30 minutes a day outdoors for four weeks.

Reproduced with permission [12].

It is well recognised by reptile hobbyists that they need to expose their pet reptiles to a source of UVB radiation in order to satisfy their animal's vitamin D requirement. Recent studies have suggested that adults exposed to UVB in a tanning bed, or children and adults exposed to sunlight can markedly raise their blood levels of vitamin D3 (see Figure 5) [12-17]. The incorporation of UVB radiation into an activity room at a UK nursing home was the most effective way of maintaining circulating concentrations of 25-hydroxyvitamin D3 (25(OH)D) (see Figure 6) [18].

Figure 6

The use of subliminal UVB lighting near the ceiling to produce vitamin D3 in the skin of nursing home residents.

Reproduced with permission [18].

Vitamin D metabolism

Once vitamin D3 is made in the skin or ingested in the diet, it undergoes a 25-hydroxylation in the liver to 25(OH)D [1-2]. Both vitamin D2 and vitamin D3 are converted to 25(OH)D2 and 25(OH)D3, respectively (D represents either D2 or D3). 25(OH)D is metabolised in the kidney to 1,25-dihydroxyvitamin D (1,25$(OH)_2$D). Once formed, 1,25$(OH)_2$D interacts with its specific nuclear vitamin D receptor (VDR) in the small intestine and bone to regulate calcium homeostasis (see Figure 1) [1-2]. Most tissues and cells not related to calcium metabolism also have a VDR, including skin, breast, colon, prostate, brain, pancreas, heart, skeletal, muscle and immune cells [19].

Recently it has been recognised that most tissues in the body also possess the 25-hydroxyvitamin D-1α-hydroxylase

Figure 7

Typical presentation of two children with rickets. The child in the middle is normal; the children on either side have severe muscle weakness and bone deformities including bowed legs (right) or knock knees (left).

(1-OHase; cyp 27B1) [20-22]. Thus the colon, prostate, lung, skin, macrophages and other tissues in the body have the capacity to locally produce $1,25(OH)_2D$. Once formed, $1,25(OH)_2D$ not only alters the transcription of a wide variety of genes that regulate proliferation and differentiation, but also induces its own destruction by enhancing the expression of the 25-hydroxyvitamin D-24-hydroxylase(24-OHase;cyp 24) (See Figure 1) [1, 2].

Vitamin D for bone health

Vitamin D is essential for the development of growth of the skeleton and for the maintenance of good bone health. Vitamin D deficiency causes rickets in children, resulting in growth retardation and bone deformities, especially of the long bones in the legs (see Figure 7) [1, 2].For adults, vitamin D deficiency is more subtle, causing osteomalacia and precipitating and exacerbating osteoporosis. Osteoporosis is a silent disease until fracture occurs. Osteomalacia, however, is often associated with isolated or generalised aching bone pain, muscle weakness and muscle discomfort. Often these patients are misdiagnosed as having fibromyalagia, or chronic fatigue syndrome, and are treated with a nonsteroidal anti-inflammatory agent [23-26].

Vitamin D and prevention of chronic diseases

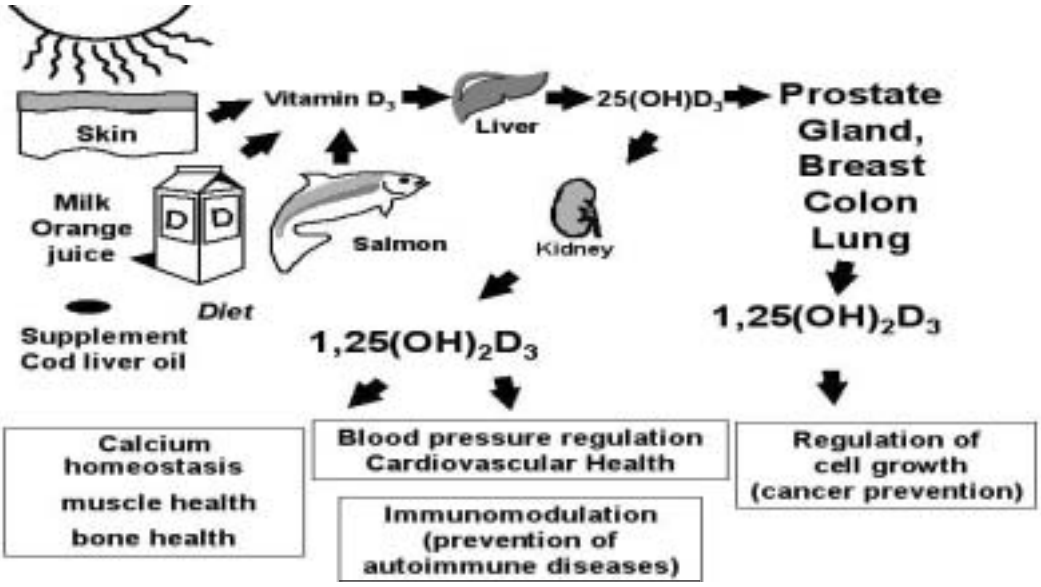
There is strong epidemiological evidence that living at higher latitudes increases your risk of many serious chronic diseases, including colon, breast and prostate cancer, type I diabetes, multiple sclerosis, hypertension and cardiovascular heart disease [1, 2, 27-45]. With the recognition that most tissues and cells in the body can produce $1,25(OH)_2D3$ locally, it is now better understood how the association of increased exposure to sunlight results in a decrease in the risk of these serious and common diseases. By raising the blood levels of 25(OH)D the 25(OH)D can be converted to $1,25(OH)_2D$ in most tissues in the body. Once formed, $1,25(OH)_2D$, among its many other functions, inhibits cancer cell growth, modulates the immune system, enhances muscle strength, increases the production of insulin and decreases the production of renin (see Figure 8) [1, 2].

Definition of vitamin D deficiency and intoxication

Most experts agree that a 25(OH)D of at least 20 ng/ml (50 nmol/l) is the minimum level for vitamin D sufficiency. However, to maximise the effect of vitamin D for health, a 25(OH)D level should be at least 30 ng/ml (75 nmol/l) [1, 46, 47]. Studies have shown that, above 30 ng/ml, PTH (parathyroid hormone) levels are at their ideal minimal concentration [46, 47, 48]. In addition, 25(OH)D above 30 ng/ml maximises intestinal calcium absorption and also provides most cells and tissues in the body with enough substrate 25(OH)D to make $1,25(OH)_2D$ [46].

Most reports suggest that vitamin D intoxication occurs when 25(OH)D levels are above 150 ng/ml (375 nmol/l) [49]. Vitamin D intoxication by definition is a markedly elevated 25(OH)D level greater than 150 ng/ml and associated with hypercalcaemia, hypercalciuria and often hyperphosphataemia. This can lead to renal calcification, nephrocalcinosis, soft tissue calcifications and kidney stones.

Figure 8



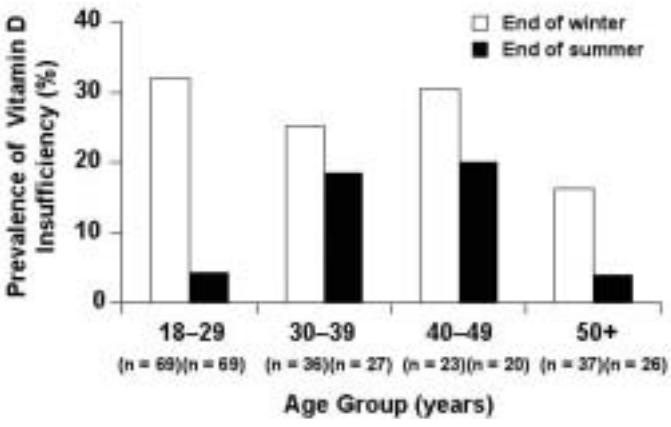
Metabolism of 25(OH)D3 to 1,25(OH)$_2$D3 in kidney and other organs, and the biological consequences.
(Copyright Michael F. Holick, 2001, used with permission.)

Recommendation

More than 90% of most people's vitamin D requirement comes from casual exposure to sunlight. Aggressive sun protection will result in vitamin D deficiency if there is inadequate vitamin D intake from the diet and supplemental sources. Very few foods naturally contain vitamin D. These include oily fish such as salmon, mackerel and herring and typically they contain 400-500 IUs/3.5 oz. In the United States and Canada milk is fortified with vitamin D. However, most European countries forbid the fortification of milk with vitamin D because of an outbreak of vitamin D intoxication in the 1950s [50]. Thus, Europeans are at very high risk of vitamin D deficiency.

It has been estimated world wide that between 30 and 50% of both children and adults are at risk of vitamin D deficiency (see Figure 9) [51-61]. This is especially true for people of colour because of their diminished capacity to make vitamin D in their skin from casual exposure to sunlight. It has been estimated that exposure to sunlight in a bathing suit to one minimal erythemal dose (MED), which is equivalent to a slight pinkness to the skin and not a sunburn, resulted in the production of vitamin D that is equivalent to taking an oral dose of between 10,000 and 25,000 IUs of vitamin D2 (see Figure 10) [1, 2]. Thus, the skin has a large capacity to make vitamin D3 and only minimum exposure for a limited time is necessary to satisfy the body's vitamin D requirement. This is even true for elderly people, who have a diminished ability to make vitamin D3 in their skin.

Figure 9



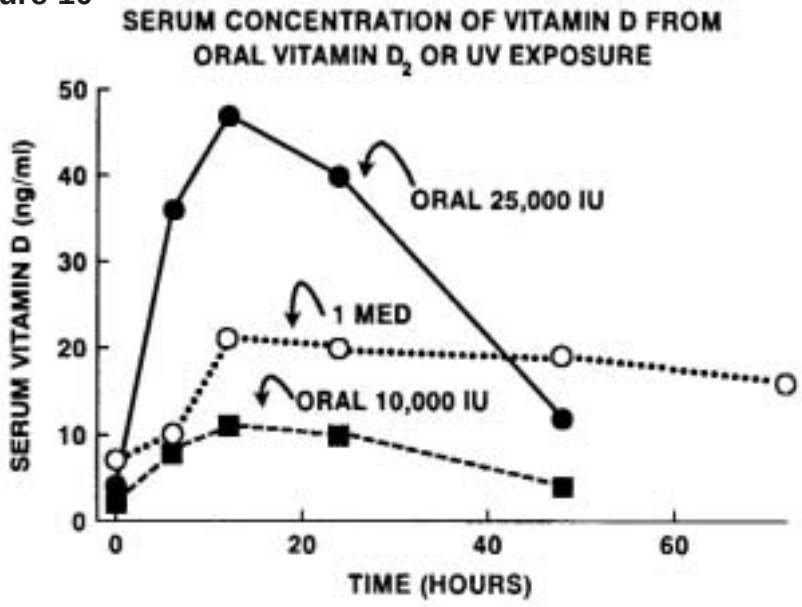
Percentage of subjects in the four age groups who were vitamin D deficient (25-hydroxyvitamin D level<20 ng/ml) at the end of winter and at the end of summer. There was a significant difference in the proportion of subjects with vitamin D insufficiency between the end-of-winter and end-of-summer groups (P<0.05).

Reproduced with permission (Am J Med 2002;112:659-662).

An alternative is to obtain vitamin D from sun exposure to an artificial ultraviolet B radiation source such as a tanning bed or a room that is outfitted with ultraviolet B radiation [12,13,14,16,18]. Both have been successful in raising blood levels of 25(OH)D in both healthy adults and in elderly infirm patients. The tanning bed is also very effective in maintaining adequate 25(OH)D levels in patients with fat malabsorption syndrome such as Crohn's disease, Whipple's disease and severe hepatic failure [62].

It has been estimated that the body uses 5,000 IUs of vitamin D3 a day [63]. In order to sustain adequate blood levels of 25(OH)D above 30 ng/ml it is necessary to ingest 1,000 IUs of vitamin D3 a day [64]. It is known that vitamin D2 is about 20 to 40% as effective as vitamin D3 in maintaining 25(OH)D levels [65].

Figure 10



Comparison of serum vitamin D levels after a whole-body exposure to 1 MED of simulated sunlight, compared with a single oral dose of either 10,000 or 25,000 IU of vitamin D2.
Reproduced with permission (Holick, MF. Vitamin D in health and prevention of metabolic bone disease. In: Osteoporosis: Diagnostic and Therapeutic Principles [ed. Rosen, C].) Humana Press, Totowa, NJ, 1996;29-43).

Vitamin D deficiency should be aggressively treated. The vitamin D tank is empty and needs to be filled. This can be accomplished by giving pharmacological doses of vitamin D, such as 50,000 IUs of vitamin D2 once a week for eight weeks, followed by maintenance with 50,000 IUs of vitamin D2 once every other week. Alternatives are to give 100,000 IUs of vitamin D3 every two to three months; 50,000 IUs of vitamin D2 every other week is equivalent to taking about 30,000 IUs of vitamin D3, and thus, 1,000 IUs of vitamin D3 a day, or 30,000 to 50,000 IUs of vitamin D3 once a month, or 100,000 IUs of vitamin D2 once a month will maintain healthy 25(OH)D levels [66]. Intramuscular and intravenous vitamin D administration have often proved ineffective in maintaining 25(OH)D levels.

Conclusions

The photosynthesis of vitamin D has been occurring on earth for more than 750 million years [1, 2]. Phytoplankton, zooplankton and most vertebrates have depended on the sun for their vitamin D requirement. Vitamin D is not only important for maintaining and maximising bone health, but also has a wide range of other functions that are critically important for maximising overall health and well-being.

There needs to be a re-evaluation of the beneficial effects of sunlight. There is no question that chronic excessive exposure to sunlight increases the risk of squamous and basal cell carcinoma of the skin [67]. However, by contrast, lifetime moderate sun exposure appears to be associated with a lower risk of malignant melanoma [67]. Most melanoma occurs on the least sun-exposed areas. Recently it has been reported that those with the most sun exposure were less likely to die of malignant melanoma once they developed the disease, and that high frequency of sunbathing by age 20 reduced the risk of non-Hodgkin's lymphoma by 30 to 40% [68, 69].

The recent recommendation by the New Zealand Bone and Mineral Society, the Australian College of Dermatologists and the Cancer Council of Australia, suggesting that balance is required between avoiding an increased risk of skin cancer and achieving enough UV radiation to maintain adequate vitamin D levels is most welcome. Hopefully this recommendation will be embraced by the regulatory agencies and the dermatology societies in Europe and the United States. It's time to stop demonising the sun and appreciate the wealth of benefits that sunlight has for human health and for the prevention of many serious chronic diseases.

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Health consequences of insufficient vitamin D

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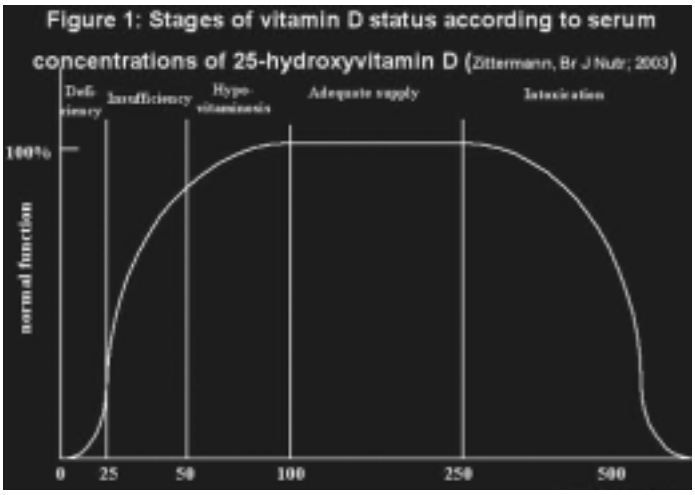
During the 18th and the 19th century, the process of industrialisation and urbanisation was associated with low sun exposure among a large percentage of infants, leading to a high prevalence of vitamin D deficiency. As a consequence rickets, also known as the English disease, was very frequent. Since the early 20th century, highly effective preventive measures such as fortification of infant foods with vitamin D, exposure of young children to artificial UV lamps, and vitamin D supplementation have helped to make rickets rare nowadays in Europe. However, there is increasing evidence that vitamin D insufficiency or even deficiency is a major health problem in adults (see later).

Vitamin D physiology and pathophysiology

Sunlight is the major provider of vitamin D for humans. The UVB spectrum of sunlight (290-315 nm) induces skin synthesis of pre-vitamin D3 from its precursor, 7-dehydrocholesterol. Food is a second source of vitamin D, but only a few foods such as eel, herring and salmon are good vitamin D sources (15-30 µg [600-1,200 IUs] per 100g edible portion). Consequently, dietary vitamin D usually contributes only 10-20% of human vitamin D supply.



The different stages of vitamin D status are deficiency, insufficiency, hypovitaminosis, adequacy, and toxicity (see Figure 1). Circulating 25(OH)D is the hallmark for determining vitamin D status. In the case of vitamin D deficiency, severe clinical symptoms such as osteomalacia, myopathy, severe secondary hyperparathyroidism (SHPT) – a serum parathyroid hormone (PTH) level of more than 65 picograms per millilitre (pg/ml) – and calcium malabsorption are seen. In the insufficient stage, pathophysiological biochemical alterations such as mild hyperparathyroidism and low intestinal calcium absorption rates are present. However, severe clinical symptoms are usually not observed. Hypovitaminosis D characterises a stage where the body stores of vitamin D are already below physiologically desirable levels. Only minor functional alterations such as slightly elevated serum PTH levels are seen. In the stage of adequacy, no disturbances of vitamin D-dependent body functions occur, while toxicity is due to vitamin D-dependent adverse reactions such as calcium hyperabsorption from the gut and net calcium resorption from bone, leading to hypercalcaemia.

Vitamin D status

In a summary of a large number of studies from North America and Europe on vitamin D status in young adults and elderly subjects, through to the end of the 1980s, healthy elderly subjects had mean 25(OH)D levels in the insufficiency range throughout the year [1]. In institutionalised subjects, most 25(OH)D levels were in the deficiency range. In Europe, young adults often had circulating 25(OH)D levels in the insufficiency range during winter.

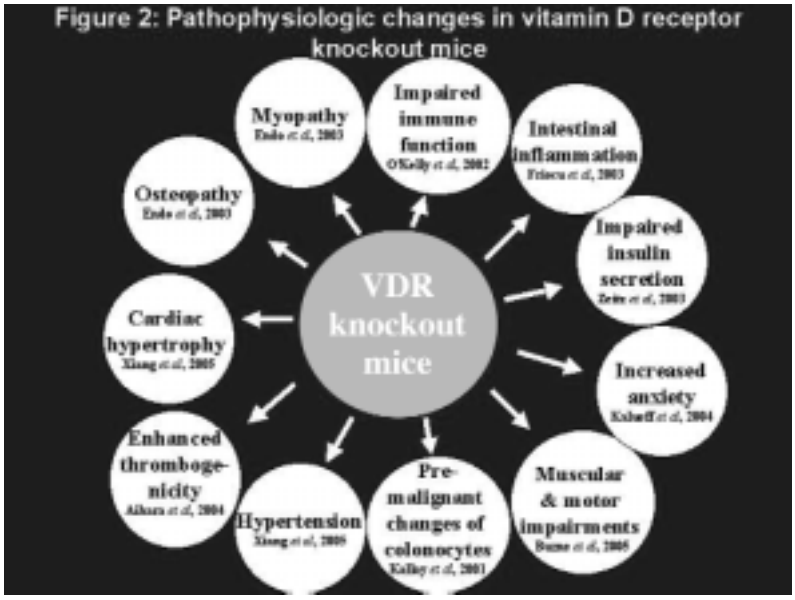
Alarming results have recently been reported in urban dwellers in Europe [2]. Middle-aged urban dwellers in Hungary had only modest seasonal variations in circulating 25(OH)D levels, and a high percentage of subjects had a low vitamin D status throughout the year, despite marked seasonal fluctuations in daily sunshine. The prevalence of 25(OH)D levels below 50 nmol/l during spring, summer, autumn and winter was 71%, 46.3%, 49.4%, and 56.7%, respectively.

Similarly, white British people in an outpatient clinic at a city hospital had mean 25(OH)D levels around 50 nmol/l throughout the year without seasonal fluctuations [3]. Moreover, mean 25(OH)D levels below 30 nmol/l in summer and below 15 nmol/l in winter were reported in South Asian immigrants in Great Britain. Very low mean 25(OH)D levels of 8 nmol/l in winter and 18 nmol/l in summer were observed in Indian physicians and nurses living in Delhi [4]. They had a daily sun exposure of only 25 minutes.

While elderly subjects and dark-skinned people living at Northern latitude are worst affected, a significant percentage of all age groups is at risk of insufficient vitamin D status. There is now increasing evidence that vitamin D insufficiency may play a role in the aetiology of various chronic diseases such as osteoporosis, hypertension, cardiovascular disease and diabetes mellitus. All these diseases are frequent in industrialised countries. Experimental studies support the assumption that the health consequences of inadequate vitamin D supply are manifold.

Experimental studies

Ex-vivo tissue studies have demonstrated that vitamin D receptors can be found in almost all mammalian tissues. Recently, two different groups of scientists have also generated vitamin D receptor-deficient (VDR) mice. Similar to patients with severe vitamin D deficiency, this animal model develops severe hypocalcaemia and secondary hyperparathyroidism [5,6]. Therefore, vitamin D receptor knockout mice provide an excellent possibility to study the health consequences of vitamin D deficiency *in vivo*. These animals have to be fed with supraphysiological amounts of calcium in order to avoid progressive worsening of the disease. The vitamin D receptor knockout mice develop a wide range of pathophysiological changes (see Figure 2). Beside bone diseases such as osteomalacia and osteoporosis, these changes include myopathy, cardiovascular risk factors, behavioural changes, altered immune response, impaired insulin secretion, and premalignant changes of specific cell lines. The wide range of adverse effects in vitamin D receptor knockout mice is in line with the wide tissue distribution of the vitamin D receptor.



