

well satisfied for UVB and vitamin D and cancer in general except for prostate cancer, for which both low and high values are associated with increased risk in Nordic countries⁹ and the US.¹⁰ The reason for this U-shaped curve is still not understood.

While the spectrum of cancers whose risk is reduced in association with vitamin D was rapidly expanded by ecological studies^{2–6} and complemented by case–control,¹¹ cohort,^{7–9,11} and laboratory studies, public health action has been virtually non-existent. The greatest advance to date was the designation of 2000 IU/day of oral intake of vitamin D as the No Adverse Effect Level by the US National Academy of Sciences (NAS).

Oral doses currently consumed in the US (an estimated mean of 320 IU/day) are far too low,¹¹ and the designation of the 2000 IU/day dosage as safe by the NAS provides latitude to the community to increase intakes to levels required to reduce risk of cancer, with essentially no likelihood of adverse effects. It is now increasingly accepted that 0.75 minimal erythemal dose of UVB on 20% of skin area is the equivalent of ~2000 IU of oral intake of vitamin D₃. The duration of solar exposure required for this dosage varies by latitude, season, time of day, and race.

Public health leaders are now in nearly the same position with breast, colon, ovarian, and several other cancers that President Franklin D. Roosevelt was in when he was stricken with polio in 1921. Observation and inference based on its strong seasonality had shown that the disease was infectious, and not primarily genetic. This led to identification of the polio virus in 1908, but no public health action was initially taken apart from isolation of cases and quarantine. Yet FDR realized that action was needed and created the March of Dimes that ultimately led to the development of the Salk vaccine by 1952. The Salk vaccine of that era was 50% effective, which is similar to the effectiveness of 1000–2000 IU/day of vitamin D₃ for prevention of colorectal cancer.

It has been 25 years since the paper by Garland and Garland¹ was published in this journal, and 15 years since evidence of the vitamin D theory was extended to breast² and ovarian cancers.³ The intake of vitamin D is far too low for cancer risk reduction in the US.¹¹ It is time to act on this research and increase oral intake of vitamin D and de-stigmatize moderate exposure to solar UVB. The health benefits of such action will aid in cancer prevention

and extend to many other diseases and conditions¹²; the costs are low, the risks are few, and the potential public health benefits are tremendous.

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Commentary: From epidemiology to molecular biology—vitamin D and colorectal cancer prevention

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In 1987 I commenced a post-doctoral position at Cornell University, Ithaca, NY. My prior 'exposure' to vitamin D was connected with studies of intestinal transport systems that were regulated by 1,25-dihydroxyvitamin D. This investigation had

been initiated by the director of my institute, Prof. Dr Meinrad Peterlik, who himself had been a post doctoral fellow at Cornell University with the well-known investigator of intestinal calcium transport and vitamin D, Prof. Robert H. Wasserman. At Cornell University I first became interested in the magical properties that 1,25-dihydroxyvitamin D had on growth, differentiation, and survival of cancer cells. My growing interest was further stimulated by some controversial papers published by the group of Garland *et al.* from the University of California San Diego (UCSD) in La Jolla, CA.¹ These papers for the first time connected enhanced incidence of colon cancer to lack of sunlight and reduced serum vitamin D. This was a daring thought and, from knowledge existing on vitamin D renal synthesis in 1980, downright heretical. While I was incredulous and wished I could join this group for their studies (I had previously been an undergraduate and graduate student at UCSD and had much enjoyed the California sunshine!) this obviously had implications for my subsequent work. In 1991, after rejoining the Department of Pathophysiology at the University of Vienna, Austria, we showed that only in nanomolar concentrations the active vitamin D metabolite inhibited growth of human colon cancer cells. Intriguingly, the picomolar concentrations that are normally found in serum rather enhanced growth of these cells.

The relevance of nutritional calcium together with vitamin D in colorectal cancer prevention postulated by the Garland group² also became obvious in our *in vitro* work: low calcium in the culture medium resulted in significantly enhanced proliferation of colon cancer cells, and vitamin D was highly effective in normalizing growth and increasing expression of differentiation markers.³⁻⁶ From our studies, and studies from other groups, it became quite clear that nanomolar concentrations of the active metabolite were necessary to provide an antimetabolic response in colon cells. Therefore, the ultimate question remained: how could higher 25-hydroxyvitamin D3 serum concentrations provide protection against colorectal cancer, if serum levels of 1,25-dihydroxyvitamin D3 were in the picomolar range?

In 1995, at the Vitamin D Meeting, we presented a poster that showed for the first time that, when incubating Caco-2 cells with 16.6 nM radioactively labelled 25-hydroxyvitamin D3, ~10% of the precursor could be converted to 1,25-dihydroxyvitamin D3.⁷ In some subsequent papers,⁸⁻¹¹ we provided evidence that this synthesis, and also the degradation of the active hormonal metabolite, depended on the degree of cellular differentiation and was regulated by 1,25-dihydroxyvitamin D3 as well as by growth factors. Ultimately, by isolating cells from recently resected human colon tumours and from adjacent mucosa from the same patient, we were able to show that this capacity to synthesize 1,25-dihydroxyvitamin D3 was not just a property of cancer cell lines, but was indeed present to a high extent in fresh tumourous tissue, whereas the normal adjacent mucosa had much less vitamin D metabolism. This solved our conceptual problem: there is extrarenal colonic vitamin D synthesis that can reach nanomolar or even higher concentrations potentially due to tissue accumulation. Since it is highly likely that different regulatory mechanisms exist for this process compared with renal vitamin D synthesis, the supply of serum 25-hydroxyvitamin D3 indeed could become limiting during vitamin D insufficiency, even if vitamin D deficiency severe enough to result in rickets is not manifest.¹² This concept of vitamin D insufficiency and

enhanced incidence of a variety of chronic diseases such as cancers, diabetes type II, and even Parkinson's Disease is becoming well accepted now.^{13,14}

Thus, the early papers from the Garland group had a snowballing effect. Not only is there intense public discussion about raising the levels of vitamin D intake, either by fortification of foods or by supplements, but first efforts are made to enhance extrarenal vitamin D synthesis to promote cancer prevention. We had previously evaluated expression of the vitamin D receptor, of CYP27B1 (the synthesizing 1 α -hydroxylase) and of CYP24 (the catabolic 24-hydroxylase), in colon tissue from cancer and non-cancerous patients and observed a striking increase of VDR and CYP27B1 early during progression, whereas in advanced cancer patients expression was diminished.^{15,16} In contrast, CYP24 expression was enhanced during late tumour progression.¹⁷ This provided the biochemical evidence for the Garland hypothesis: we showed that synthesis in colonic tissue might reach therapeutic levels, but this capacity was diminished in anaplastic cells. We, therefore, concentrated our efforts on finding means that could raise 1 α -hydroxylation and reduce 24-hydroxylation. Recently we demonstrated that estradiol, as well as genistein, a phytoestrogen contained in soy, can enhance CYP27B1 expression,^{18,19} whereas low nutritional calcium will