Osteoporosis

Carefully performed intervention trials have demonstrated that vitamin D supplementation, in combination with an adequate calcium supply, is able to reduce osteoporotic fracture risk in elderly subjects [7-9]. Although some recently performed intervention studies have questioned the beneficial effects of oral vitamin D supplementation on fracture prevention [10-12], these investigations contain several flaws. The study by Aloia *et al* [10] was performed

in Afro-Americans, a population that has a relatively low risk of developing osteoporotic fractures; in the studies by Porthouse *et al* [12] and Grant *et al* [11], the supplemented vitamin D dose was rather low (20 µg, or 800 IUs, a day) and no serum concentrations of 25-hydroxyvitamin D levels were measured during follow-up, making it impossible to assess study compliance. In order to reduce fracture risk significantly, a serum 25-hydroxyvitamin D level of at least 70 nmol/l is necessary. Moreover, we have to keep in mind that osteoporosis is a paediatric disease. Peak bone mass, which is usually achieved in the second or third decade of life, is an important predictor of the risk of developing osteoporosis in later life. In this context, it is central that the increase in bone mineral density in young adolescent girls is directly related to serum 25-hydroxyvitamin D levels [13].

Diabetes mellitus

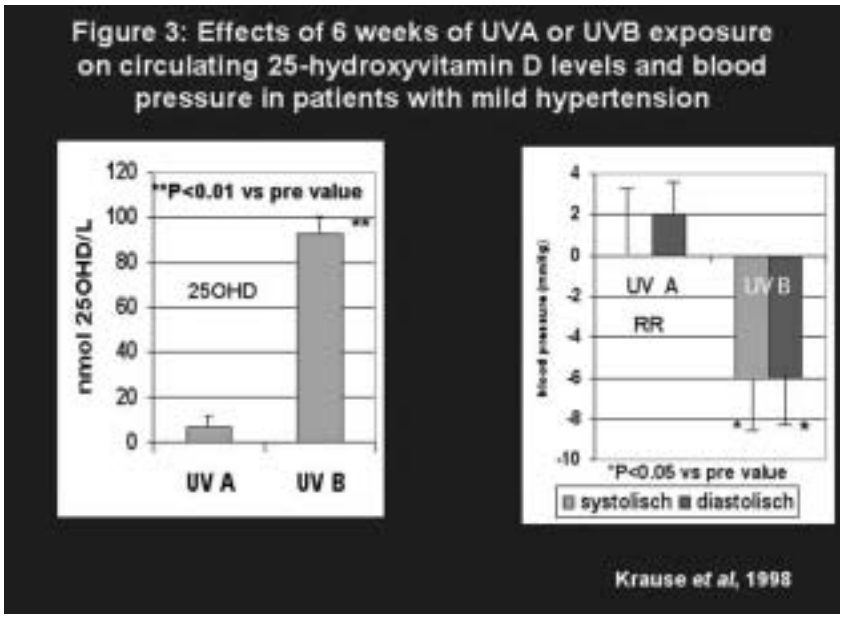
The prevalence of diabetes mellitus is four- to five-fold higher and serum 25(OH)D is significantly lower in dark-skinned Asian immigrants in the UK than in British Caucasians [14,13]. Moreover, serum glucose and the prevalence of diabetes rise [15] and serum 25(OH)D falls with age [1]. In a study performed in elderly subjects with insufficient vitamin D status (mean 25[OH]D levels: 42 nmol/l), the subgroup with the lowest tertile of 25(OH)D had a significantly higher blood glucose increase and a higher blood insulin increase after an oral glucose load, compared with the subgroup with the highest tertile of 25(OH)D levels [16].

In a large study with glucose-tolerant young subjects whose 25(OH)D levels ranged between six and 200 nmol/l, 25(OH)D showed an independent negative relation with plasma glucose at fasting, 90 minutes, and 120 minutes during an oral glucose tolerance test [17] Moreover, there was also an independent positive correlation between 25(OH)D and the insulin sensitivity index.

In a Finnish study, regular vitamin D supplementation of 50 µg/day during infancy in the 1960s was associated with a marked reduction in the risk of type I diabetes 30 years later, in comparison with un-supplemented infants (relative risk 0.12). Children suspected of having rickets during the first year of life had a three-fold increased prevalence of type 1 diabetes, in comparison with those not thought to have had rickets [18].

Hypertension

It has been demonstrated that regular exposure to UVB radiation but not to UVA radiation increases circulating 25(OH)D above a level of 100 nmol/l and also significantly reduces blood pressure by approximately six mmHg in hypertensive patients with initial 25(OH)D levels of 26 nmol/l, within an intervention period of six weeks [19] (See Figure 3).



In another study, elderly women were supplemented with calcium and 20 µg vitamin D daily, or with calcium alone [20]. Initial 25(OH)D levels in the two study groups were 24.6 and 25.7 nmol/l, respectively. Compared with calcium supplementation alone, supplementation with vitamin D and calcium resulted in an increase in serum 25(OH)D

of 72 %, a decrease in serum PTH of 17 %, a decrease in systolic blood pressure of 9.3 %, and a decrease in heart rate of 5.4 %.

Cardiovascular disease

In humans, strong evidence of a role for vitamin D in the pathogenesis of cardiovascular disease comes from patients with end-stage renal disease (ESRD). In these patients, adjusted cardiovascular mortality is 10 to 20 times higher compared with the general population [21]. In patients with ESRD, the vitamin D metabolite, 1α-vitamin D, and the vitamin D analogue, paricalcitol, are very effective drugs in reducing the risk of death from cardiovascular disease [22,23]. ESRD is also frequently associated with vascular calcification, and the very high serum PTH levels are regarded as an important risk factor in the pathogenesis of cardiovascular disease [24].

In the general population, the presence of vascular calcification is a predictor of poorer five-year survival [25]. Keeping in mind the inverse relationship between 25(OH)D and PTH, it is interesting that in the Tromsø study the rate of coronary heart disease was higher in the subjects with serum PTH › 62 pg/ml than in those with normal or low serum PTH levels (relative risk 1.67 in men and 1.78 in women) [26]. When the mean 25(OH)D concentrations from different studies in children, adolescents, and young adults are plotted against geographic latitude, an inverse association between 25(OH)D and geographical latitude does exist, while there is a direct association between geographical latitude and ischaemic heart disease (see Figure 4).

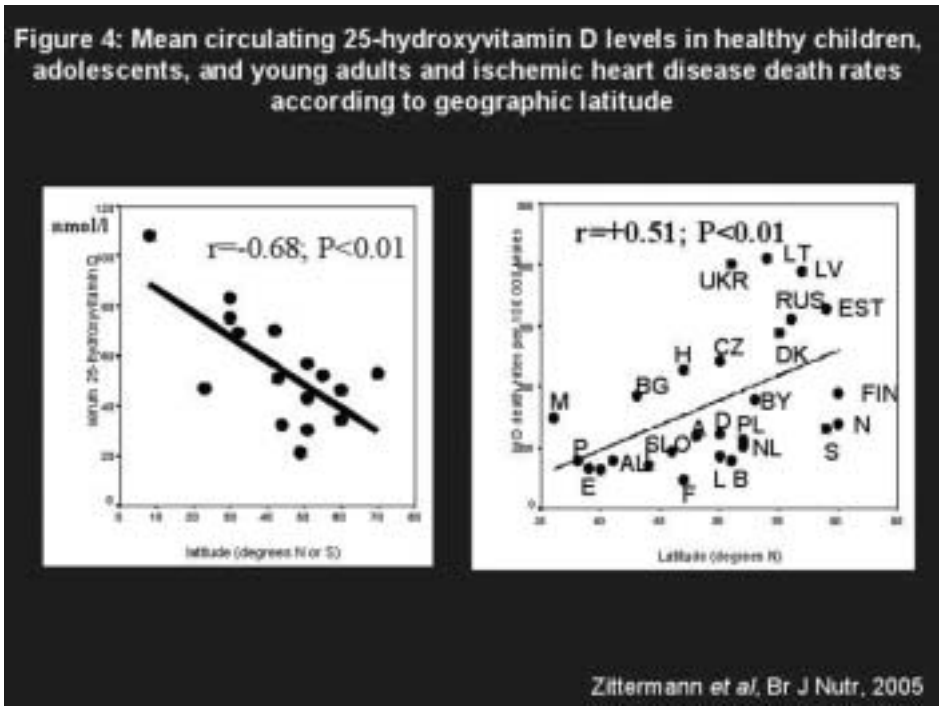


Figure 4: Mean circulating 25-hydroxyvitamin D levels in healthy children, adolescents, and young adults and ischemic heart disease death rates according to geographic latitude

Inflammatory and autoimmune diseases

The active vitamin D metabolite calcitriol is an important modulator of the immune system. Calcitriol is able to suppress pro-inflammatory cytokines and to enhance anti-inflammatory cytokines. A disturbed cytokine metabolism seems to play an important role in the aetiology of rheumatoid arthritis and also of multiple sclerosis. In patients with rheumatoid arthritis, treatment effects of activated vitamin D are dose-dependent. Moreover, high doses of vitamin D and 25-hydroxyvitamin D are also able to significantly improve pain symptomatology (see Figure 5).

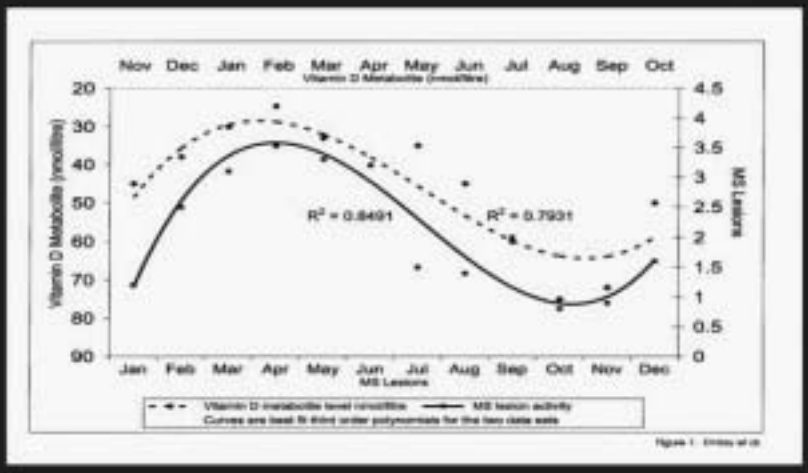
There is increasing evidence from animal studies and from epidemiological and intervention studies in humans that vitamin D insufficiency increases the risk of developing multiple sclerosis [27]. In patients with multiple sclerosis in South Germany, seasonal variations in disease activity are inversely related to seasonal fluctuations in vitamin D status (see Figure 6).

Figure 5: Results of intervention studies with vitamin D (metabolites) in patients with rheumatoid arthritis

Duration	Treatment	Results
8 weeks	I µg 1α Vitamin D/d	No effects
16 weeks	I oder 2 µg 1α Vitamin D/d	No effects
3 months	2 µg 1α Vitamin D/d	Reduced disease activity
1-2 years	2500 µg 1α Vitamin/d	Reduced disease activity
30 days	50 µg 250HD/d	Pain reduction

References: Hein & Öitzner, 2000; Yamauchi *et al*, 1989; Andjelkovic *et al*, 1999; Brohult & Jonson, 1973; Dottori *et al*, 1982

Figure 6: Disease activity in German patients with multiple sclerosis in relation to vitamin D status



Reference: Embry *et al*, 2000

Prevention of vitamin D insufficiency

At present, no effective strategies exist in Europe to improve the vitamin D status of those adults who are at risk of vitamin D insufficiency. There is no doubt that environmental UVB exposure is the most important natural source of vitamin D. Therefore, strategies to improve vitamin D status should include regular weekly UVB exposure (for example, one-quarter of one minimal erythemal dose [MED] most days of the week). The use of lamps with artificial UVB, in a tanning bed for instance, would offer the opportunity to improve vitamin D status at home. Such a measure would also have the advantage that exact recommendations could be given for UVB exposure times as well as for the percentage of body surface which should be exposed to the UVB radiation. Dietary intakes that are needed to maintain adequate circulating 25(OH)D levels range between 50 and 100 µg (2000-4000 IUs) daily [28,29]. Since almost all foods naturally contain less than 10 µg (400 IUs) of vitamin D per 100 g edible portion, dietary advice would not be a good choice. Even fortified foods are usually enriched with not more than 10 µg vitamin D per 100 g edible portion. However, a daily vitamin D supplement could be very effective. Unfortunately, over-the-counter supplements usually contain no more than 25 µg vitamin D per tablet and in some countries, such as Great Britain, they contain even less. Thus, a minimum of 2-4 tablets have to be taken to achieve adequate circulating 25(OH)D levels in the absence of UVB exposure. Such a measure may be impractical for a high percentage of people at risk. Prevention of vitamin D insufficiency or deficiency must become a major target for public health services in the future. Many countries will have to change their guidelines on UVB exposure and/or their food legislation.

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Genes, environment and prostate cancer risk: sunlight and vitamin D-related genes

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Prostate cancer is a major cause of morbidity and mortality, accounting for 10,164 deaths in the United Kingdom in 2003 [1]. The lifetime risk of being diagnosed with prostate cancer is one in 13 [2]. Prostate cancer is the second biggest cancer killer in males, resulting in 13% of all cancer deaths [1]. In the United States, prostate cancer is now the leading cause of cancer death for males, having recently overtaken lung cancer. With an ageing population, prostate cancer incidence will increase and consume an increasing proportion of healthcare resources. Its causes are multifactorial, with risk dependent on interactions between environmental and genetic factors. Twin studies suggest that prostate cancer risk is approximately equally derived from genetic and environmental factors [3].

In this review we consider evidence indicating that ultraviolet radiation (UVR), skin pigmentation and related genetic factors mediate prostate cancer susceptibility.

We provide support for this view by considering four questions that we argue are linked to the hypothesis: (1) Are levels of UVR exposure lower in prostate cancer cases than controls? (2) As skin type mediates UVR-induced cutaneous synthesis of vitamin D, is it associated with prostate cancer risk? (3) If skin type mediates prostate cancer risk, are polymorphisms associated with this phenotype determinants of prostate cancer risk? (4) If UVR mediates risk through a vitamin D-related mechanism, do polymorphisms in the vitamin D receptor (VDR) influence risk?

Ultraviolet radiation

Humans are repeatedly exposed to UVR in daily life. Sunlight reaching the earth's surface comprises UVR (wavelength, 290-400 nm) and visible light (400-780 nm). UVR has a direct effect on the skin, leading to formation of cyclobutanepyrimidine dimers that can give rise to characteristic DNA mutations. [4]. Such mutations are linked to skin cancers by a complex series of events. Excessive UVR exposure is also related to immune suppression, premature ageing of skin and cataract formation [5]. Accordingly, public health, government and scientific agencies including Cancer Research UK have emphasised the dangers of sunlight and the need to adopt lifestyles that reduce exposure.

Despite these adverse associations, UVR offers substantial health benefits. The importance of this was recognised in the early 20th century with the realisation that inadequate exposure to sunlight, particularly common in industrialised areas, was associated with rickets. This resulted from inadequate vitamin D synthesis due to pollution blocking UVR passage to the earth. Over recent years it has become clear that, apart from its essential role in preventing rickets, vitamin D has a vital role in many key biochemical, immunological and carcinogenic pathways.

(1): Are levels of UVR exposure lower in prostate cancer cases than controls?

As early as the 1930s, there were reports that extent of exposure to UVR was inversely related to certain cancer mortality rates. It was not until 1980 that an ecological study linked colon cancer mortality in the United States to extent of exposure to UVR and production of vitamin D [6]. Further ecological studies have found similar inverse relationships between non-Hodgkin's lymphoma, ovarian and breast cancer [7-11]. In 1990 Hanchette and Schwartz looked at prostate cancer mortality data in the United States [9]. They found that prostate cancer mortality exhibited a significant north-south trend, with lower mortality rates in the sunnier south.

These data, based on an ecological approach, support the hypothesis that UVR protects against sporadic prostate cancer. Subsequent ecological studies have shown similar relationships for cancers of the breast, bladder, colon, oesophagus, kidney, lung, ovary, pancreas, rectum, stomach and uterus and regional UVR [12]. While interesting, it has been suggested that data derived from an ecological approach require cautious interpretation because associations may result from unrecognised confounding factors.

We hypothesised that UVR exposure is protective against development of prostate cancer via a mechanism in-

volving individual vitamin D status. In 1999, we initiated a study into the relationship between UVR and prostate cancer susceptibility, based on 210 prostate cancer cases and 155 benign prostate hypertrophy (BPH) controls [13]. All men were North European Caucasians resident in North Staffordshire (latitude 53.01° N). We used a previously validated questionnaire to determine acute and chronic UVR exposure patterns.

Low cumulative exposure to UVR was associated with increased risk of prostate cancer (odds ratio=3.03, 95% CI [confidence interval]=1.59-5.78). We showed that childhood sun-burning (odds ratio=0.18, 95% CI=0.08-0.38), regular foreign holidays (odds ratio=0.41, 95% CI=0.25-0.68) and regular sunbathing (odds ratio=0.83, 95% CI=0.76-0.89) were associated with reduced risk of prostate cancer. Furthermore, cases with low UVR exposure developed cancer at a significantly (p=0.006) younger median age (67.7 years, inter-quartile range [IQR]=61.5-74.6) than cases with higher exposure (72.1 years, IQR=67.5-76.4); p=0.006. These findings are compatible with UVR having a protective role against prostate cancer susceptibility.

Because we had studied only a small group we performed a confirmatory study starting in 2001, comprising 212 new prostate cancer cases and 135 BPH controls, to determine whether our previous findings, showing a protective effect for UVR exposure, could be reproduced [14]. Data from this new study confirmed that higher levels of cumulative exposure, childhood sun-burning, adult sunbathing and regular holidays in hot climates were again each independently and significantly associated with a reduced risk of prostate cancer. Collectively, these two studies add further evidence for the relationship between UVR exposure and prostate cancer, at least in northern Europe, an area with limited sun exposure for about half the year.

Data indicating that the association between UVR and prostate cancer risk was relevant in sunny environments come from recent studies by John *et al* in Caucasian Americans from the San Francisco area of California [15]. John *et al* measured constitutive pigmentation on the upper arm (a sun-protected site) and facultative pigmentation on the forehead (a sun-exposed site), using a reflectometer as a surrogate for UVR exposure, and calculated a forehead/upper arm index. Risk of advanced prostate cancer was reduced in patients with high sun exposure as assessed by the index. While it has been argued that there is no formal relationship between forehead/upper arm index and chronic exposure [16] these data provide further support for the UVR hypothesis.

Clearly, a problem with assessing the link between UVR and cancer risk (and ultimately agreeing safe levels of exposure) is our ability to accurately assess the intensity and duration of an individual's UVR exposure patterns over a lifetime. Our questionnaire recorded various parameters of UVR exposure. When assessing lifetime UVR exposure retrospectively, individuals may suffer from recall bias. Our questionnaire assesses sunbathing score, regular foreign holidays in sunny climates, time spent indoors/outdoors at work, as well as cumulative UVR exposure.

We believe this sunbathing score offers a realistic measurement of deliberate UVR exposure. Many people sunbathe within the critical time period of 11a.m. to 3p.m., when UVR intensity is maximal. What is often not recorded or recalled is whether individuals used sunscreen or covered up their body during this exposure period, and the extent to which this could affect UVR efficacy. Regular foreign holidays suggest individuals have increased UVR exposure and this may allow increased vitamin D levels. Time spent working indoor and outdoors is not necessarily a good measure of exposure. Individuals do not always expose themselves to UVR while working outdoors and, with no vitamin D being produced from October to April in the UK, this measurement is not very specific. We tended to use cumulative exposure as one of the main factors in determining UVR exposure. The questionnaire recorded median levels of exposure of 1,100 hours a year (approximately three hours a day), which appears high and which includes the non-vitamin D productive months between October to April. Thus, this parameter may not be an accurate reflection of vitamin D levels.

Unfortunately, there is no suitable alternative to date. 25-hydroxy vitamin D (25(OH)2D) levels have been examined, but these only reflect a snapshot in time and can vary substantially with seasons [5]. The aetiological steps of tumorigenesis are likely to develop over a long period of time and point measurements of 25(OH)2D levels may not provide an accurate representation of long-term vitamin D adequacy. What is needed is a marker for long-term vitamin D levels, like the glycosylated haemoglobin 1C (HbA1c) used to access long-term serum glucose levels.

UVR exposure is difficult to calculate, and the parameters we have used are semi-qualitative measures. Combinations of several of these parameters may offer a more realistic view of chronic UVR exposure.

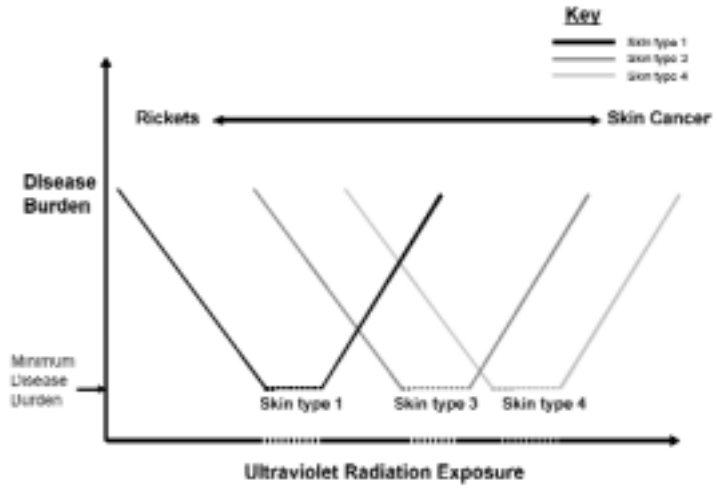
(2): As skin type mediates UVR-induced cutaneous synthesis of vitamin D, is it associated with prostate cancer risk?

Skin pigmentation mediates an individual response to UVR. Thus, deeply pigmented skin has a sun-protective factor of about 10 compared with a pale skin [17]. Skin type can readily be classified using the Fitzpatrick skin

classification. This defines four main types of skin response to UVR in Caucasians. Type 1 skin always burns and never tans, type 2 usually burns and tans gradually, type 3 burns rarely and tans gradually and type 4 never burns and readily tans. Assigning individuals into these groups is usually straightforward, though there is overlap (particularly between types 2 and 3), and with increasing exposure individuals can move groups.

The Radiation and Environmental Health unit of the World Health Organisation (WHO) proposed a U-shaped curve relating exposure to UVR and disease burden [18]. This curve demonstrates that as exposure to UVR is increased, the disease burden level decreases (see Figure 1). This is evident in the case of rickets. With increasing exposure, rickets disappears and disease burden lessens. There comes a point where the curve flattens out and where it is estimated health is optimised. Once UVR exposure increases past this point, disease burden increases because of increased risk of skin cancer. Skin type affects an individual's response to UVR, so the different skin types have alternative starting positions on the graph. Therefore, individuals have their own optimal exposure level. Such UVR levels have been proposed for skin types and latitude by Holick [19].

Figure 1



Individuals have differing UVR exposure patterns and the impact of these may vary with host factors such as skin type. We hypothesise that 'ideal' UVR exposure varies with individual skin type.

It could be hypothesised that since men who tan readily have high melanin levels in skin and produce less vitamin D they will be at highest risk of prostate cancer. Unfortunately, human conditioning means that at least some individuals with sun-sensitive skin (skin types 1 and 2) tend to avoid UVR [20]. Accordingly, it is possible that some skin type 1 individuals develop less prostate cancer because they synthesise vitamin D more effectively, or that they contract more prostate cancer due to their sun avoidance.

We hypothesised that the impact of skin type on risk would be related to the level of UVR exposure. We investigated whether skin type and level of UVR exposure were associated with prostate cancer risk in 453 cancer cases and 312 BPH controls [20]. Using a recursive partitioning approach, we examined if the effects of skin type 1 were more evident in men with low levels of cumulative exposure per year or low sunbathing score. This type of analysis allows prediction of a dependent variable on the basis of a number of predictors. The software algorithm partitions predictors (cumulative exposure per year, sunbathing score and skin type) so that more homogenous groups (cases or controls) are obtained. In the first partition the algorithm lists the predictors in order of their Bonferroni-corrected p values. The algorithm then effects further partitioning into each node.

Analysis showed that in men who never or very rarely sunbathed, those with skin types 2-4 were at significantly increased risk of prostate cancer compared with skin type 1. In those men with high UVR exposure levels skin type did not have an association with prostate cancer. While these results do not prove the hypothesis, they suggest that in individuals with low UVR exposure, inability to pigment is beneficial. We interpret this effect to be due to increased vitamin D synthesis.

(3): If skin type mediates prostate cancer risk are polymorphisms associated with this phenotype determinants of prostate cancer risk?

Humans differ from other primates in that they have lost most of their body hair [21]. This enables humans to sweat more effectively but has the detrimental effect of reducing skin protection against UVR-induced damage [21].

Humans synthesise melanin from tyrosine in a reaction catalysed by tyrosinase. Melanin helps to absorb electromagnetic radiation both in the visible and ultraviolet wavelengths. This helps protect DNA and other proteins from UVR-induced damage. The two types of melanin, eumelanin (brown black) and pheomelanin (red yellow) exert their effect on individuals' skin pigmentation. For example, pale-skinned, red-haired individuals often have large amounts of pheomelanin and tanned, dark-haired people more eumelanin. Skin response to UVR is linked to skin pigmentation. This means those with paler skin are more sensitive to UVR in terms of burning and vitamin D production.

Human skin pigmentation is a complex genetic characteristic. In man, skin pigmentation is polygenic with a prominent determinant being the melanocortin 1 receptor (MC1R). The MC1R encodes a 317 amino acid G-protein coupled receptor. The gene is intronless (see Glossary) and is highly polymorphic. Binding of α-melanocyte stimulating hormone (α-MSH) to the MC1R leads to increased intracellular cAMP and this alters transcription of a number of key intracellular genes, mostly from the tyrosinase family, which are important in melanin synthesis. MC1R activity is associated with individual phenotypes such as red hair and freckles, a tendency to burn rather than tan and an increased risk of skin cancer.

With our findings that UVR alters susceptibility to prostate cancer and that skin pigmentation alters an individual's response to UVR, we hypothesised that polymorphism in genes that mediate skin pigmentation will influence susceptibility to prostate cancer. We examined susceptibility to prostate cancer in relation to MC1R and tyrosinase single nucleotide polymorphisms (SNPs) [22]. In 210 prostate cancer cases and 155 BPH controls we showed that MC1R Arg(160)/Arg(160) homozygotes were at increased risk (odds ratio=1.94, p=0.027), while tyrosinase A2/A2 homozygotes were at reduced risk of prostate cancer (odds ratio=0.48, p=0.033). These associations remained significant after correction for UVR exposure. Stratification of cases and controls by quartiles of exposure showed that the protective effect of tyrosinase A1/A2 (odds ratio=0.075, p=0.006) and A2/A2 (odds ratio=0.055, p=0.003) was particularly strong in subjects who had received the greatest UVR exposure.

These data showed, for the first time, that genes linked with skin pigmentation synthesis are associated with prostate cancer risk, possibly because they indirectly mediate the protective effects of UVR. Importantly, susceptibility is associated with an interaction between host genetic predisposition and UVR exposure. To date there is no further published work on skin pigmentation genetics and prostate cancer.

Glossary

Cyclic adenosine monophosphate (cAMP): intracellular chemical messenger
Exons: DNA segments in a gene that encode the amino acid sequence of a protein
Introns: DNA in a gene that separates the exons and does not encode the protein
Homozygotes: carry two identical copies of that gene, one maternal and one paternal
Dimerisation: a unit from two chemical structures
Haplotype: the collective genotype of a number of inherited variants on a single chromosome
T/C substitution: change in the base in a sequence of DNA from thymine (T) to cytosine (C)

(4): If UVR mediates risk through a vitamin D-related mechanism, do polymorphisms in the vitamin D receptor (VDR) influence risk?

Systemic or locally produced 1,25-dihydroxy vitamin D ($1,25(OH)_2D$) binds to the nuclear VDR, causing a conformational change in the VDR followed by dimerisation with the retinoid X receptor [23]. This complex interacts with the vitamin D response element (VDRE) in target genes, initiating transcription. 1,25(OH)2D and the vitamin D receptor (VDR) are central to the hypothesis that UVR exposure mediates prostate cancer risk. The UVR hypothesis makes the VDR a good candidate gene to study. The VDR gene is located on chromosome 12 and has over 238 single nucleotide polymorphisms (SNPs) [23]. The VDR has a promoter, coding and regulatory region. The F/f30875 (Fok1) SNP, situated in exon 2, alters transcription, and a T/C substitution causes a smaller protein to be produced [24].

Recently, SNPs have been identified at specific transcription factor binding sites. The G/A1229 (Cdx2) SNP was identified within the exon 1e region of the gene [25]. This is within the binding site of the Cdx2 protein, a transcription factor that regulates VDR gene expression in the small intestines and other tissue [23]. The G/A3944 (GATA) SNP within the exon 1a region was identified in 2004 [26]. This lies within a core sequence of a likely GATA-3 binding site. Polymorphisms within this region have been linked to susceptibility and outcome in malignant melanoma [26].

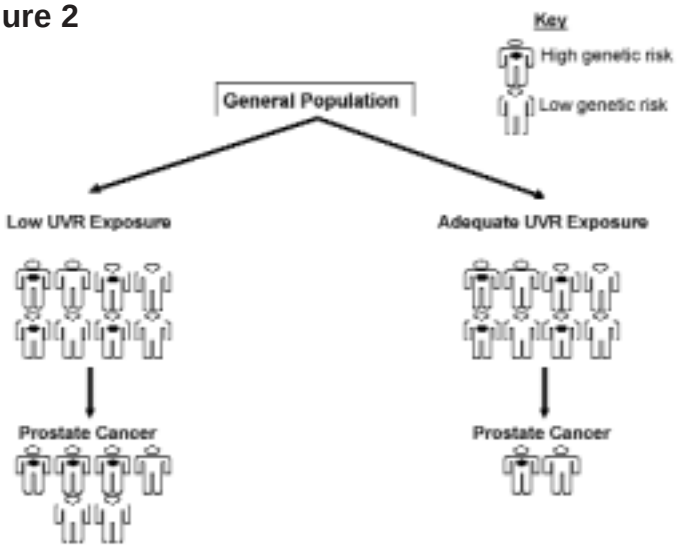
To date, molecular epidemiological studies have shown conflicting results regarding an association of VDR polymorphisms with prostate cancer risk. Early genetic epidemiology studies examined the relationships of the Taq1, poly (A) micro satellite repeat, Bsm1 and Fok1 SNPs. Results were contradictory and inconclusive, in part because many studies were underpowered. Some of these data were included in a recent meta-analysis based on 17 published studies which assessed the associations of Taq1, poly (A), Bsm1 and Fok1 polymorphisms in relation to prostate cancer [27]. These four SNPs were thought to be unlikely to be a major determinant of susceptibility to prostate cancer.

More recently, we examined the relationship of VDR SNPs by stratifying polymorphisms by UVR exposure (a surrogate for vitamin D status) [28,28,29]. We examined SNPs within the promoter and coding region to identify susceptibility candidate genes. The GATA GG genotype, present in the promoter region, was lower in the cancer than in the BPH patients (odds ratio=0.63, 95 per cent CI=0.41-0.98, p=0.039). When we then stratified SNPs by UVR exposure, the Fok1 ff allele was associated with a significant increased risk of prostate cancer with UV exposure greater than the median. For the first time this linked environmental and genetic factors, in the form of UVR exposure and VDR genotype. A confirmatory study by John *et al* in the United States showed similar results [15]. Again, they assessed VDR SNPs and linked genotype frequencies to levels of UVR exposure.

Our most recent work on the VDR has shown that the 5' haplotype promoter region plays an important role in determining susceptibility, and SNPs within this region may have a synergistic effect on prostate cancer risk (unpublished data). This is supported by new evidence suggesting that SNPs in this region do have functional significance [30].

Our work has shown that prostate cancer susceptibility is mediated by UVR [28,29] We have also predicted, on the basis of the hypothesis, genetic factors that are important in determining susceptibility to sporadic prostate cancer [22,28,29,31]. Combinations of genetic and environmental factors have further strengthened the relationship. Thus, in the general population there are individuals with strong genetic risk while others have a lifestyle that confers a strong environmental risk. Who does and does not develop prostate cancer depends on the impact of these and presumably other largely uncharacterised factors such as diet (see Figure 2).

Figure 2



Suggested influence of gene-environmental interaction in determining susceptibility to prostate cancer. Individuals with high genetic risk and low UVR exposure have a high risk of prostate cancer. Individuals with adequate UVR exposure and low genetic risk are at low risk of prostate cancer.

Migration studies

If the UVR/vitamin D story is correct, we may be able to identify individuals who are at increased risk of disease or advise more scientifically on disease-avoidance approaches. Using prostate cancer as an example, we would expect increased rates of prostate cancer in males who have emigrated from Africa and Asia to Northern Europe. Thus, they receive less UVR exposure in Northern Europe compared to their native continents. The same may be true for a Caucasian population. If Caucasians move to an area where UVR exposure is high compared to their native climate, we might expect lower rates of cancer. Australia is a potentially interesting test bed since its Caucasian population arises mainly from the United Kingdom and Ireland, where UVR exposure is relatively low. We might simplistically expect that the descendants of Caucasian immigrants to Australia will have higher levels of UVR exposure than their UK relatives and, accordingly, less prostate cancer.

It is emphasised, however, that there does not need to be a clear relationship between ambient exposure and

that received by an individual. Indeed, an important factor regarding UVR exposure is sun avoidance. Due to increased rates of skin cancers many people practise sun avoidance, so actual UVR exposure in individuals in sunny climates may be similar to that of Northern Europeans. Data from the Australian Institute of Health and Welfare show that the incidence of prostate cancer has remained static since the mid-1990s after the introduction of PSA testing [32] Interestingly, mortality for prostate cancer is less in Australia than the United Kingdom. This could be due to several confounding factors, but UVR exposure may have a role.

However, when comparisons are made between different countries' national statistics, problems can arise. National statistics reflect population trends, not individuals' risk factors. The only way to fully compare the two would be by age-matched comparison studies. To date there appears to be no published work on prostate cancer and UVR in a native Australian population. Studies looking at Middle Eastern and Near Eastern immigrants to Australia have shown a reduced incidence of prostate cancer compared to a native Australian-born population [33,34].

Multiple sclerosis (MS), like prostate cancer, is a disease that is related to latitude and possibly UVR exposure. Data from Australia show that MS incidence increases with latitude from north to south [35,36]. This same trend is seen in migration studies of British individuals who emigrated to Australia [35]. These findings provide further support for the UVR hypothesis and emphasise the need to determine individual exposure through cases and controls.

Conclusion

Prostate cancer is a common malignancy in ageing men, with numbers likely to increase with time. The hypothesis that prostate cancer risk is mediated by exposure to sunlight is compatible with the known influence of vitamin D on key biological processes. A link between susceptibility to prostate cancer and UVR exposure is suggested by our data, some of which has been independently replicated. Skin pigmentation, as a surrogate for pigmentation efficiency, does affect susceptibility to prostate cancer in a low UVR exposure group, with skin type 1 offering relative protection. SNP studies in both the VDR and the MC1R have been associated with susceptibility to prostate cancer. Although sun-burning and excessive tanning do have significant risks for skin cancer and skin ageing, moderate sensible exposure to the sun in order to prevent hypovitaminosis D, particularly for people with deeply pigmented skin, may be beneficial.

With known low levels of vitamin D in the UK population, and many people not synthesising endogenous vitamin D from October to April, is there a role for increased vitamin D fortification of food, as well as vitamin D supplementation? Indeed, is it safe to inform the public to expose themselves to a 'safe' level of UVR during the summer months? Holick has created such tables, suggesting appropriate UVR exposure for differing skin types [19]. We are not advocating widespread deliberate UVR exposure, but a consensus on adequate exposure does need to be formulated. The possible benefits of UVR must be weighed against the risks of sun-induced skin cancers.

However, caution is required in using these data to derive public health advice. Encouraging people to increase exposure may be inappropriate if we are not yet sure what levels of exposure are significant in increasing skin cancer risk. Indeed, advice may need to be tailored to an individual's own characteristics such as level of pigmentation or ability to initiate a pigmentary response to sunlight. It is reasonable to state that these data are interesting and worthy of investigation, since the potential public health benefits are huge.

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Vitamin D: photobiology and relevance for cancer

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The sun is our most important source of vitamin D. Exposure to ultraviolet radiation from sun-beds can also give substantial amounts of vitamin D. This is even true for so-called UVA sun-beds, since they emit some UVB, and since UVB is orders of magnitude more efficient than UVA both with respect to vitamin D photosynthesis and melanogenesis.

UVB exposure of the skin leads to conversion of 7- dehydrocholesterol (7-DHC) to previtamin D3, which is converted in a heat-driven reaction to vitamin D3. Vitamin D3 binds to D-binding protein, and goes to the liver where hydroxylation to 25-hydroxyvitamin D3 (calcidiol) takes place. Calcidiol is present in human serum in concentrations of the order of 10-100 nmol/l, and is regarded as a reliable measure of the vitamin D status of a person. Calcidiol is further hydroxylated to 1,25-dihydroxyvitamin D3 (calcitriol) in the liver. Calcitriol is believed to be the active hormone. This is certainly true with respect to bone metabolism. With regard to cancer protection, however, calcidiol may be more important. Many tumours have receptors for calcidiol. Our data show that the calcidiol level is 20-50% higher in late summer than in late winter. We believe that this explains improved survival in a number of cancer forms when treatment is started in the season of high calcidiol levels.

Rickets is prevented at a calcidiol serum level above about 12.5 nmol/l. However, the general optimal level is somewhere between 100 and 250 nmol/l. To reach such a level, a daily intake of 100-200 µg vitamin D is required. This equals about 50-100 g of cod liver oil. Sun or sun-bed exposures amounting to 2 MEDs (minimal erythemal dose) per week would give the same calcidiol level. One MED is the UV exposure giving a slight erythema (skin redness). In the Nordic countries the sun gives about 1 MED in 10-20 minutes at midday in midsummer.

An adequate vitamin D level counteracts many cancer forms (prostate, breast, colon, lung cancer as well as lymphomas). The incidence rates or the severity of several other diseases are decreased by sufficient vitamin D3 levels: multiple sclerosis, diabetes, rheumatoid arthritis and cardiovascular diseases. The action mechanisms of vitamin D may be related to its immune- and cell-differentiating effects. Even though most of the 250 deaths a year from skin cancer in Norway may be due to sun exposure, there are probably large health advantages of increased sun or sun-bed exposure, notably for old persons and immigrants with dark skin or who seldom expose their skin to the sun.

The importance of vitamin D

Vitamin D has played an important role in the entire animal and plant kingdom for millions of years. It absorbs radiation in the same wavelength band as proteins and DNA (290-320 nm); that is, in the UVB region. This suggests that it may have played a sun-protective role since the beginning of life on Earth.

Plants make vitamin D2 (ergocalciferol) from ergosterol, while animals mainly produce vitamin D3 (cholecalciferol) through UVB absorption by 7-dehydrocholesterol (7-DHC). Animals with fur secrete 7-DHC in sweat. When the sun shines on fur containing 7-DHC, vitamin D3 is formed, and the animals ingest it when they lick their fur. Cow's milk contains more vitamin D in summer than in winter. In humans, a dark skin colour reduces vitamin D production. Early hominids living in Africa probably had a dark skin colour, as have Africans today. Migration out of the Equatorial regions led to decreasing pigmentation [1]. These considerations clearly show the biological impact of the vitamin.

It may even have played a role in the Wurm period (70,000-30,000 years ago), when the Neanderthals disappeared and the Cro-Magnons took the lead. The former had little or no vitamin D-containing fish on their menu, while the latter had. Bones of Neanderthals bear sign of rickets or osteomalacia [2]. The same is true for bones of the Nordic people who emigrated to Greenland in the 9th century, but mysteriously disappeared in the 15th century.

Urbanisation and the changes in lifestyle brought by the industrial revolution made rickets a serious health problem from the 15th to the 20th century [3]. In the 1820s, it was found that sun exposure could heal rickets [4]. After the First World War, it was observed that radiation from a mercury lamp had a similar effect [5]. At that time, it was

also shown that cod liver oil healed dogs with rickets [6]. Food was fortified by UV exposure, and thus enriched in vitamin D2. The research activity and curiosity about vitamin D was wide-ranging in those days: exposure of rat cages was found to heal rickets in rats put into them! Vitamin D2 might have been formed in traces of food or in rat excrement under UV-exposure. A synergistic action of basic research, clinical research and public information campaigns almost eradicated rickets and osteoporosis in a couple of decades.

Changes in diet and/or less outdoor work may explain the rising trends in incidence of these bone diseases in recent years [7]. Migration of people with a dark skin colour to temperate, northern regions may also play a role. Vitamin D deficiency is observed in many countries, even in large groups of people with white skin. It is an open question if the numerous campaigns against exaggerated sun exposure have reached the wrong populations: anxious people, rather than sun-worshippers.

In recent years there has been a revitalised interest in vitamin D and its positive health effects.

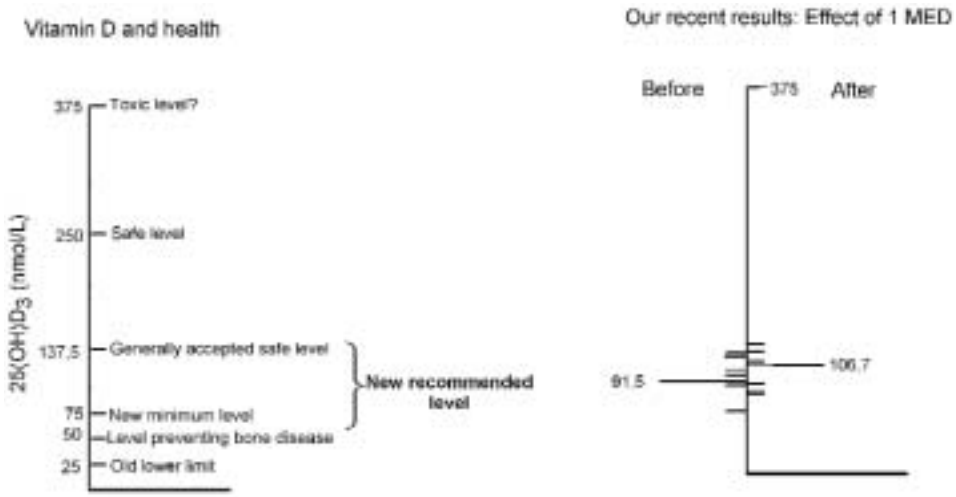
The photosynthesis of vitamin D_3 in skin

7-DHC is present in the skin of most vertebrates. Humans have 0.1-0.2mg/cm2 in the dermis, 0.1-1 mg/cm2 in the basal layer and 0.7-1.5 mg/cm2 in the epidermis [8]. Skin thickness decreases with age and so do the concentration of 7-DHC and the efficient photo-conversion of 7-DHC. The photobiosynthesis of vitamin D3 decreases by a factor of about four between the ages of 20-30 years and 60-80 years [9].

The fluence rate of UVB decreases rapidly with increasing depth below the skin surface, and only a small fraction (about 2%) of the 7-DHC in the dermis (where the blood vessels are) is photoconverted, while this percentage is about 20-30 in the epidermis. Africans with black skin (skin type 6) need 10-15 times more UV radiation than a white person to get the same amount of vitamin D3 [10].

Sun-beds are extremely efficient vitamin D3 producers (see Figure 1) [11 and own unpublished results]. The action spectrum of 7-DHC conversion to previtamin D3 peaks at about 295 nm [12]. Exposure to a sun-bed emitting radiation just in the wavelength region around 295 nm would give more vitamin D3 than sun exposure, since previtamin D3 and vitamin D3 are photolabile with different action spectra [12].

Figure 1



Based on a literature survey, calcidiol levels related to optimal health were assessed. The right-hand part of the figure shows preliminary data from investigations of the effect of one suberythemal whole-body exposure given on a UVA sun bed.

UV exposure of previtamin D3 produces lumisterol and tachysterol. After about 10-15 minutes of Equatorial sun the maximum level of previtamin D3 is reached, after which only lumisterol is formed [13]. 7-DHC is squeezed between polar heads of long-chained fatty acid molecules in cell membranes and in the skin [8]. These surroundings stabilise the photoproduct previtamin D3 until it can undergo a heat-driven isomerisation to vitamin D in about 12 hours [12].

Loomis proposed that the high melanin concentration in African skin protected the Africans against vitamin D intoxication [1]. However, sun-induced vitamin D toxicity has never been observed. This may be due to the photolability of both previtamin D3 and vitamin D3 [10]. Under moderate UV fluence rates vitamin D3 needs to be

photo-protected, and this is achieved by it being transported away from the skin to the liver, bound to D-binding protein [14].

Vitamin D biochemistry

Vitamin D is hydroxylated to calcidiol (25 (OH) D) in the liver. Normally its concentration is 30-100 nmol/l in human serum. The cytochrome P-450 enzyme in the kidneys transforms calcidiol to 1,25 (OH) D (calcitriol) by the addition of one more hydroxyl group. Calcitriol has been regarded as the active hormone, which is certainly true with respect to bone metabolism. Two isomers of calcitriol are formed: 1,25 $(OH)_2$D and 24,25 $(OH)_2$D. Their relative significance is disputed [15]. A number of tissues have calcidiol receptors and produce calcitriol [16].

The effects of vitamin D metabolites on cell differentiation and tumour progression are well-documented [15,17,18]. Calcidiol may be more important than believed until now. Our research shows that tumour prognosis is related to the calcidiol level and not to the calcitriol level, which is constant throughout the year [19-21]. The biological efficiency of calcitriol, on a molar basis, is 125-400 times that of calcidiol [22] and not 2,000 as earlier believed [23]. Since the concentration of calcidiol in serum is 500-1,000 times that of calcitriol one can estimate that calcidiol probably contributes some 70-90% to the overall biological effect, and not simply 15-30%, as earlier thought. Newer observations support the important role of calcidiol [24-27].

What is an 'optimal' vitamin D status?

The answer to the question of what constitutes 'optimal' vitamin D status is dependent on sex, age and physiological conditions like pregnancy, breast-feeding, overweight and abnormalities of the calcium metabolism. It is likely that there are different optimal levels, depending on what is being considered: cancer, multiple sclerosis, arthritis, diabetes, cardiovascular diseases or bone metabolism. Relevant proposed optimal levels can be found in the references [28]. Figure 1 summarises this. Levels found by us in our sun-bed experiments are also given in the Figure.

If these values are correct, there is vitamin D deficiency in large populations in the Western world [29-37]. Winter values are notably low. Among elderly people, extremely low levels are reported: 18 nmol/l in Switzerland, 10 nmol/l in France. Children in Brazil have around 105 nmol/l, while veil-bearing women in sunny Turkey have only 10 nmol/l [18]. In Norway, average values of around 50 nmol/l are found. A north-south gradient seems to exist: 40-50 nmol/l at around 50-70°N and 70 nmol/l at 0-30°N. Non-human primates have higher levels than humans. Rhesus monkeys, for instance, have 450 nmol/l [38]. We can guess that increases above 50 to 70 nmol/l play a role in cancer progression, in view of our data on the seasonal dependency of cancer prognosis.

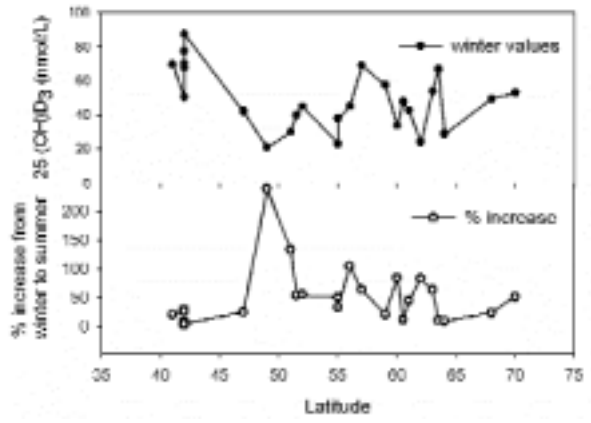
Vitamin D from food and sun

From October to March no vitamin D3 is produced in skin at northern latitudes, due to the low UVB fluence rate in solar radiation [13]. Summer values are 30-100% higher than winter values (see Figure 2). We found similar values to those reported in an early study in Tromsø [37]. However, although photosynthesis of vitamin D3 is about 30% more efficient in South Norway than in North Norway, this is almost compensated for in the north by a 20% higher vitamin D intake from food, mainly cod liver.

A daily supplement of 1.4 µg D2 per kg weight (children) gave 71 nmol/l D2-calcidiol in winter (when the D3 calcidiol level was 62.5 nmol/l) [39]. Vitamin D3 seems to be 70% more efficient than vitamin D2 [39]. Similar findings were reported by another group: vitamin D3, 1 µg per day for 60 days, led to a calcidiol increase of 0.7 nmol/l [40]. Daily supplements of 25, 125 and 250 µg D3 led to an increase in the calcidiol level from 70 nmol/l to 88, 125 and 205 nmol/l, respectively, in healthy men (see figure 2 overleaf).

To maintain summer values of calcidiol, food supplements of about 13 µg vitamin D3 per day are needed in the dark season [40,41]. For persons with 20 nmol/l serum calcidiol, a daily supplement of 10 µg vitamin D3 raised the level to 40 nmol/l within three months [42]. For healthy men without vitamin D3 deficiency a similar food supplement raised the calcidiol level by only 11 nmol/l [43]. A linear calcidiol increase was found through taking a daily supplement of up to 1,250 µg vitamin D [43]. Such a daily supplement (corresponding to 600 ml of cod liver oil) gave 640 nmol/l calcidiol in the serum. Obese people need a higher vitamin D intake, since the vitamin is stored in fatty tissue [44].

Figure 2



Winter values (upper panel) and winter-summer percentage increase (lower panel) in calcidiol concentrations at different latitudes. Data from references 29-37.

A number of meteorological parameters affect the fluence rate of UV radiation and, consequently, the rate of vitamin D photosynthesis in skin. For instance, the UV fluence rate is almost doubled when snow is on the ground. It should be noted that the action spectra for pigment induction, erythema and vitamin D3 production (probably also that for non-melanoma skin cancer induction) practically overlap, and are mainly located in the UVB region. Thus, a sun-bed giving pigmentation without producing vitamin D3 cannot be manufactured. However, it is possible to optimise the spectrum of a sun-bed to maximise vitamin D3 production and, at the same time, to minimise the skin cancer risk. Skin cancer risk is always an accompanying factor in radiation, whether from sun-bed or sun.

Fifteen minutes of midsummer sun exposure of face and hands at noon has been suggested, to give sufficient supplementation of vitamin D3 [45]. Regular exposure of this magnitude, which may be about the average exposure of an English office worker, gave a calcidiol level of 36 nmol/l [46]. A similar study of elderly persons in the Netherlands raised serum calcidiol concentration from 18 to 60 nmol/l in three months [42]. 1.5 MEDs per week to 1,000 cm^2 of skin produced a level similar to supplementing food with 10 µg (about 5 g of cod liver oil) per day. In psoriasis patients who were exposed weekly to three whole-body MEDs, calcidiol increased from 50 to 200 nmol/l over eight weeks [47]. Similarly, 0.7 MEDs given three times per week raised the level from 55 to 150 nmol/l [48]. Three MEDs as a single whole-body dose gave 25 nmol/l, as determined after one week. One MED whole-body exposure corresponded to ingestion of 400 µg vitamin D2 [49].

In popular terms, therefore, one can say that one hour of midday sun per week during midsummer in Northern Europe would give a calcidiol level within the range 70 to 150 nmol/l. This corresponds to food supplements of 100-200 µg per day, or 50-100g cod liver oil. Old, dark-skinned or obese people need more of either sun or vitamin D supplements.

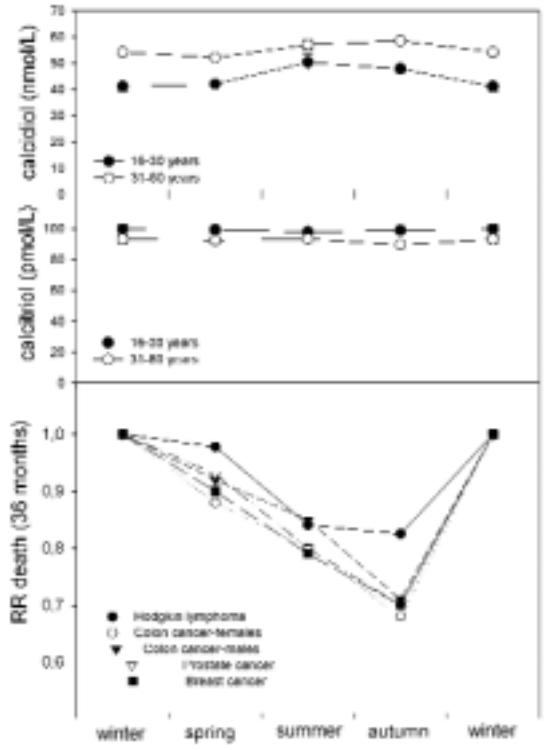
Sun-beds are extremely efficient vitamin D3 producers if used with care. Even UVA sun-beds emit enough UVB to produce substantial amounts of vitamin D [49,50].

Practically all sun lotions with sun-protecting factors reduce vitamin D3 photosynthesis. The reduction factor is almost as large as the factor of erythema protection, since the action spectra of erythema and that of vitamin D3 production are quite similar. Experimental data agree with this conclusion [51].

What about cancer and other diseases?

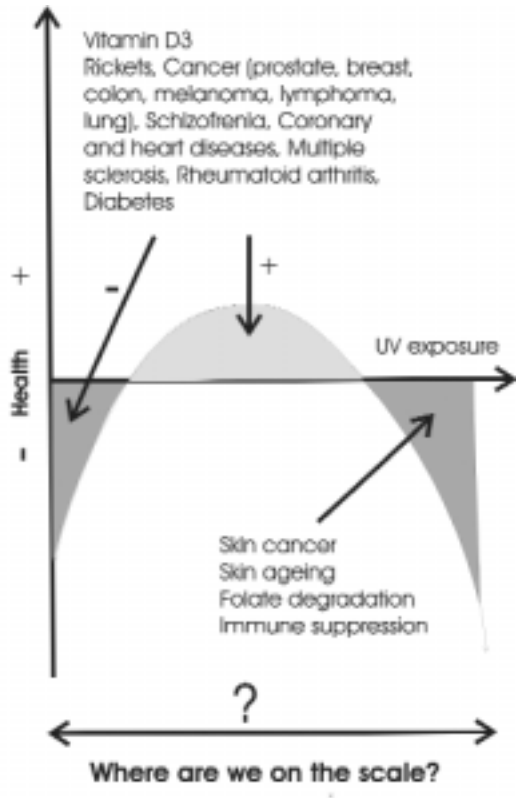
A number of cell and animal experiments, as well as epidemiological studies, have shown that vitamin D protects against many cancer forms or, at least, improves their prognosis. North-South gradients have been demonstrated for prostate, breast and colon cancer [52-56]. There is a correlation between high risk of prostate cancer and low sun exposure early in life [57]. Persons who were frequently sunburned as children had lower than average risks of getting lymphomas later in life [58]. Even in the case of cutaneous malignant melanoma, for which sun-burning is an accepted risk factor, the prognosis seems to be best for those with signs of high sun exposure in the skin surrounding the melanomas [59]. We have found a seasonal variation in the prognosis of all the above-mentioned cancer forms (see Figure 3) [19-21], and propose a role for calcidiol, which varies with season (upper panel, Figure 3), rather than for calcitriol, which is constant throughout the year (middle panel).

Figure 3



Seasonal variation of calcidiol in human serum in two age groups (upper panel). Seasonal variation of serum calcitriol in the same age groups (middle panel). Relative risk of death within three years after diagnosis of four cancer forms (lower panel) at various times of year [19-21].

Figure 4



Positive and negative health effects of exposure to ultraviolet radiation. The scale of the exposure axis will be different for different persons.

Rickets, osteoporosis and osteomalacia are clearly related to a low vitamin D level. In addition, recent investigations have shown that sun exposure has a number of beneficial health effects, probably via its vitamin D-producing property (see Figure 4). Sun exposure can reduce high blood pressure and the incidence rates of cardiovascular diseases [60,61]. It can improve the symptoms of patients with multiple sclerosis [62,63]. It can lead to a reduction in the incidence rates of diabetes [64], and it can relieve the symptoms of arthrosclerosis [65].

Several of the mentioned diseases are of an autoimmune nature, and the well-documented immuno-modulating effects of vitamin D may be involved.

Conclusion

Sun exposure is our best source of vitamin D. Non-erythemogenic exposures, both to sun and sun-beds, give substantial vitamin D production in the skin. An adequate level of this vitamin is associated with large health benefits, relieving symptoms and reducing the incidence rates of many diseases, as well as of internal cancers. Our restrictive attitude to sun and sun-beds should be re-evaluated. Over-exposure should be avoided, both because of skin cancer induction and because of photodegradation of previtamin D3 and vitamin D3 caused by erythemogenic exposures.

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Insufficient sunshine as a cause of multiple sclerosis: evidence for the correlation

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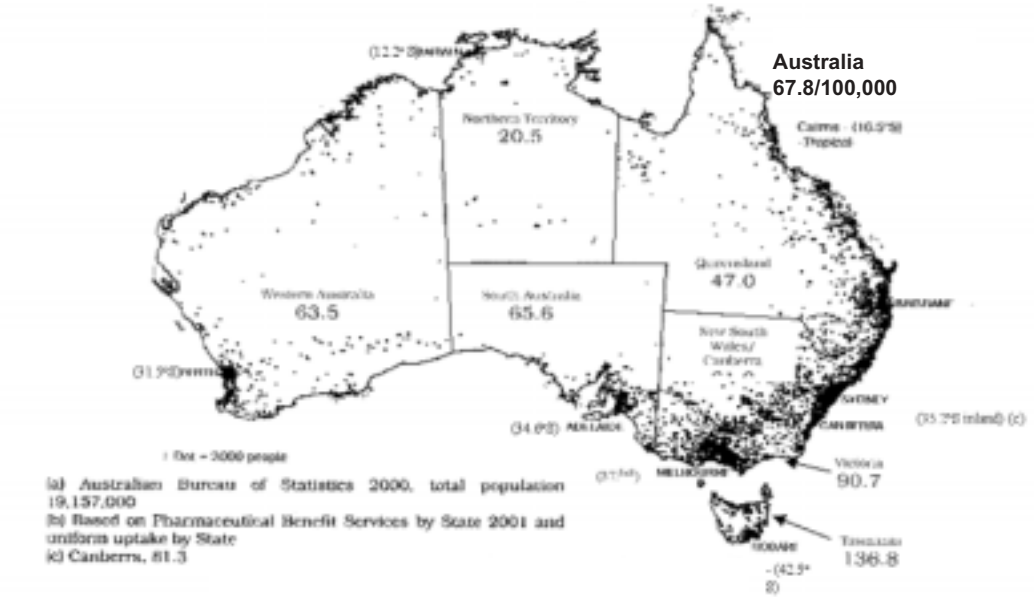
Multiple sclerosis (MS) is the commonest chronic neurological disease of young adults, and here in the UK there is a prevalence of about one in 750. In Scotland it's quite a bit higher than that, probably at least one in 500, maybe even one in 400. Sociologists say the average circle of acquaintances and friends that people have is about 2,000 and that gives you some idea of how common the disease is, because most of you are likely to know one or two people who have MS. It's a cruel disease. After 15 years about 50 per cent of MS patients are unable to walk unassisted, and after 25 years at least half will be in a wheelchair, or worse. It's familial about 20 per cent of the time.

There are enormous economic, social and medical costs. In the UK, there are about 750 new cases a year. That works out to about two a day, and the lifetime cost in each case is about £1.5 million. Very crudely, £3 million a day in terms of financial commitment accrues just for new cases and that's not counting the approximately 70,000 existing cases in the UK. So it's an enormous financial burden. I won't discuss the social costs, but they are best understood by those who've had a parent with it. This is a burden for many, many children.

Now, the information in Figure 1 has been known for a long time, although this is a relatively new slide. This is the geography of Australia, and I'm showing Australia for a particular reason. The Figure shows the distribution of MS in this sub-continent, by tracking the distribution of interferon prescriptions. It ties in extremely well with data obtained in other ways. So, in Tasmania there are 136 cases per 100,000, up in the northern territories there are about 20, and Queensland's rate is about 47. So there's a very big 5- or 6-fold difference in rate, going from the south to the subtropical north. (The MS gradient in the southern hemisphere goes from south to north, and in the northern hemisphere from north to south.)

The limitation in looking at data from Australia is that really you are not looking at a gradient per se, you are looking at the huge dominance of urban centres in a sub-continent which is largely devoid of people in the centre (the dots represent population numbers). So this is not the best way of examining potential gradients. But the differences are very, very large and they are very influential. The fact that people are diagnosed and put on the slide based upon where they happen to live isn't necessarily what you want if the risk is determined early in life. What you really want is where people are born or perhaps where they spent their childhood, and those are data which are rather difficult to get.

Figure 1 **POPULATION DISTRIBUTION, AUSTRALIA (a) & ESTIMATED MS PREVALENCE BY STATE (b)**
(estimated MS population 13,000)



What you'd really like to have is a situation in which people don't move from where they are born and they are distributed in a way that is homogenous. Rather than them being in urban centres, you'd like to have a situation in which individuals are distributed in an even, homogenous way in the country. It's not something that springs to mind easily, but there is a place where you can actually get the ideal sort of circumstance for the geography of this disease.

It turns out, most improbably, it comes from France. In France, there are two different healthcare systems. One healthcare system is for the general population and there is a separate healthcare system for farmers and their families. What's ideal for our purposes about farmers? They don't move, they are evenly distributed throughout the country, and they are not urban dwellers. Looking at MS prevalence per 100,000 inhabitants in France, you get about a 2-fold drop as you go south, from 103 up in the north-eastern part of France down to 45 per 100,000 in Corsica. So it's very clear-cut, and based on reasonably good numbers. It shows a very clear pattern which is the inverse of Australia (see Figure 1) but climatologically coherent. There's a little bit of an anomaly along the coast. The coastal dwellers in France actually have a lower rate of MS than would be expected based on latitude. It is possible that this may have something to do with eating fish.

The work on this is being carried out by my colleague Christian Confavreux in Lyons. Interestingly, George Chaplin and I have been able to correlate some rather high-tech information to it, drawing on NASA data for France relayed by the Toms satellite, which has been orbiting the earth eight times a day for over 30 years. It calculates the ultraviolet radiation virtually anywhere in the world, through a variety of paradigms that have been validated over a number of years. Its picture of the UV MED, or minimal erythematous dose (the dose of UV causing minimal pinkness of skin) is similar to the map of MS prevalence in France which the Lyons group has put together.

A number of years ago I initiated a network of clinics in Canada which essentially spans the country. There are 16 university centre sites where MS patients are looked after, and over a period of about 20 years we were able to put together a population which is now in excess of 25,000 MS patients. This allowed us to ask some questions that can only be answered by very large numbers.

The first thing we did was studies of twins. It took us about 20 years to collect 450 pairs, which is pretty much the number of twins you would expect to be found, based on the prevalence rate in Canada. We found that if you are an identical twin, your risk of MS is 30% if your twin has it, whereas if you are a fraternal or non-identical twin, which is for genetic purposes the same as having a non-twin brother or sister, then the rate is 4% – a big difference between identical twins and fraternal twins.

Because the rate for fraternal twins wasn't much different from the rate for just brothers and sisters who are not twins, this indicated that the increased familial environment that you would have in fraternal twins – by being the same age, and sharing the same maternal environment and many other things more than would ordinarily be shared by brothers and sisters – didn't seem to have any impact on risk. That was the first indication that the prevailing notion at the time, that MS had something to do with some sort of viral infection, probably wasn't going to be right.

The next thing we did was a study in people who were adopted at birth, and it took 20,000 MS cases to do this study because adoptions are relatively uncommon. In Canada 1.2% of the population is adopted and most of those are adopted around the time of birth. We knew that the rate for a biological brother and sister was 40 times greater than the general population rate of one in 1,000. Of course that could be genes, or it could be environment. So we decided to look at the rate of MS in those individuals who grew up with a non-biological relative destined to get MS, compared to a biological relative; for example, the unrelated adoptive brothers and sisters of someone destined to get MS.

The answer was black and white. The rate for the non-biological relative in the same environment was one in 1,200, which is the same as the general population rate of one in 1,000, whereas you would have expected 25 cases to have occurred based on the biological risk among sufferers' actual brothers and sisters. It was clear-cut that the risk within a family was not determined by the common familial environment. So familial risk is genetic and we could not show any effect of shared familial environment on risk.

The next studies were done in half-sibs, the first systematic half-sib studies in any disease. We didn't expect that we would get as much out of them as we did. These studies are very well-utilised in animal husbandry and if any of you have an agricultural background you will know a lot about half-sib studies because that's what people in agriculture do. They have a sire or a dam that will have offspring with one common parent, but not two. A lot of the original studies that bear very strongly on gene/environment effects actually come from agriculture.

We had the opportunity of collecting these, and we had a bit of an advantage sociologically, stemming from the rising divorce rate. Because the divorce rate has risen so rapidly over the last generation or two, there are a lot of half-sibs, so it's actually a much more common situation now. In a family where you've got one parent in common

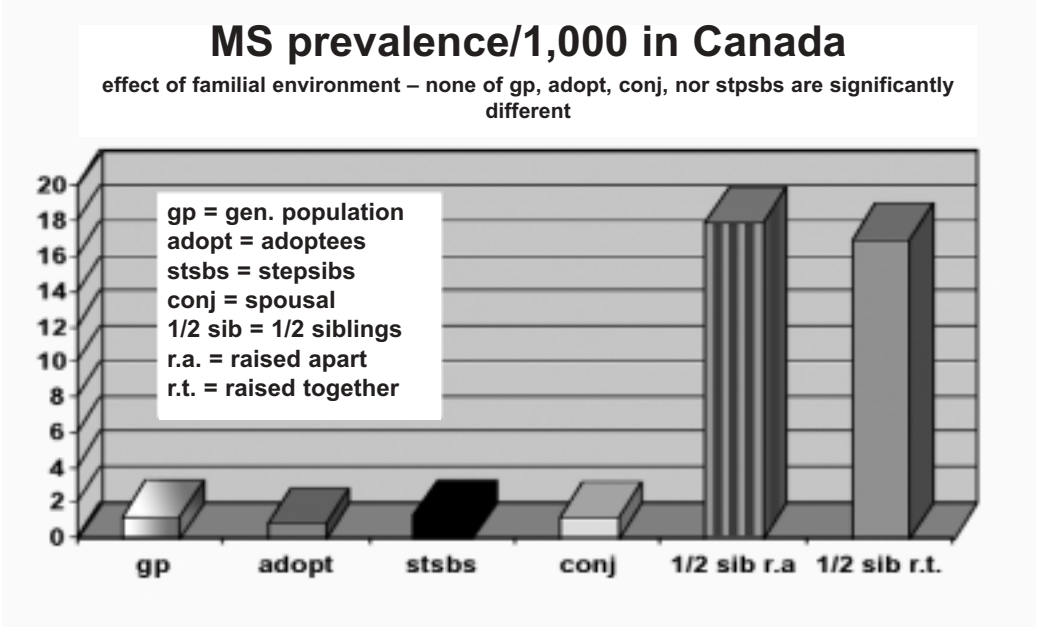
but not two, you can ask some interesting questions.

Conveniently, it turns out that among half-sibs, roughly half are raised together and about half are raised apart. That's helpful because it's kind of like the twin study approach where you get identical twins separated at birth, reared apart and then try and see what happens to them. Of course, you can't do that study in MS or any other particular disease because there just aren't enough people on the planet in that position, it's a rare event. And they would have to be separated, not only just apart but apart by risk and, of course, that almost never happens. So in fact the half-sib study is what you really want. It's much more powerful than a twin study and once you realise the potential of this then you have increasing admiration for our agricultural colleagues who twigged to the power of this methodology a long time ago.

In half-sibs it turns out their risk is about half that of full sibs, and that's important. The reason is that it tells you something about the complexity of inheritance. What it says is that if the risk only drops by half that means the complexity genetically can't be very great, and that's contrary to what everyone has been thinking. So now you can ask, what's the rate for those raised together and those raised apart, and you can also ask, if one parent is in common but not two, does it matter which parent it is? Does it matter if it's the father in common or if it's mother in common? And it turns out it matters a lot and the raised together/raised apart issue also turns out to be very important.

Figure 2 (below) is a graph showing the rate of MS per 1,000 in Canada, looking at a variety of different populations. It includes the general population of one in 1,000; the adopted relatives, one in 1,000; the rate for step-sibs of MS patients, which is one in 1,000, and the conjugal one, looking at the rate for husbands and wives of MS patients, and that's one in 1,000. So we can demonstrate no effect of shared common familial environment all the way from birth right through to marriage. What happens in the half-sibs that are raised apart compared to the half-sibs that are raised together? We found that the ones who were raised apart have a slightly higher rate than those who were raised together. So there is no effect of the common familial environment.

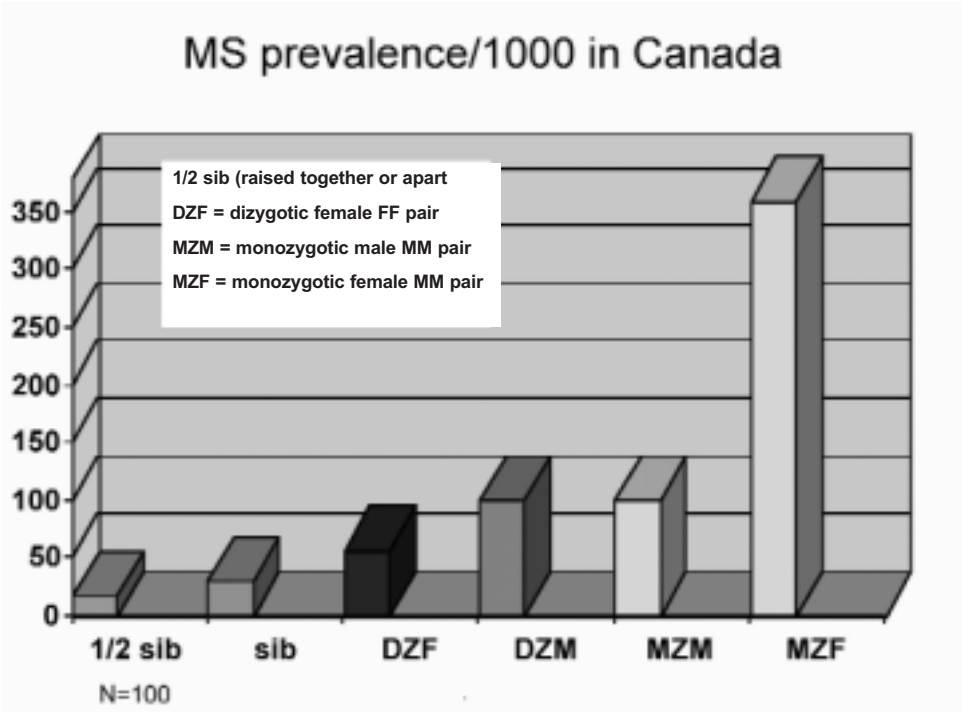
Figure 2



Half-sibs raised together and apart, as shown in Figure 2, are a kind of anchor point for Figure 3, because now we are seeing an almost 400-fold difference in risk. The half-sibs raised together (1/2 sib r.t.) bar at the right end of Figure 2 is now to the left in Figure 3. The incidence in monozygotic female twins concordant for MS is 380 per 1,000 twins (right hand side of Figure 3) which is almost 400 times the general population incidence of one in 1,000. The incidence in concordant monozygotic female twins is about seven times that in concordant dizygotic female twins, but the incidence of MS in sibs is only twice that in half-sibs. From the point of view of genetics these two ratios might be expected to be the same. This provides an important clue about the nature of susceptibility to MS. Unlikely as it may seem, susceptibility to MS appears to have gender specificity.

The familial microenvironment can't be demonstrated to contribute anything to risk, yet there is a huge

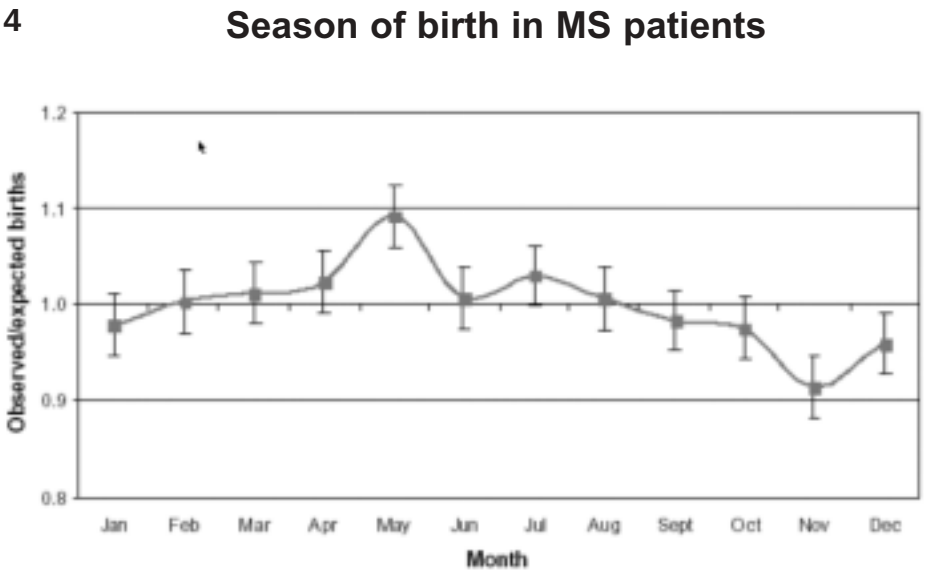
Figure 3



environmental effect reflected in an unambiguous latitude gradient in every country that's been studied. Basically, this leaves climate or diet or even the consequences of that to explain the influence of environment in MS. And actually, diet is not very attractive because in fact it's largely familial unless there are differences in regional diets, which does happen in some countries. People in a family tend to eat the same things, so you would have expected to see some impact of that common familial diet. But we can't see anything.

So it leaves us with climate, the direct or indirect consequences of climate, and that's a broad area.

Figure 4



Ratios of Canadian MS births compared to controls

(inverse is seen for unaffected sibs and for S.Hemisphere patients)

Nevertheless, the notion that something within the familial environment triggers the risk can't be supported. We looked at it another way and asked about the genetics. If parents who are first cousins have a child with MS, the risk to subsequent children is increased by 100-fold, showing the impact of the shared genetics on risk.

One of the difficulties with trying to establish what actually determines MS risk has been the heavy reliance on data from migrants. For various reasons, migrants are often selected for studying the timing of differential geographic risk, but there tend to be relatively few of them. It's been possible in Canada to do a study which we would describe as an intra-familial migration study. This came up because one of my patients was an oil engineer from Edmonton who spent three years in Bahrain, and he had two children there, and four more in Edmonton. Knowing that one of them got MS, which was the one? We're in the process of finalising these data, but in the interests of passing on some knowledge, I can tell you that the results support the view that risk is determined within a family by where the individual was born. There's a clear difference between offspring born in areas of high risk or low risk.

One of my students was interested in examining season of birth in MS, and came up with the results in Figure 4, which shows the season of birth in MS patients in Canada. The last time something like this was seen, it turned out to be a very strong hint as to the cause of neural tube defects. A long time ago, in the 1950s, it was recognised that the timing of birth influenced the risk of neural tube defects, and it took another 35 years before anybody figured out what it meant. Hopefully, on this occasion, it won't take that long. But there is a season of birth effect in MS which is pretty clear. In Canada and the northern European countries, risk is increased by about 10 per cent by being born in May, and it's decreased by 10 per cent by being born in November, and if you go to the southern hemisphere, in Argentina or Australia, you see the reverse. In the unaffected sibs of these southern hemisphere individuals, you see the reverse; that is, there are more May births and fewer November births. I told my students I was not about to get up in front of an audience and say that being a Taurus would increase your risk of disease, and made them replicate this data in four other countries.

The environmental factor in MS acts at a population level and determines the risk differential between Tasmania and northern Queensland, which is 5- or 6-fold (see Figure 1). If we could convert the rate in Tasmania to the rate in Queensland, we could prevent 80% of the cases of MS there. The evidence is all circumstantial at this point. It doesn't have to be vitamin D, it could be something else related to sunlight. There are a variety of potential considerations. Vitamin D has to be entertained as a possibility.

The first trials to test whether the primary prevention of MS is related to the sun and/or vitamin D are now at the planning stage. This is probably going to happen in a couple of places. One is in Canada, where a prevention study is being geared up, the other is in Australia.

When we examined the sex ratio for incidence of MS in Canada by year of birth, going back to 1920, we found that the rate of MS in Canada appears to have been steadily increasing for the last 50 years, and I think the same is true of the UK, although there isn't much data. Everybody has been doubtful of this, including myself, because there have been changes in diagnostic methodology, and a variety of other factors confound the evidence.

Most of the increase in incidence of MS during the 20th century is due to an increase in the number of women who have contracted the disease. Contemporary reports from 1920 suggest that equal numbers of men and women developed MS at that time, although our retrospective determination of the sex ratio in 1920 puts this slightly higher. In fact we believe that the sex ratio has moved from around equity in 1920 to about 3.5 to 1 in 1975-79. More than three women develop the disease today for every man who does so. The reason for this is not yet clear but there must be a powerful environmental factor driving this difference forward. Again this suggests that understanding why women are so vulnerable to the disease will yield important information about the cause.

Just to summarise what I've said. MS is a very important disease. It's hugely important economically and socially. It looks like it may be increasing in rate. The risk is partly determined by genes and environment. The environmental part is certainly something that acts at a broad population level. Vitamin D is a good candidate, but not the only candidate. I think some additional work needs to be done. But it's very hard to get direct evidence to implicate vitamin D especially if this is operative decades before onset of the disease. If anyone can think of a way of getting direct evidence – we're going to require information on something that might have happened 25 or 30 years ago, which is notoriously difficult and believe me, we've tried – then let me know.

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How much vitamin D is enough for optimum health?

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In 1950, one of the most famous scientists in England, Sir Richard Doll, essentially proved that smoking shortens your life expectancy [1,2]. Not too long ago, he wrote: 'In retrospect, it can be seen in medical evidence that the harm done by smoking has been accumulating for 200 years, and it took until 1950 to appreciate that and do something about it [3].' I put it to you that the vitamin D story is probably very much like that. If you are a smoker and you stop smoking, you reduce your all-cancer mortality risk by 30%. Based on other presentations offered here, if you are British, and if you were to take substantially higher doses of vitamin D supplement, you might be lowering your odds of dying of cancer to a similar degree. However, without a prescription in the UK, you are not permitted to consume enough vitamin D to make a meaningful difference to your health.

In one of his last publications, Richard Doll reported on the use of vitamin D in older adults [4]. The researchers invited older British adults into a study involving three pills a year. Participants were randomised either to 100,000 IUs of vitamin D, or a placebo. The dose was equivalent to 821 IUs a day of vitamin D. Participants in the vitamin D group reported one-third fewer first hip, wrist, forearm or vertebral fractures than participants in the control group. If that kind of effect were for a commercial product, it would be on every newspaper page as an advertisement.

Data from the National Health and Nutrition Examination Survey in the United States (NHANES) show that average bone density increases with average serum 25-hydroxyvitamin D concentration; that is, serum 25(OH)D, the measure of vitamin D nutrition, that comes from UV exposure of skin, or from diet or supplements. Based on the NHANES population data for bone density, one should wish to have a serum 25(OH)D concentration that is higher than 100 nmol/l [5].

Anyone in the UK wishing to take the preceding research to heart, and opting to take available supplements, would fail to affect bone, because the resulting increase in serum 25(OH)D would be negligible. With the highest permitted non-prescription dose of vitamin D in the UK, serum 25(OH)D will increase by about 10 nmol/l, from a typical UK value of 40 nmol/l, up to 50 nmol/l [6]. The amounts of the vitamin D available over the counter in the UK are of negligible benefit to adults, and all scientists knowledgeable about vitamin D know this.

The benefit of vitamin D, shown at the highest level in the hierarchy of evidence, is the prevention of fractures. Prospective, randomised, placebo-controlled trials have shown repeatedly that vitamin D prevents fractures – if consumed in adequate amounts. Bischoff-Ferrari *et al* published a meta-analysis in the Journal of the American Medical Association, in which they combined the clinical trial data available up to the year 2005 (see Figure) [7] The research studies that addressed the primary prevention of fractures produced a persuasive picture; that if vitamin D supplementation increases the serum 25(OH)D concentration to a value higher than 72 nmol/l, there is a statistical reduction in the risk of fracture.

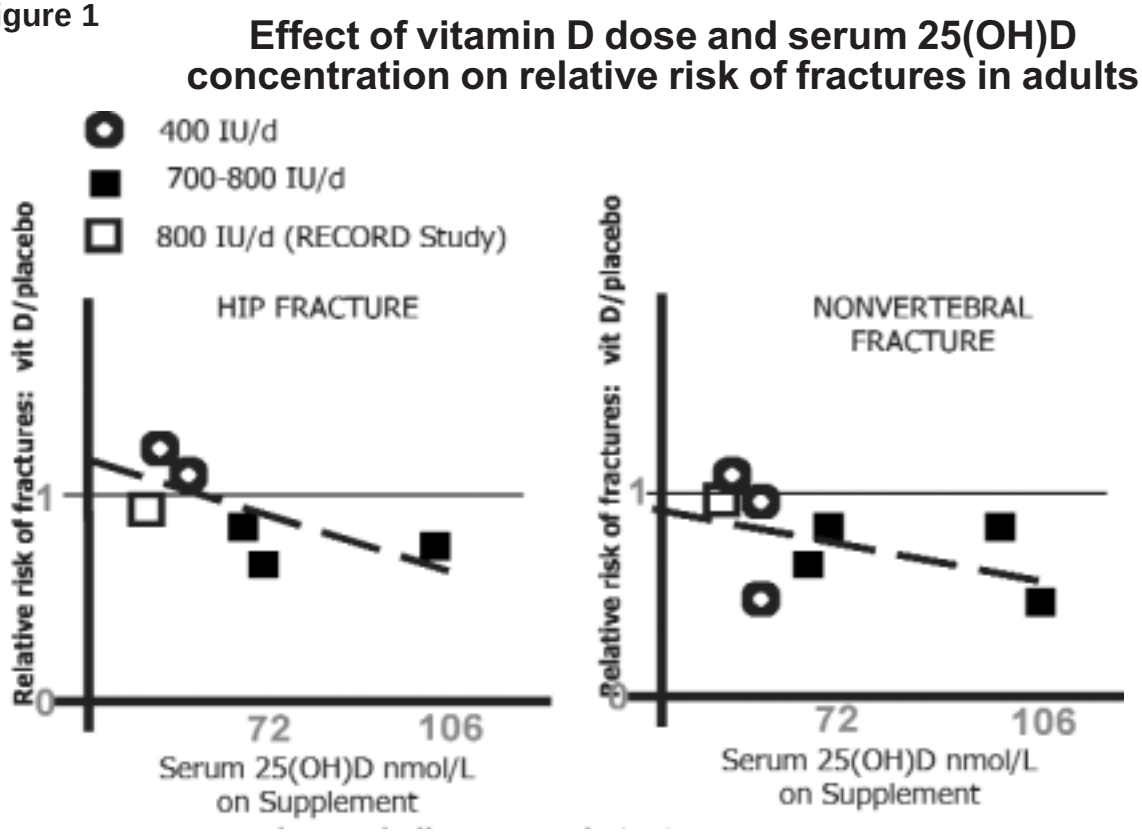
The more recent British RECORD study [8] garnered much interest, with some newspaper headlines saying, 'Calcium and vitamin D are useless'. There were several problems with the study. First, the RECORD study was a secondary prevention study; that is, it focused on subjects who had already suffered fractures, thus it was a therapeutic intervention. The other studies summarised in Figure 1 are primary prevention; that is, they deal with nutrition for healthy people. For them, the data consistently show that vitamin D lowers risk of fracture.

Furthermore, there was a high drop-out rate in the RECORD study, with 30% of participants leaving the study, yet the statistical analysis was of a style referred to as 'intention to treat'. This means that despite their withdrawal from the study, subjects were still counted as if they had remained in the study. (If people did not take part in a trial, and nothing happened, the conclusion that vitamin D does nothing is a very weak one.) In addition, even participants who did complete the RECORD study were evidently not compliant, and they did not consume all their doses. The serum 25(OH)D concentrations reported for treated subjects in the RECORD study were equal to the serum 25(OH)D concentrations of subjects in other vitamin D trials who had taken only 400 IUs a day.

By incorporating the data from the RECORD study into the graph summarising data from the primary preven-

tion studies, it comes as no surprise that the RECORD study concluded that the vitamin D was ineffective – the serum 25(OH)D levels were not high enough, there were too many drop-outs to be convincing, and its subjects already had osteoporotic fractures. Participants in the RECORD study should have received more aggressive treatment.

Figure 1



This figure is redrawn from the meta-analysis of primary prevention studies by Bischoff-Ferrari et al, where citations are given for the complete group of studies [7]. Updated in this figure are data from a secondary prevention study, the RECORD Study, published more recently [8]. Symbols indicate the dose used, and the RECORD study is shown with the open boxes. The horizontal line indicates the ratio of risk expected if there is no difference between the groups. The dashed lines are regressions through the data weighted for sample size, and they show that fracture risk decreases as serum 25(OH)D increases.

A recent consensus conference in Lausanne addressed the question, what serum 25(OH)D concentration is the minimum desired for fracture prevention? The consensus recommendation was that we should be wanting 25(OH)D concentrations to be higher than 75 nmol/l [9]. The question addressed was, how much would the average person have to take in order to have a 25(OH)D concentration at that target? The consensus recommendation was to consume 800 to 1,000 IUs a day (20-25 µg a day) of vitamin D.

In the UK, the public cannot purchase these doses of vitamin D without a prescription. Current British guidelines for vitamin D nutrition declare that adults under 50 years of age do not need any vitamin D supplementation [10]. Only breast-feeding mothers, expectant mothers and the elderly are advised to take 400 IUs a day, and any more than this is by prescription-only in the UK. The official safety recommendation for vitamin D in the UK exists only as a draft document, three years after its publication and the disbandment of the Expert Group on Vitamins and Minerals (EVM) that wrote it.

The seemingly innocent statement, 'For guidance purposes only, a level of 25 micrograms per day (1,000 IUs a day) supplementary vitamin D would not be expected to cause adverse effects in the general population' is, in reality, a nutritional millstone around the neck of the British public. It is partly because of this statement that the British are prevented easy access to vitamin D supplements in amounts that might compensate for the insufficient amount of vitamin D acquired through sun exposure. Doses of 1,000 IUs per day – or larger – are probably needed if health benefits including prevention of cancer (see the reports of others at this symposium) and fractures

(see Figure) are to be realised.

Osteoporosis fracture prevention and bone density preservation are the best evidence that an optimal level of vitamin D nutrition is a serum 25(OH)D concentration higher than 72 nmol/l. Prevention of osteoporosis fractures requires at least 800 IUs/day of vitamin D (20μg/day). This is cheap and readily available in North America, but not in the UK.

Now to return back to the issue of public health and Richard Doll. The solution to the problem of smoking was easy to deal with compared to vitamin D. It is easy to tell people not to do something, such as to quit smoking. On the other hand, vitamin D is itself still perceived by many as toxic [11], and this makes the implementation of public health measures that involve doing something, like consuming more vitamin D, all the more difficult. Outdated perceptions, such as those built into official UK documents relating to vitamin D, are like a millstone around the neck of the British public. The outdated guidelines in the UK make it impossible to solve the problem of vitamin D insufficiency through the use of a vitamin supplement.

We do not need the highest standard of evidence for every potential health benefit of vitamin D to establish its value. We only need one – osteoporosis. If you address that benefit by permitting the public access to products that contain more vitamin D, you make it possible for the public to derive benefit for the less well-proven health effects as well.

The practical message for the British is that legislation surrounding vitamin D must change in the UK. The public should be able to purchase vitamin D in a pharmacy without a prescription, in amounts that are at least 800 IUs a day (20μg day). This dose has been objectively shown to reduce fractures, and it is a conservative suggestion for an 'optimum' dose of vitamin D for adults. This dose is safe, and it is a fraction of the amount of vitamin D obtained by exposing skin to summer sun.

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Vitamin D insufficiency in the UK and diabetes

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During my talk I demonstrated that vitamin D insufficiency is a current problem in Britain and presented data showing how infant vitamin D supplementation or vitamin D deficiency early in life may contribute to the risk of type 1 diabetes. The elderly and those of black or Asian ethnic minority groups are known to have a high risk of vitamin D deficiency, but a significant proportion of the adult British Caucasian population is also affected. Children who grow rapidly and who do not get sufficient exposure to sunlight are at increased risk of rickets. Evidence from Mediterranean countries indicates that even in a sunny climate vitamin D deficiency is a serious concern in breast-fed infants who do not receive supplemental vitamin D. There is a need to re-evaluate vitamin D supplementation recommendations for infants in the UK and to ensure that appropriate supplements are made widely available.

Vitamin D and type 1 diabetes

In vitro studies and animal experiments have shown that the active hormonal form of vitamin D, calcitriol, has important influences on T-cell activity, which may have profound effects on the autoimmune process leading to beta cell destruction in type 1 diabetes [1]. There is increasing evidence from animal experiments indicating that administration of calcitriol may reduce the progression to type 1 diabetes, and complete protection from the disease has even been achieved when sufficiently large doses have been used [2]. Although calcitriol is also known to be important for normal insulin secretion [3,4], it is not clearly established whether these direct effects on the beta cell are a mechanism by which vitamin D might reduce the risk of developing type 1 diabetes.

To date, there are few data on the effect of vitamin D intake or status on diabetes risk in humans, and studies have been restricted to looking at either very early exposure (that is, vitamin D supplementation in uterus/during infancy) or vitamin D status and supplementation after diabetes diagnosis.

The first report on the association between vitamin D supplementation in infancy and diabetes risk came from the EURODIAB study that combined data from seven European countries [5]. Pooled analysis of this multinational case-control study suggested a 33% reduction in the subsequent risk of developing type 1 diabetes if the child had received vitamin D supplementation during the first year of life [5]. In a Norwegian case-control study published a year later, the offspring of mothers who had taken cod liver oil supplements during pregnancy had a reduced risk of type 1 diabetes, whereas their findings on the effect of vitamin D supplementation in infancy were inconclusive (the suggested effect ranged from a nearly 90% reduction in diabetes risk to a two-fold increase) [6].

In our own study on the 1966 Northern Finland Birth cohort, there was a remarkably consistent association between several indicators of vitamin D intake and status with the risk of type 1 diabetes, which was robust to adjustment for a wide range of neonatal, anthropometrical and social indicators [7]. The incidence of type 1 diabetes by age 31 was reduced by over 80% if vitamin D supplementation during the first year was regular, compared to no supplementation.

Furthermore, among children who had received vitamin D supplementation regularly, a further 80% risk reduction was seen if the dose given to the infant had been at least at the level of the contemporary recommendation of 2,000 IUs (50 µg) per day [7]. Infants suspected of having had rickets during the first year of life had a three-fold risk of developing diabetes compared to others. Although studies on the association between vitamin D and type 1 diabetes have given promising results, it is clear that more research, including intervention studies, is needed to establish if the occurrence of type 1 diabetes is reduced by increasing vitamin D intake.

Link between changing supplementation recommendations and incidence of type 1 diabetes in Finland?

Although the incidence of rickets is still much lower than half a century ago, an increase in its incidence was observed during the 1980s in Finland [8]. The recommended dose of vitamin D supplementation has been reduced to a tenth of the level recommended in the early 1960s. The reduction was implemented in steps. In 1964 the recommended dose was reduced from the dose interval of 4,000-5,000 IUs to 2,000 IUs per day [9], and in 1975 the daily dose was further reduced to 1,000 IUs. The change to the current recommendation of 400 IUs in Finland was made in 1992.

There is also some indication of lower compliance in giving vitamin D supplementation to infants in the early 1990s when compared to that observed in the 1966 cohort.

In the STRIP Baby intervention study (1991-1993), 93% of one-year-olds were given vitamin D supplementation [10]. According to a small survey carried out in Finland in 1993, 65% of 138 children under two had received vitamin D supplementation regularly [11]. The corresponding proportions in the Northern-Finland Cohort 1966 Study were 99.7% and 88%, respectively. Therefore, it seems plausible that the constant increase in the incidence of type 1 diabetes observed in Finland during the past decades could be related to the combination of changes in the recommendations of vitamin D supplementation, and compliance in giving the supplementation to the infants.

Vitamin D supplementation and status in Britain

Evidence from Mediterranean countries indicates that even in a sunny climate, vitamin D deficiency is a serious concern in breast-fed infants who do not receive supplemental vitamin D [12]. However, in the UK, no vitamin D supplementation is routinely recommended for breast-fed infants (although it is included as part of the Healthy Start Programme, the reform of the Welfare Food Scheme).

Risk groups for vitamin D deficiency in Britain include breast-fed infants who do not receive supplementation. Infants from black or ethnic minority groups are at particularly high risk of developing vitamin D deficiency. Indeed, individuals (of all age groups) from ethnic minority groups are commonly affected by vitamin D deficiency, due to reduced vitamin D synthesis in the skin as the result of darker skin pigmentation or cultural clothing habits [13-15]. Vitamin D synthesis is also reduced in the elderly [16], and vitamin D deficiency is an especially severe problem among individuals living in institutions [17,18].

Data from the British 1958 Cohort (aged 44-45, 2002-2004) confirmed the extremely high rates of vitamin D insufficiency in ethnic minority groups [19]. However, vitamin D deficiency and insufficiency also affect significant proportions of the British Caucasian adult population. Overall, one quarter of the British Caucasians had insufficient levels of vitamin D (25(OH)D <40 nmol/l), while nearly two-thirds of individuals in ethnic minority groups were affected. Problems of vitamin D deficiency and insufficiency were particularly prevalent during the winter and spring months, when reserves built up during the previous summer had been depleted. According to the data, nearly half of the adult Caucasian population in Britain are estimated to have insufficient levels of 25(OH)D during winter/spring, and would be in need of supplementation.

Vitamin D as a public health concern in Britain

Vitamin D status in the general British population is not satisfactory, and increased intake of dietary vitamin D is required to correct for the lack of exposure to ultraviolet light (and hence vitamin D synthesis in the skin), especially during winter and spring. Commercially available infant milk formulas are currently fortified with vitamin D, so that a child consuming one litre per day receives around 400 IU, corresponding to the dose currently recommended for infants in Canada and several European countries. However, there is no doubt that breast milk is the best food for babies, as it contains important protective immunological factors in addition to optimal amounts of all nutrients, with the exception of vitamin D. There is clearly a need to re-evaluate vitamin D supplementation recommendations for infants in the UK and to ensure that appropriate supplements are made widely available.

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Evidence of deficiency and insufficiency of vitamin D in the UK: National Diet and Nutrition Survey (NDNS) data, 1994-2004

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The following data summarise the findings for vitamin D status and for vitamin D intake as a proportion of recommended nutritional intakes (RNI) for children, the elderly and high-risk groups, that are contained in the published reports of the UK National Diet and Nutrition Survey (NDNS), 1995-2004 [1-5]. This is a population-based survey carried out in people of all ages across the UK; no specific figures were provided for South Asians and the data provided on this group, recognised to be at high risk for hypovitaminosis D, have been culled from work published in peer-reviewed journals [6-9].

The following points should be noted:

- The cut-offs used to define hypovitaminosis D are based, for deficiency, on evidence of association with bone disease (rickets in children and osteomalacia in adults) and, for insufficiency, on evidence of association with non-bony as well as bony disorders. Thus, throughout, the prevalence of insufficiency includes those with deficiency
- Vitamin D deficiency is currently 'defined' using a cut-off of serum 25(OH) vitamin D of about 25 nmol/l. Where NDNS data are not given for this cut-off level the data given are for the cut-off nearest to that level, and the exact level of cut-off is shown in the Tables
- Vitamin D insufficiency is currently defined using a cut-off of serum 25(OH) vitamin D of 50 nmol/l, though recent work suggests 70-75 nmol/l is more correct. Thus, the data given for insufficiency is given for both cut-offs when possible. Where NDNS data are not given for precisely these cut-off levels the data quoted are for cut-offs as near as possible to those levels and the exact cut-off levels shown in the Tables.

Vitamin D status of UK population

Table 1: Children aged 1 to 4 [1]

Age years		1.5-2.5	2.5-3.5	3.5-4.5
Deficiency				
Serum 25(OH)D<25 nmol/l	Boys	1%	1%	0
	Girls	1%	1%	0
Insufficiency (inc deficiency)				
Serum 25(OH)D<50 nmol/l	Boys	17%	23%	12-22%
	Girls	17%	23%	12-22%
Serum 25(OH)D<65 nmol/l	All	64%	62%	54%

Table 2: Children aged 4-18 [2]

Age years		4-6	7-10	11-14	15-18	Average
Deficiency						
Serum 25(OH)D <25 nmol/	Boys	3%	4%	11%	16%	8%
	Girls	7%	7%	11%	10%	8%
Insufficiency						
Serum 25(OH)D <50 nmol/l	Boys	23%	26%	40%	54%	36%
	Girls	25%	26%	44%	49%	36%
Serum 25(OH)D <70 nmol/l	Boys	55%	62%	77%	76%	>50%
	Girls	53%	53%	71%	80%	>50%

Table 3: Adults aged 19-64 [4]

Age years	19-24	25-34	35-49	50-64	Average
Deficiency					
Serum 25(OH)D <25 nmol/l					
Men	24%	16%	12%	9%	14%
Women	28%	28%	13%	15%	11%
South Asians					38-95%
Serum 25(OH)D <30 nmol/l					
Men and Women					22%
Insufficiency					
Serum 25(OH)D <50 nmol/l					
Men	70%	57%	58%	49%	57%
Women	67%	50%	57%	49%	60%
Serum 25(OH)D <70 nmol/l					
Men	90%	80%	85%	85%	84%
Women	83%	76%	84%	78%	80%

Table 4: Adults over 65 living independently [5]

Age years	65-74	75-84	>85	Average
Deficiency				
Serum 25(OH)D <25 nmol/l				
Men	5%	5%	13%	6%
Women	6%	15%	25%	10%
Insufficiency				
Serum 25(OH)D <50 nmol/l				
Men	17%	33%	46%	23%
Women	37%	39%	55%	3%

Table 5: Adults over 65 living in residential homes [5]

Age years		65-84	>85	Average
Deficiency				
Serum 25(OH)D <25 nmol/l	Men	36%	42%	38%
	Women	38%	36%	37%
Insufficiency				
Serum 25(OH)D <40 nmol/l	Men	69%	68%	69%
	Women	75%	86%	80%

Table 6: Adults over 65, using higher definitions of deficiency and insufficiency [5]

	Independent	Residential
Deficiency		
Serum 25(OH)D <30 nmol/l	8%	37%
Insufficiency		
Serum 25(OH)D <75 nmol/l	60%	77%

Table 7: Pregnant women [9-11]

	South Coast UK [10]	South Asian [11]
Insufficiency		
Serum 25(OH)D <50 nmol/l	50%	54%

Table 8: Average vitamin D levels in blood over a year from north to south of the UK: mean 25(OH)D nmol/l over the seasons [2-4]

Age years	Boys 4-18 [2]	Girls 4-18 [2]	Men [4]	Women [4]
Scotland	63.0	60.7	43.7	42.5
N of England	58.5	63.5	50.9	52.4
Central and SW England & Wales	64.2	62.4	48.6	51.1
London and SE England	62.6	56.0	6.7	46.9

Intakes of vitamin D in the UK

The tables that follow show the recorded intake of vitamin D as a percentage of the daily recommended nutritional intake [RNI]. The RNIs for vitamin D in the UK are as follows: Children < 3 years: 7 µg (~290 IUs)/day; High-risk adult groups*: 10-20 µg (400-800 IUs)/day; Aged > 65: 10 µg (400 IUs)/day

*There is no RNI for 'normal' adults in the UK; that is, adults who are not in high-risk groups. High-risk groups may be defined as people who are confined indoors, or adults who work indoors all day, pregnant women, those with dark skin, those wearing veils or all-over clothing, vegetarians, those eating low-fat diets, those over 65, and those regularly using sunscreen at factor 8 or above or avoiding summer sunshine. Many women regularly use foundation cosmetics containing sunscreen and they may well also be at high risk.

Table 9: Children aged 1-4 [1]

Age years	1.5-2.5	2.5-3.5	3.5-4.5	Average
Total intake	26%	26%	26%	26%
Intake from food	28%	26%	26%	27%

Table 10: Children aged 4-18 [2]

Age years	Boys	Girls
Mean total intake vitamin D	2.6 µg (104 IUs)	2.1 µg (84 IUs)
% from cereals	37%	35%
% from fats (fortified) and meat	20%	20%
% from oily fish	7%	9%

Tables 11 and 12, which follow, show the percentage of people failing to reach various intakes, allowing for their intake from food alone or from food plus supplements. More people will fail to take in, say, 2.5 µg from food alone than will fail to make that intake if you include supplements as well as food in their intake.

Table 11: Adults aged 19-64 failing to reach given average intake [3]

	Food and supplements		From food only	
Average intake	**Men**	**Women**	**Men**	**Women**
<2.5 µg (100 IUs)	32%	41%	34%	59%
<5.0 µg (200 IUs)	71%	70%	79%	89%
<10 µg (400 IUs)	93%	90%	97%	98%

Table 12: Adults aged over 65 failing to reach RNI (400 IUs/day) [5]

	Food and supplements		From food only	
	Men	**Women**	**Men**	**Women**
Living independently	46%	33%	41%	29%
Residential	39%	34%	38%	33%

Commentary

A continuing high prevalence of full-blown vitamin D deficiency in the UK is demonstrated in the Tables shown, which are based on data from the National Diet and Nutrition Survey published 1995-2004 for the population as a whole, and from other published data for British South Asians. The attendant risks of rickets in children and of osteomalacia and increased fracture rates in adults are especially regrettable in the country that identified vitamin D almost a century ago.

It has been known since the 1920s that these problems do not arise with adequate exposure to summer sunlight, even in this northern country, and that dietary supplementation (with, for example, cod liver oil) can both cure and prevent these problems. Furthermore, the continuing high prevalence rates of hypovitaminosis D is likely to be increasing the prevalence of the many non-bony disorders that are strongly associated with vitamin D inadequacy. These disorders include many common cancers (for example, breast, colon, prostate), type 2 diabetes, ischaemic heart disease, tuberculosis, rheumatoid arthritis, periodontal disease and autoimmune diseases such as type 1 diabetes of childhood and multiple sclerosis, as well as increased fracture rates in old age. These chronic disorders place heavy burdens upon individual sufferers and on the state, both in terms of the cost of their care to the NHS and in terms of the care and support needed in the community. Such costs would be expected to fall with avoidance of hypovitaminosis D in the population at large. Trials using really adequate vitamin D supplementation (for instance, 100,000 IUs orally once every four months, as studied by Trivedi, Doll and Khaw [12]), can reduce fracture rates in elderly people in the UK. Trials of similarly adequate supplementation for reduction in risks of chronic non-bony disorders are long overdue.

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Do we need more sun exposure?

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In his paper, Oliver Gillie discusses the health consequences of not enough exposure to sunlight resulting in vitamin D insufficiency and calls for a shift in public health messages concerning sun exposure. I will argue that the evidence that such a shift will reduce the population burden of disease, especially cancer, is inadequate, that we receive more than enough sun exposure during recreational activities and that changing population lifestyles to synthesise 'adequate' vitamin D during adventitious sun exposure is fanciful.

The incidence of skin cancer, and cutaneous malignant melanoma in particular, continues to rise in many countries, including the UK, and is predicted to continue rising for some years to come. The rise is commonly attributed to changing lifestyles resulting in increasing intermittent, high-dose exposure to sunlight, especially during childhood, as a consequence of outdoor pursuits and vacations at sunny locations. In an attempt to stabilise or even reduce this upward trend, the Health Education Authority introduced the Sun Know How campaign in 1995 and, following its demise in 2000, Cancer Research UK took on the SunSmart campaign.

The focus of these campaigns is to advise people who intend spending prolonged periods in strong sunshine how to limit their exposure. It's not about telling people to avoid the sun. The particular core message is a warning not to get over-exposed such that the skin gets sunburnt. Yet Oliver Gillie has suggested that these campaigns are killing many more people than saving lives and has called for the SunSmart programme to be abandoned as soon as possible. And so what we're now seeing in the media are confusing public health messages about just what is appropriate behaviour in the sun.

So the question I want to examine is: 'Do we need a revised public health policy on sun exposure?' And in order to answer this question, I'm going to explore a number of subsidiary questions.

First of all, how much sun exposure do we actually receive in this country? Our sun exposure on a day-to-day basis depends primarily on three factors: it depends upon astronomical considerations of the height of the sun in the sky; it depends upon what the weather is like and, most importantly, it depends upon how long we are out of doors and what we're doing when we are out there.

Broadly speaking, we can divide our sun exposure into adventitious exposure, which is the sort of exposure that all of us got this morning as we were walking to the meeting, and elective exposure, when we deliberately go to seek the sun for recreational purposes, usually during summer weekends and during our summer holidays.

By combining average monthly values of measured ambient UV radiation in the UK with exposure (relative to ambient) on sites such as the face and hands, together with estimates of time spent outside (but not in vehicles) during weekdays and at weekends, it is possible to give some indication of the range of daily exposures at different times of the year (see Figure 1). The data shown for holiday exposure in Figure 1 relate to someone who is ambulant; for keen sunbathers who are prone or supine, daily exposures of 10 SED or higher are easily achievable. (An exposure of 2-3 SED [standard erythema dose] is necessary for a minimal erythema [MED] in unacclimatised white skin that burns easily.)

During the winter months between November and February in the UK, there is insufficient ambient UV to synthesise vitamin D, especially when low ambient temperatures mean it is unlikely anything more than the face and hands will be exposed when outdoors.

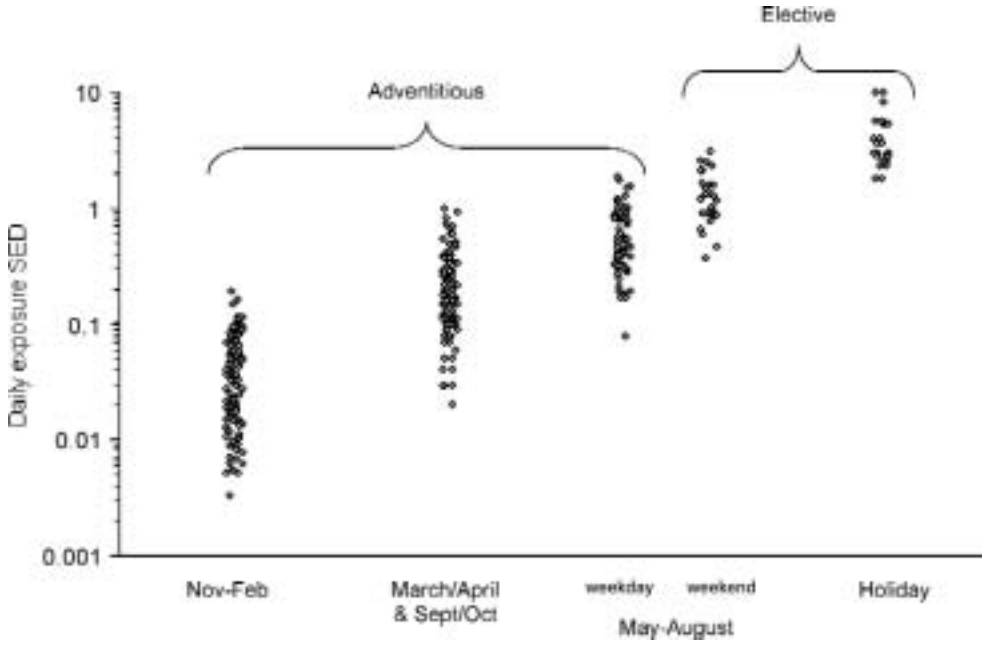
On the other hand, elective (that is, recreational) sun exposure during weekends and holidays in the summer months (May to August), when an appreciable area of the body surface is likely to be exposed for one or more hours in largely unshaded sunshine, will result in more than enough exposure for adequate synthesis of vitamin D. This will be true even if sun protection measures such as sunscreens are employed, due to their imperfect nature. Since sun exposure regulates the cutaneous production of vitamin D by causing its photodegradation, the production of vitamin D is limited, no matter how long a person is exposed to sunlight. Hence it is simply not possible to synthesise large stocks of cutaneous vitamin D by prolonged sun exposure. Campaigns such as the Cancer Research UK SunSmart programme are intended to advise people primarily during their recreational exposure for extended periods in strong sunshine and there is no need to compromise on the key messages in these campaigns to ensure adequate sun exposure.

This leaves our adventitious sun exposure from March to October and during summer weekdays when we are at work. We live in a time-poor society, however. Data from the UK 2000 Time Use Survey, where thousands of

people were asked to fill in a diary of how many minutes they spend each day on different activities, showed that on average each day British adults spend 508 minutes sleeping, 221 minutes at work on weekdays, 148 minutes watching TV, 85 minutes travelling, but just 14 minutes engaging in outside activities. We live very pressured lives in our modern society such that during the so-called 'vitamin D window' around the middle of the day there are many things competing for our time. We may be at work. We may be travelling. And the notion proposed by Oliver Gillie in his paper that people should sunbathe during this time in order to synthesise 'adequate' vitamin D is unlikely to be realised.

Figure 1

Representative daily UV exposure of an ambulant indoor worker in the UK



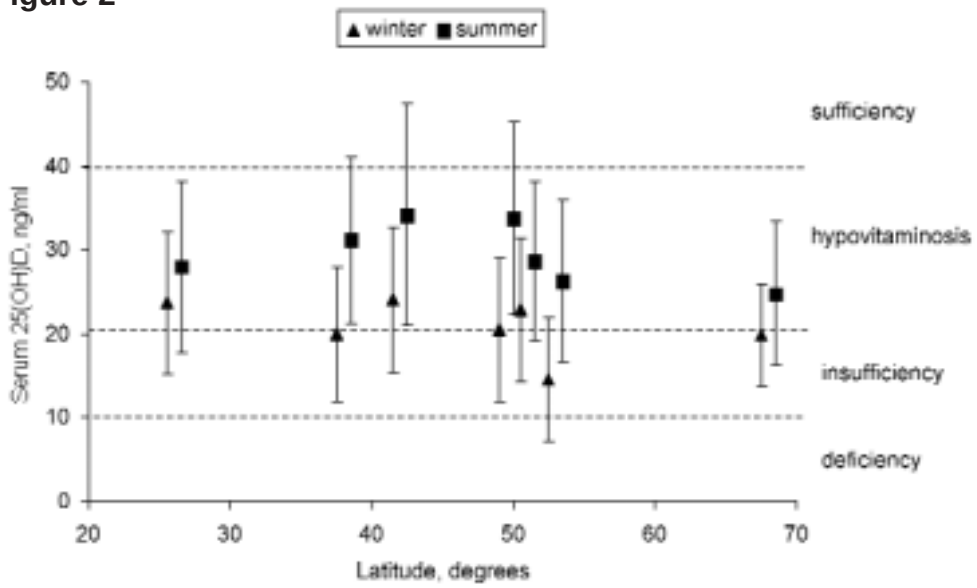
So rather than advocate primary prevention of vitamin D insufficiency by prescriptive sun exposure which, because of the many confounding factors of time of day, season, latitude, weather, presence of nearby shade, behaviour and area of skin exposed is complex and will only lead to confusion, it might be better to rely on secondary prevention by encouraging more outdoor physical activity. Not only would this be beneficial to the nation's health in terms of obesity, diabetes and coronary disease, but people would also receive some subliminal UV exposure in the process.

That brings us to the next question. Even if people could be persuaded to increase the duration and anatomical extent of their sun exposure, is there any evidence that this would change the vitamin D status of the population? Figure 2 shows the variation in serum 25-hydroxyvitamin D (25(OH)D) levels with season and latitude. While these data will be confounded by differences in population demographics and dietary intake of vitamin D between the studies, compounded additionally by problems that might be present in comparing results due to non-standardisation in 25(OH)D assay, two points emerge.

First, it is clear from these data that there is only a modest seasonal variation in mean vitamin D status but, more importantly, mean population levels of people living in sunny regions like Florida and Australia are not appreciably different from people living at much more northerly latitudes, including the UK and Norway. Furthermore, the overall mean winter and summer levels from all studies of 21 and 30 ng/ml, respectively, fall into the band between 20-40 ng/ml (50-100 nmol/l), which Armin Zitterman has termed hypovitaminosis.

So whatever the health benefits of vitamin D may be in diseases like cancer, it would appear that living in a sunny location or modifying lifestyle to achieve greater sun exposure is not likely to be an effective means of significantly changing population vitamin D status. The more likely consequence is an increase in the adverse effects associated with sun exposure.

Figure 2



Mean (+1 standard deviation) levels of serum 25-hydroxy-vitamin D of adults in winter and summer in Miami 26° N, Geelong 38°S, Boston 42°N, south west Germany 49°N, Calgary 51°N, Bristol 51°N and northern Norway 65-71°N. (For comparison, the UK encompasses the latitudes 50°-60°N). The broken lines indicate differing vitamin D status.

Is there then strong evidence that sun exposure – not vitamin D *per se* – reduces cancer incidence and mortality? The approach I take is *Pluralitas non est ponenda sine necessitate*; words of the medieval English philosopher and Franciscan monk, William of Ockham (about 1285-1349) which can be paraphrased as 'keep it simple'.

The annual ambient solar UV radiation in southern Australia and New Zealand is about two to three times that in northern Europe (UK, Ireland, Scandinavia and the Baltic States), rising to more than a four-fold increase in northern Australia. The maximum UV index (a measure of midday sunburning intensity in the summer) is 14 in Brisbane and only 6-7 in London, and studies of individual exposure to sunlight demonstrate that median doses in Australia are appreciably higher than those measured in a similar cohort of subjects in England. Consequently, there is overwhelming evidence that people living in Australia and New Zealand are exposed to considerably more solar UV radiation than those living in northern Europe.

The health impact of this difference in the solar UV environment is most convincingly seen in the Table, which shows that the incidence and mortality of melanoma in Australia and New Zealand is about four and two times higher, respectively, than in northern Europe. Yet when the incidence of other cancers that are claimed to be modified by exposure to solar UV is examined, a very different picture emerges.

Colorectal cancer is less common in northern Europe than in Australia and New Zealand, with little difference in mortality (see Table), an observation that makes it difficult to believe that sun exposure can be having any important protective benefit in this cancer. Similar conclusions can be drawn about prostate cancer. And despite the considerable differences in population solar UV exposure, the incidence and mortality of female breast cancer, one of the principal cancers for which sun exposure has been said to be protective, is virtually identical in both regions.

In support of the epidemiological observation of large differences in melanoma incidence, there are animal models confirming the role of UV radiation in the induction of skin cancers, including melanoma. There are no animal data supporting the protective role of UV exposure in other cancers.

The rise in melanoma incidence over the past decades is commonly attributed to increased opportunity for sun exposure. It might be expected, therefore, that if sunlight were protective in other cancers we would observe a corresponding fall in incidence. Yet, as Figure 3 demonstrates, not only has an upward trend in melanoma been apparent for the past 30 years in the UK, but there have also been increases in the incidence of breast, colon and prostate cancer over the same period. 60

Let me make it clear that I am not saying that UV or vitamin D may not have some role in cancer incidence and mortality. But when I look at data like these, they do not persuade me that living in a sunny country is a sure way of reducing my risk of getting, or dying from, cancer. And that's important, because if we're going to have a change in public health policy, we need to base it on firm evidence. I think the data presented by others are interesting and important but nevertheless insufficient for defending a change in public health policy concerning sun exposure.

Now, moving on to perhaps the most pertinent question. Is the SunSmart campaign impacting adversely on the

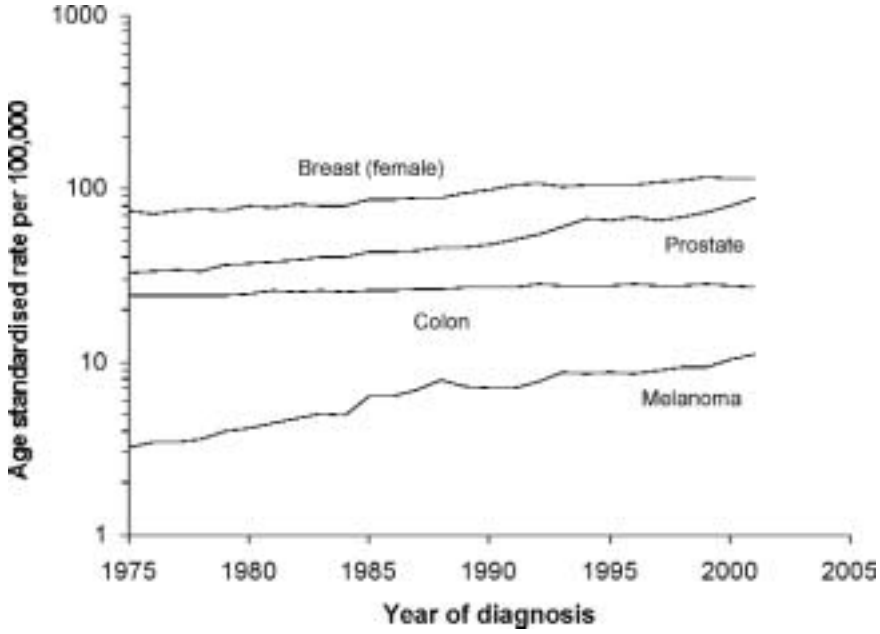
Table: The age-standardised incidence and mortality rates per 100,000 person years with 95% confidence intervals for selected cancers in Australia/New Zealand and in Northern Europe. (GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC CancerBase No. 5, version 2.0, Lyon: IARC Press, 2004.)

Males	Melanoma		Colorectal		Prostate	
	incidence	mortality	incidence	mortality	incidence	mortality
Northern Europe	8.4 (8.2-8.6)	2.2 (2.1-2.3)	37.5 (37.1-37.9)	17.6 (17.3-17.9)	57.4 (56.9-57.9)	19.7 (19.4-20.0)
Australia/New Zealand	37.7 (36.7-38.7)	5.2 (4.8-5.6)	48.2 (47.1-49.3)	19.4 (18.7-20.1)	79.9 (78.6-17.5)	18.1 (17.5-18.7)

Females	Melanoma		Colorectal		Breast	
	incidence	mortality	incidence	mortality	incidence	mortality
Northern Europe	10.0 (9.8-10.2)	1.6 (1.5-1.7)	26.4 (26.1-26.7)	12.7 (12.5-12.9)	82.5 (81.9-83.1)	22.6 (22.3-22.9)
Australia/New Zealand	29.4 (28.5-30.3)	2.8 (2.6-3.0)	36.9 (36.0-37.8)	14.1 (13.6-14.6)	84.6 (83.2-86.0)	19.4 (18.7-20.1)

Figure 3

Trends in cancer incidence in Great Britain since 1975



(Courtesy of Cancer Research UK)

population sun exposure that we get? The messages of the SunSmart code are about keeping in the shade, making sure you don't burn, covering up, taking extra care of children and using factor 15+ sunscreen. The question we should ask, though, is that although those may be the messages, are they changing behaviour?

Figure 4 is a photograph taken on Brighton Beach around the middle of the day, during summer. Not many people seeking the shade, are there? Not many people covering up. But does this picture surprise many readers? What you may have been more surprised about is if I'd showed a picture of an empty Brighton Beach because everybody was seeking the shade. The point is that although people know the messages, it's very difficult – particularly in this country – to get people to adopt them. So if this is the situation during our elective exposure, how much less effective is a message about avoiding the sun between 11 a.m. and 3 p.m. going to be during our casual exposure? When was the last time you saw the London parks deserted around lunchtime in the summer because people were scared to go out in the sun? So the message may be there, but the reality is that it's not having much of an impact.

If we were to abolish the messages in the SunSmart campaign it would almost certainly make little or no difference to population levels of vitamin D in this country. The one thing we could well see, however, is an ever-upward, or

Figure 4

Brighton beach around the middle of the day, during summer.

perhaps an accelerating, trend in the number of people getting and dying from skin cancer.

Finally, in adopting changes to public health policy, consideration needs to be given to the social and psychological consequences of the action. Cancer is a disease that is perhaps most feared by people, and public health messages that make patients feel blameworthy that their cancer may be self-imposed (for example, not getting enough sunlight in this instance), or that they should move away from family and friends to a sunny country in the belief that this would extend their life need a strong evidence base.

So, in conclusion, we cannot justify presently public health campaigns to increase the burden of solar ultraviolet radiation in the white population of the UK as a whole, as a means of reducing the incidence and mortality of cancer and other chronic diseases. Consequently, there is no need for British people to deliberately spend more time outdoors in strong sunshine. Nor should we abandon current sun awareness campaigns in the UK, which are not a message for year-round outdoor behaviour, but rather are aimed primarily at avoiding excessive exposure in strong sunshine that can result in acute signs such as skin reddening and increase the lifetime risk of skin cancer. This is especially true for children and adolescents, where there is epidemiological evidence that exposure to high levels of sunlight during this period is a strong determinant of subsequent risk of melanoma. Furthermore, the continuing popularity of overseas holidays and global warming will act as drivers for increasing UK population exposure to high levels of sun exposure.

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A new health policy for sunlight and vitamin D

Oliver Gillie, PhD, director of the Health Research Forum

Insufficient vitamin D, obtained from diet or sunlight, is beginning to be recognised as a major 'lifestyle' risk factor which may be as important as smoking, obesity or alcohol abuse. Low levels of vitamin D are now very common in all industrial countries and are associated with a wide range of chronic disease. Increasing evidence suggests that lack of vitamin D is a significant cause of much of this disease. Other papers in this volume provide evidence of this.

Vitamin D insufficiency differs from other major risk factors in the ease with which it may be remedied. Vitamin D intake can be raised to healthy levels in three different ways: by taking supplements, by increased consumption of fortified foods, and by sunbathing. These three ways of increasing vitamin D levels need not involve any substantial change in personal habits or way of life.

No difficult personal choices are required for vitamin D levels to be improved. There is no need to give anything up, as smokers must do, and no need to curb the appetite, as must those who eat or drink too much. Nevertheless, there are serious practical obstacles which require government action if vitamin D levels are to be raised substantially in the UK and other industrial nations.

Optimal daily intake of vitamin D

The optimal daily intake of vitamin D is probably between 3,000 and 5,000 IUs per day [1]. However, in the UK hardly anybody gets anything near an optimal intake of vitamin D. Some 60% of people in the UK have serum levels of vitamin D that are insufficient (serum 25(OH)D <25nmol/l) and some 12% have levels that are actually deficient (serum 25(OH)D <50 nmol/l) [2,3].

Those with frank deficiency are at risk of rickets or osteomalacia and those with insufficient levels are at risk of osteoporosis. In addition, everyone with insufficient or deficient levels is at risk of the numerous chronic diseases associated with sub-optimal levels of vitamin D that are documented in this report and elsewhere [4,5].

An average UK diet may provide about 150 IUs of vitamin D per day. Together with two teaspoons of cod liver oil (600 IUs) an average person in the UK could obtain 750 IUs of vitamin D. The remaining vitamin D requirement must be obtained from the sun. In the following article I discuss in turn the problems of obtaining enough vitamin D from supplements, from food and from sunlight.

Incorrect government advice on supplements

Advice from the UK government says incorrectly that no vitamin D supplement is needed by healthy adults in the UK [6]. This advice was formulated at a time when the optimal uptake of vitamin D was thought to be much lower than it is today. Standard advice from doctors and health professionals continues to follow this government line and so discourages the public from taking a vitamin D supplement.

In fact, most people in the UK have sub-optimal levels of vitamin D (84% of adults aged 19 to 64 have serum levels <75 nmol/l) and would benefit from taking a supplement or otherwise improving their vitamin D status [2]. New UK government advice on daily vitamin D requirements for adults is urgently required.

Even if an adult in the UK wanted to take a vitamin D supplement the products that are readily available in the shops have a low potency. A dose of 200 IUs a day is commonly provided in over-the-counter products in the UK. Cod liver oil can provide 600 IUs a day but relatively few people are prepared to take it, even though its palatability can be much improved in formulations with orange juice. So over-the-counter supplements in the UK can improve vitamin D levels in only a minor way. More potent products providing a useful daily dose of 1,000 or 2,000 IUs vitamin D can be obtained via the internet. Similar high-dose vitamin D3 products need to be available over the counter in the UK. If government changed its recommendations these products could be made available quickly.

Some of the vitamin D products in the shops in the UK are formulated with vitamin D2 (ergocalciferol), an analogue of the natural compound, vitamin D3 (cholecalciferol), with about one-third of its potency. Most of the prescription products in the UK are also formulated with vitamin D2. The different potencies of vitamin D2 and D3 are well described in the scientific literature [7] but this information has not yet reached standard medical and pharmacological texts and is not reflected in any way in the labelling of products. This means that people who buy D2 products are unwittingly obtaining a dose which has a potency one-third of what is in any case a low dose. Labelling

which clarifies the differing potency of D2 and D3 is urgently required.

Once these problems are solved and suitable vitamin D products are available in the shops supplements could be promoted in a massive government health campaign. This would be a sensible approach which could be expected to pay dividends since disease caused by vitamin D insufficiency is believed to cost billions of pounds per year in the UK and billions of dollars per year in the US [4,8].

However, many people don't like to take supplements, can't be bothered, or don't remember. So, to ensure that everyone in the population gets enough vitamin D, other means of providing it need to be used as well.

Infant vitamin drops in the UK

In 1940, when Britain was fighting desperately for survival in World War 2, some forward-looking doctors and nutritionists started the Welfare Food scheme which provided free or reduced-cost foods including milk, concentrated orange juice and cod liver oil, to all infants under five in the UK [9]. Cod liver oil is the best natural source of vitamin D and has been used in Europe as a traditional health tonic for hundreds of years. Provision of vitamin D in early life is now thought to be important for prevention of diabetes type 2, for establishment of strong bones [11], and probably for prevention of multiple sclerosis (see George Ebers' paper in this report) and other chronic disease.

The UK Welfare Food Scheme began as a universal programme for all children regardless of family income. To begin with, some Welfare Foods were completely free and others were subsidised but by the 1970s free Welfare foods were only given to families on benefits. In 1975 cod liver oil was changed to a mixture of vitamins A, C and D provided in the form of drops, known as NHS infant vitamin drops. Beneficiaries dwindled over the years to a few thousand and the government ceased to promote NHS infant vitamin drops for sale with any enthusiasm. It seems that increasing affluence encouraged the idea that most people were well fed and so infant vitamins were no longer needed. This, of course, overlooked the fact that vitamin D insufficiency is extremely common in the UK and bears no relation to social class or quality of diet as it is commonly understood.

About two years ago NHS infant vitamin drops, which were made specially for government under licence, were found to leak in storage. The product was withdrawn and since then has not been available. Instead a commercial preparation, Abidec, has been made available to the small number of women who can claim the vitamins as a benefit; but Abidec is not sold in mother and baby clinics as the NHS infant vitamins were, and so infant vitamins have ceased to be a routine part of healthcare for babies. And there is another problem. Abidec is formulated with vitamin D2 which has one-third the potency of D3, and so infants given Abidec are getting a less than adequate dose of vitamin D.

It is a pathetic tale of government mismanagement which could be put right at little cost. Infant vitamins could prevent not only rickets, which has re-emerged as a problem disease among Asian families in the UK in recent years, but it might be expected to prevent at least some MS or diabetes and in so doing save millions if not billions of pounds. Rickets and D-deficiency are particular problems in breast-fed babies because mothers living in the UK generally have low serum levels of vitamin D and hence insufficient vitamin D in their breast milk.

Government advice on this is completely inadequate. In *Feeding your child*, the Department of Health advises: 'Generally... if you are still breastfeeding after your baby is six months old, he or she should have baby vitamin drops containing vitamins A, C and D.' This advice may date from the old observation that rickets does not tend to become evident and be diagnosed until babies are about six months of age [12]. By this time any vitamin D gained by the baby while still in the womb is totally exhausted. However, it is more logical to provide the baby with a vitamin D supplement before this point is reached. Vitamin drops containing D should be given from birth to breast-fed babies. Mothers would also be well advised to take a supplement containing vitamin D during pregnancy.

Fortification of food

The second way of increasing vitamin D intake is from food, but that too is difficult in the UK and other countries. The quantity of vitamin D obtained by individuals from food in the UK varies over a wide range. This is because we obtain vitamin D from a limited number of foodstuffs which are not a part of everybody's diet. Some 50% of vitamin D in the UK diet comes from cereals or margarine, which many people do not eat [2].

You may choose, as I do, a Mediterranean diet with olive oil, a wholemeal breakfast cereal such as oats or muesli, or wholemeal bread, and fruit. And you may think it is a healthy diet as, indeed, evidence suggests it is in general. But it is relatively deficient in vitamin D. On the other hand, a more traditional British cooked breakfast including white bread, margarine, a fortified breakfast cereal such as, for example, Kellog's Special K, followed by fried egg

and sausage will contain a great deal more vitamin D.

Wholemeal products may be expected to reduce available vitamin D because the phytate present in bran binds calcium and prevents it from being absorbed from the bowel. This causes a more rapid breakdown or turnover of vitamin D, leading to lower serum levels [13]. So there is much to be said for choosing a brown, rather than wholemeal, bread which includes the wheatgerm that provides so many important B vitamins but excludes the fibre that contains phytate.

Much more vitamin D could be obtained from the diet if more foods were fortified with vitamin D. At present there are no legal measures in the UK that prevent this, but tighter European Union regulations will be introduced over the next year or so as part of procedures aimed at harmonisation of legislation. The food industry is not likely to be interested in fortifying more foods with vitamin D unless suitable health claims are permitted, which enable a market for D-fortified foods to be established. Health claims are tightly regulated so it will be necessary to negotiate a suitable health claim for vitamin D before many foods are likely to be fortified with it.

Government should take steps to facilitate approval of suitable health claims for vitamin D-containing foods, and take initiatives with industry to encourage the creation and promotion of D-fortified products. This could be done quite quickly if enthusiastic government backing was given.

Vitamin D from the sun

The third source of vitamin D is sunlight. This is in fact the major source of vitamin D for most people in the world except for those living in Polar regions. Inuit (Eskimos) obtain their vitamin D from fish and marine produce while Lapps obtain theirs from reindeer meat, which is relatively rich in vitamin D because the deer feed on moss rich in the vitamin.

The quantity of vitamin D obtained by exposure of the skin to the sun varies with season, skin type, latitude, weather and, of course, the amount of skin exposed. The northern location of the British Isles and our maritime weather produce a climate that is extreme in its lack of strong sunlight. People resident in the British Isles obtain no vitamin D at all from the sun in winter because the sun is too low in the sky and most of the UVB rays, which make vitamin D in skin, are absorbed by their long transit through the atmosphere. Casual exposure of hands, arms and face to the sun in summer in the UK produces some useful vitamin D, up to about 450 IUs per day, but this is nowhere near enough to provide an optimal level of vitamin D in the blood (Dianne Godar – personal communication).

The Scots, at 560 N, get almost one-third less sun than the southern English and this shows up in lower average blood levels of vitamin D [14]. It may also account for many of the unexplained differences that epidemiologists have found between the health and mortality of the Scots and the English, which are shaken off when the Scots migrate south to England [15,16]. The higher levels of certain cancers [17], heart disease [17], multiple sclerosis [18] and other conditions in Scotland cannot be entirely accounted for by higher levels of smoking or greater poverty. Epidemiologists have been left with an unexplained gap which may well be filled, at least in part, by vitamin D insufficiency. A number of reports have been written on health in Scotland and none of them have looked seriously at vitamin D insufficiency as a possible cause of disease other than that of bone.

A person with black skin (type 5 or 6) will get about one-fifth of the vitamin D that is obtained by someone with a white skin in the UK [19,20]. It is impossible for a person with a dark skin to obtain enough vitamin D for good health simply by casual exposure to the sun in the UK. This explains why rickets occurs in the UK predominantly in the babies of mothers with dark skins [21], and may also explain why certain other diseases such as diabetes and hypertension have been noted to be particularly problematic in dark-skinned minorities living in the UK [22].

Vitamin D gain from sunbathing

Major gains in vitamin D can be made in the UK by sunbathing. Exposure of the whole body to the sun can supply up to 10,000 IUs of vitamin D a day [23,24], or rather less at the beginning and end of the British summer when the sun is weak. There are 182 days (26 weeks) when the sun may be strong enough to make vitamin D in the skin in the UK. But, the sky will be clear and the air warm enough for sunbathing in less than half of these.

People able to sunbathe for half their weekends and bank holidays and half of their summer holidays might be able to sunbathe for 36 days a year in the UK. Averaged out, this will enable them to obtain about 2,000 IUs of vitamin D per day during the summer. Sunbathing in the lunch hour on weekdays when it might only be practical to expose legs, arms and possibly shoulders could produce some more useful vitamin D and might even bring the amount of vitamin D obtained over the summer into the optimum range. Even in the UK, the sun is potentially our best source

of vitamin D and can provide a great deal more vitamin D than can be obtained from food.

Some of the vitamin D obtained over the summer may be stored and used in the darker autumn and winter days that follow, but how much is not known for certain. The half-life of vitamin D when measured by isotopic decay of 25(OH)D in the body is about 10 days [25]. However, measurement of 25(OH)D in real-life situations gives a different answer. Submariners returning after a 68-day voyage have been found to have levels of 25(OH)D reduced by 39%, giving an *in vivo* 'steady-state half-life' of the vitamin D pathway which is nearly three months [26,27]. Toxicity studies have also suggested a half-life of 'several months' [25], while studies of the winter decline in 25(OH)D in people living in Canada and Italy suggest that the decline does not continue in a linear fashion [28,29].

If this is correct, then sunbathing in summer may provide vitamin D which is surplus to immediate needs that may be stored for use in autumn and winter. The details of how vitamin D may be stored and how levels are maintained in winter are not well understood. Nevertheless, it is clear that higher levels achieved in summer will be followed by higher levels in winter and so it must be advantageous to achieve high summer levels.

So it makes sense to obtain high levels of vitamin D by sunbathing whenever possible in summer, while taking care not to burn. The alternative is to take high-dose vitamin D tablets which at present may only be obtained through the internet. People with darker skins (darker than types 1 and 2) would be advised to take a supplement in any case.

The SunSmart policy

The UK government has contracted the charity, Cancer Research UK, to be largely responsible for its policy on sunlight. The policy devised by CR-UK is called SunSmart. The name is identical to a policy developed in Australia and the SunSmart recommendations bear a remarkable similarity to recommendations of the Australian SunSmart policy. But Cancer Research UK says it is its own invention. Wherever it came from, it is completely unsuited to the climate of the British Isles. The British government has so far spent more than £3 million on promoting SunSmart and similar unsuitable policies [30].

SunSmart (see Box 1) consists of five principal recommendations which spell the word SMART down the left-hand side when arranged in order. The key recommendation is that for four hours during the middle of the day, the body should be covered up to protect against the sun; alternatively, a person may remain indoors or in the shade during those four hours. SunSmart also advises that suncream be applied 20 minutes before going out, although this is not clear from its five-point summary. A person adhering to this advice will get very little exposure to ultraviolet light which is, of course, strongest at midday, and so will make very little vitamin D.

A child enveloped in a sun protection suit. Not recommended. Parents using such clothing risk causing serious vitamin D insufficiency, if not frank deficiency, in their children unless they also take a high-potency vitamin D supplement not available in the UK.

Some people have taken the SunSmart advice to extremes and designed special head-to-toe garments for children which are reminiscent of chemical warfare suits (see photograph above). A child made to wear a suit of this kind, together with suncream on face and hands, is going to get virtually no vitamin D from the sun. It is difficult to see how a child dressed in this way could avoid consequent chronic disease of some kind unless also given a substantial vitamin D supplement.

Such total protection suits are the result of cancer scare stories used to promote SunSmart. These scares have induced some parents to take extreme measures to protect their children and have also persuaded some adults to take extreme measures to avoid sunlight. Such measures are likely to cause vitamin D deficiency with all its consequences, which quite probably include an overall increase in the risk of cancer.

The SunSafe advice

Some 28 years ago I began with others at *The Sunday Times* newspaper to compile information about lifestyle and health. The idea, encouraged by Harry Evans, our visionary editor, was to provide a guide to healthy living. The readership of *The Sunday Times* was such that our advice went out to millions of people. We took the job very seriously and compiled the advice in a book which we called *The Sunday Times Book of Body Maintenance* [31]. This exercise compelled me and others involved to think about what sort of advice is most valuable to the public and the best ways of promulgating it.

I continued to provide advice to readers when I went to *The Independent* and have continued to do so from time to time in books. I mention all this as a preface to advice which I provide here on sun exposure, to show that provision of advice is not a new departure for me and that I understand the serious considerations which must go into formulating it. The SunSafe advice (see Box 2), which I advocate here, has been carefully thought out for the reduction of risks of chronic disease from too much or too little sun. The SunSafe advice is conservative and reflects the advice given on sunlight in the UK in the past before prevention of skin cancer became the sole aim of sunlight policy.

The SunSmart programme (see Box 1) contains no positive statements about sunlight, only negative ones. SunSmart not only fails to encourage people to expose themselves to the sun, which is necessary for maintenance of healthy vitamin D levels, it actively discourages people from sun exposure of any kind. There is a clear risk that such negative advice will do harm by making people vulnerable to a variety of chronic diseases caused by vitamin D insufficiency, including cancer, as reviewed in other papers in this report. The SunSmart strategy is risky. It risks causing more cancer than it prevents. For this reason I have suggested that the SunSmart programme should be abandoned and replaced with a positive programme.

The SunSmart Advice

- **S**tay in shade between 11 a.m. and 3 p.m.
- **M**ake sure you never burn
- **A**lways cover up
- **R**emember to take extra care of children
- **T**hen use factor 15 sunscreen

Box 1: The SunSmart advice from Cancer Research UK is not recommended. All its messages about sunlight are negative and so it can be expected to prevent or discourage exposure to the sun with consequent risks of increasing vitamin D insufficiency, deficiency and disease.

The SunSafe programme (see Box 2) provides positive guidelines for sun exposure which are based both on up-to-date evidence and common sense. This programme encourages people to expose themselves safely to the sun. As a result, they will gain substantially more vitamin D during the summer, with consequent benefits the following winter and spring. At the same time, SunSafe warns against burning, which is the only risk of sun exposure that has been clearly linked with skin cancer. The SunSafe programme provides a practical approach which codifies what many sensible British people already do in summer.

The SunSafe Advice - safe and smart

1. Sunbathe safely without burning – every day if you can.
2. The middle of the day is a good time for sunbathing in the UK.
3. Start by sunbathing for 2-3 minutes each side. Gradually increase from day to day.
4. Don't use sun screen while sunbathing.
5. If feeling hot or uncomfortable expose a different area, cover up, move into the shade – or use sun screen.
6. When abroad, where the sun is generally stronger, expose yourself for shorter times until you find out how much is safe.
7. Children benefit from sun exposure, but need guidance.
8. A tan is natural and is generally associated with good health.

Box 2: The SunSafe advice is based on up-to-date scientific evidence and on the common-sense approach to sun exposure that was taken in the UK before advice such as SunSmart was promoted. It encourages safe exposure to the sun, which is our major source of vitamin D, and so can be expected to contribute to prevention of disease caused by vitamin D insufficiency.

In support of the SunSafe approach it is worth remembering that sunlight is a natural source of vitamin D for human beings. White skins have evolved so that sunlight can be used most effectively. It cannot be wise to suggest that a lifestyle which makes use of these natural means should be abandoned without very clear scientific evidence showing an overall benefit from such a change. Cancer Research UK and others suggest that the people in Britain lurk in the shade for four hours in the middle of the day, or put on sun screen and wait 20 minutes before emerging fully clothed, with hat, into full sunlight. These suggestions should be ignored because there is no clear scientific evidence that such crude sun avoidance measures have any overall benefit to health.

Protection against cancer

Some 16 different cancers have been shown to occur more frequently in northern states of the United States or in northern countries of Europe, compared with southern states or countries [32]. The incidence of these cancers varies systematically with latitude and/or intensity of sunlight. Using such data Bill Grant, an independent researcher, has calculated the number of 'extra' cancer deaths in the UK attributable to lack of exposure to sunlight [8]. Put crudely, these are deaths that would not occur if the UK had the same climate as Florida. However, it is not necessary to go to live in Florida to improve sun exposure. This can be done in the UK by sunbathing.

The estimated number of deaths per year from insufficient exposure to sun in the UK is much higher than deaths from all types of skin cancer. This in itself suggests that any measure, such as SunSmart advice, which further reduces general sun exposure may increase the overall risk of cancer. This can be seen to be even more likely when it is realised that only a proportion of the risk of melanoma may be caused by sun exposure – some estimates put it as low as 10% [4,33]. When this is borne in mind the overall risk of death from skin cancer can be seen to be small compared with the risk of death from cancer that is attributable to too little sun exposure.

Melanoma is a desperately tragic disease which is difficult or impossible to treat successfully once metastasis has occurred, and so we are all eager to prevent it if we can. Several studies have shown an association between cutaneous melanoma and sunburn, but other studies have shown that outdoor workers, who get much more sun exposure than indoor workers, are less vulnerable to the disease [34-36]. At least one careful study has shown that people who have greater lifetime exposure to the sun have a lower risk of melanoma [37], and another study has shown that people who have had greater sun exposure survive longer once melanoma has developed [38].

So much emphasis has been put on sunlight being a cause of melanoma that other possible causes of the disease are seldom mentioned. There are a few clues suggesting what these other causes may be. A link between cutaneous melanoma and higher social class or education has been found in a number of countries [39]. And several studies have found an increased risk of melanoma in those with greater adult height [40,41]. These clues suggest that melanoma may have similar causes to those proposed for other cancers [42].

For example, it has been suggested that plentiful food in childhood leads to higher growth hormone levels and greater adult height [42]. At the same time the high growth hormone levels may cause rapid cell growth and persistence of cells which are not fully differentiated. These cells are at high risk of developing into cancer cells. Vitamin D is known to act on cells to direct development towards full differentiation or apoptosis (regulated cell death) [43].

Evidence that melanoma is one of a group of cancers caused by some common factor or factors comes from studies showing that people with melanoma are particularly vulnerable to other cancers, possibly as a result of special conditions, such as too plentiful a diet in childhood and adolescence. A person who has had one melanoma has a 5-10% chance of developing another melanoma, as well as a significantly increased risk of developing other cancers [44-46]. Increased levels of insulin or insulin-like growth factors may well explain this increased vulnerability to melanoma and other cancers [47].

Vitamin D in the diet [48,49], as well as from the sun [37], may help to protect against melanoma, while obesity and lack of exercise may increase the risk of melanoma [41,50]. When melanoma is understood in this way, as a disease having multifactoral causes, then it can be seen that a more sophisticated prevention policy is needed that avoids sunburn but maintains or increases sun exposure so that vitamin D levels are improved and not reduced.

Conclusion

Many scientific studies suggest that insufficient vitamin D is a contributory cause of a wide range of chronic disease which probably includes multiple sclerosis, diabetes, heart disease and several types of cancer, in addition to the classic bone diseases. Evidence from scientific trials suggests that taking a vitamin D supplement may reduce the risk of fracture and other bone disease, hypertension and arthritis. At least 60 per cent of the adult population of the UK obtain insufficient vitamin D. So whatever the assessment of the evidence linking vitamin D insufficiency with chronic disease, it makes good sense for individuals to optimise their vitamin D levels. Much more could be done by governments and the European Union to make it easier for people to gain optimal vitamin D levels. Even so there is much that individuals themselves may do to improve their vitamin D levels and reduce the risk of chronic disease. A summary of what government and individuals may do follows.

What the government could do to raise population levels of vitamin D and reduce associated chronic disease falls into five categories:

1: Encourage non-mandatory fortification of a wide range of foodstuffs with vitamin D at suitable levels and agree suitable health claims for vitamin D. Announce a national campaign to promote such foods at a date agreed with producers.

2: Re-introduce a universal vitamin D supplement for all infants up to age five. Breast-fed babies should commence the supplement from birth. Other babies could commence the supplement on weaning because bottle milk is already fortified and so supplement is not needed until weaning. Uptake of these supplements should be promoted with an extensive national campaign. Vitamin D is not expensive. The main cost of this programme will be the cost of packaging, distribution and promotion.

3: Recommendations on use of vitamin D supplements and dose of vitamin D supplements for people of all ages are too low and need to be urgently reviewed.

4: Special government campaigns are needed to persuade people with darker skin living in the northern countries to take a year-round vitamin D supplement.

5: The SunSmart programme should be abandoned and regular safe sunbathing should be promoted.

How individuals may boost their vitamin D levels:

1: By taking a vitamin D supplement of 1-2,000 IUs per day all year round. A higher dose of 3,000 IUs per day might be better but is not yet approved by British or EU authorities.

2: By sunbathing safely (without burning) at every opportunity, following the SunSafe advice.

3: For those who can afford it, a winter sunshine holiday between January and March below latitude 35°, or in the southern hemisphere, will boost vitamin D levels when they are at their lowest. Suitable destinations include the Canary Islands, Florida, Caribbean, or any sub-tropical or tropical location.

4: Boosting calcium in the diet increases vitamin D levels in the body. Calcium may be increased relatively easily by consuming more milk, yoghurt and cheese, or by taking a calcium supplement. Eating brown, rather than wholemeal, bread will also boost calcium because wholemeal bread contains phytate which binds calcium and prevents it being absorbed from the bowel. Brown bread retains the wheatgerm which is a major source of B vitamins, and only lacks fibre. But lack of wheat fibre should not be a problem if plenty of vegetables and fruit, which are the best source of fibre, are eaten.

Vitamin D uptake may be boosted by altering the diet but this presents difficult choices and cannot provide sufficient vitamin D by itself. So it is not recommended as a priority. Margarine is one of the best sources of vitamin D but margarine contains trans-fatty acids, which have been linked to coronary heart disease. Certain breakfast cereals are fortified but these tend to be the more highly processed cereals that would not otherwise be a first choice.

Oily fish is a very good source of vitamin D for those who like it but the UK Food Standards Agency recommends that women who are or might become pregnant or are breast-feeding should eat no more than two portions per week and that men and children should eat no more than four portions a week. This is because fish accumulates pollutants, such as dioxins, that are discharged into the sea.

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Brian Diffey, professor of medical physics at the University of Newcastle, is clinical director of the Northern Regional Medical Physics Department, the largest such department in the UK, employing around 300 physicists, engineers and technologists within 13 hospitals across the north of England. He is based at Newcastle General Hospital and also holds a personal chair in photobiology within the University of Newcastle's Medical School.

He has had a considerable involvement in studies of human exposure to sunlight, its effects on normal and diseased skin, and in measures that can be taken to reduce excessive exposure – especially the use of sunscreens, an area in which he has pioneered novel ways of measuring broad-spectrum protection by sunscreens that have been adopted world-wide by the sunscreen industry.

He has published more than 350 papers in the medical and scientific literature and advises a number of bodies including Cancer Research UK and the World Health Organisation on the impact of sun exposure on skin cancer.

George Ebers is Action Research professor of neurology in the Department of Clinical Neurology at the University of Oxford. Professor Ebers is a graduate of the University of Toronto and did his postgraduate work at Montreal, Cornell University, and the Rockefeller University. He is an active clinician but his research interests have primarily been in the area of neurological genetics and multiple sclerosis. His laboratory found the first genetic linkages for paramyotonia congenita and episodic ataxia, and co-reported the molecular defect in Thomsen's disease. He initiated and led with co-investigators the Canadian Collaborative Study of MS. He has studied the natural history of the disease with findings which have been relevant to the design, execution and interpretation of clinical trials in this area. His main interests at present are studying gene/environment interactions in MS.

Ian Gibson is Member of Parliament for Norwich North, and honorary professor at the University of East Anglia. Dr Gibson was born in Scotland and educated at Dumfries Academy. He attended the University of Edinburgh, where he was awarded a BSc and a PhD. After working at the Universities of Edinburgh, Indiana and Seattle, he joined the University of East Anglia where he became dean of the School of Biological Sciences and served as head of a 10-strong research team investigating various forms of cancer. In 2003, the University awarded him an honorary professorship.

In 1997, 2001 and 2005, he was elected as Member of Parliament for Norwich North. He specialises in science and health issues and chairs the All Party Parliamentary Group on Cancer, and the All Party Parliamentary Group on Cuba. He is the former chair of both the House of Commons Select Committee on Science and Technology and the Parliamentary and Scientific Committee. He is also co-manager and occasional pivotal defender in the Parliamentary football team. His work in Parliament has been recognised by MPs and members of the Lords. Dr Gibson has twice won the e-politix award for Health Champion, as well as the Backbencher of the Year award in 2003.

Oliver Gillie, founder of Health Research Forum, is a freelance medical writer and journalist with 25 years' experience working for national newspapers in the United Kingdom. Over the last three years he has been engaged in researching environmental causes of chronic disease, in particular the effects of vitamin D

deprivation. This has led to the publication of *Sunlight Robbery* – a report which shows how health benefits of sunlight are denied to the public by current government policy – and to the foundation of Health Research Forum, a not-for-profit organisation for discussion of public health policy. His writing on this subject has been recognised by awards from the Medical Journalists' Association and the Association of British Science Writers.

Oliver Gillie has won 14 other awards for his journalism and has been awarded the Royal Jubilee medal by the Queen for his work in science and medical journalism. He has been medical correspondent of *The Sunday Times* and medical editor at *The Independent* where he started the Health Page, which was an immediate success and was copied by all the other national quality dailies. He has BSc and PhD degrees from Edinburgh University where he studied developmental biology and genetics under Professor C.H. Waddington, the distinguished geneticist and embryologist. He also worked at the National Institute for Medical Research in Mill Hill, London, under Sir Peter Medawar, and has published several scientific papers on microbial genetics.

Michael F. Holick is professor of medicine, physiology and biophysics, director of the General Clinical Research Center and director of the Bone Health Care Clinic and the Heliotherapy, Light and Skin Research Center at Boston University Medical Center.

After earning a postgraduate degree in biochemistry, a medical degree, and completing a research postdoctoral fellowship at the University of Wisconsin, Madison, Dr Holick completed a residency in medicine at the Massachusetts General Hospital in Boston.

Dr Holick has made numerous contributions to the field of the biochemistry, physiology, metabolism, and photobiology of vitamin D for human nutrition. He determined the mechanism for how vitamin D is synthesised in the skin and demonstrated the effects of ageing, obesity, latitude, seasonal change, sunscreen use, skin pigmentation and clothing on this vital cutaneous process. Dr Holick has established global recommendations advising sunlight exposure as an integral source of vitamin D. He has helped increase awareness in the paediatric and medical community regarding vitamin D deficiency in the US population, and its role in causing metabolic bone disease, and osteoporosis in adults.

Dr Holick's laboratory recognised the important role that parathyroid hormone-related peptide (PTHrP) played in regulating skin and hair cell growth. He recently completed a study demonstrating that the topical application of PTH (1-34) is safe and efficient for treating psoriasis. These observations offer a novel approach for developing new dermaceuticals for treating skin and hair growth disorders.

Dr Holick is a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Nutrition, and a member of the American Academy of Dermatology and the American Association of Physicians. He has been the recipient of numerous awards and honours, including the American College of Nutrition award in 2002 and the Robert H. Herman Memorial Award in Clinical Nutrition in 2003 from the American Society for Clinical Nutrition. Dr Holick has served on a number of national committees and editorial boards and has organised and/or co-chaired several international symposia. He has authored more than 230 peer-reviewed publications, and written more than 200 review articles, as well as numerous book chapters. He has acted as editor and/or co-editor on eight books, and has recently written *The UV Advantage*, published by ibooks, New York.

Elina Hyppönen is a lecturer at the Institute of Child Health, University College, London. She holds a Department of Health (UK) Public Health Career Scientist position and has been appointed as docent in epidemiology at the University of Tampere, Finland. She has a PhD in epidemiology (University of Tampere, 2001). Dr Hyppönen graduated from the University of Kuopio, Finland, in 1996 with a Masters degree in health science and at the same time qualified as an authorised nutritionist. She also has Masters degrees in public health (University of Kuopio, 1997) and medical statistics (London School of Hygiene and Tropical Medicine, 2000). Her main research interests are short- and long-term health effects of vitamin D, diabetes, and inter-generational and genetic influences on growth and disease risk.

Johan Moan is a research scientist at the Institute for Cancer Research, The Norwegian Radium Hospital, and professor at Oslo University. Since 1976 Professor Moan's main research field has been photochemotherapy of cancer (PCT). This led to the start of clinical photochemotherapy at the Norwegian Radium Hospital in 1991. He began research in the field of environmental physics and biology in 1987. The project is mainly concerned with UV-photobiology, the biological consequences of ozone depletion and the relationship between skin cancer and ultraviolet radiation. The activity of the group has led to several patents, some of which have been utilised

by the company Photo Cure. Professor Moan has won numerous prizes for his work, including the national prize from the Sigval and Nankis Bergesen Foundation, the prize of honour from the European Society for Photobiology, and the Birkeland prize for physics. He has published 385 scientific papers.

Richard Strange is professor of clinical biochemistry at Keele University Medical School, North Staffordshire, and clinical director of pathology services at the University Hospital of North Staffordshire. Professor Strange is a Fellow of the Royal College of Pathologists. His current research interests are in the application of molecular epidemiological approaches to determine the impact of selected genetic polymorphisms on disease risk and outcome. Of particular current interest is the role of ultra-violet radiation in determining susceptibility to prostate cancer, basal cell carcinoma and multiple sclerosis via a vitamin D-mediated mechanism.

Reinhold Vieth is professor in the Department of Nutritional Sciences and the Department of Laboratory Medicine and Pathobiology at the University of Toronto. He began research in the field of vitamin D in 1974. He is a Fellow of the Canadian Academy of Clinical Biochemists, and since 1992 has been director of the Bone and Mineral Laboratory at Mount Sinai Hospital's Pathology and Laboratory Medicine Department, which serves as the regional reference laboratory for biochemical tests related to vitamin D nutrition and bone disease.

Dr Vieth is recognised internationally as an expert in the toxicology and clinical nutrition of vitamin D. His work is the basis of current European guidelines for the safe adult intake of vitamin D. His longstanding, controversial perspective – that adult requirements for vitamin D are much higher than those currently recommended – is gaining broad acceptance.

Armin Zittermann is clinical research manager at the Department of Cardio-Thoracic Surgery, Heart Center North-Rhine Westfalia, Germany, and University Lecturer at the Department of Nutrition and Food Sciences, Bonn, Germany. Dr Zittermann's main research interests are human vitamin D status, including prevalence and consequences of vitamin D insufficiency in different population groups. He is also interested in immunological aspects of heart transplantation. Moreover, he has a longstanding interest in nutritional aspects of osteoporosis and cardiovascular diseases and their relation to the interaction of environmental factors and biomedical risk factors. His work spans nutrition, epidemiology, physiology, and biochemical methods, including the basis for causal inference.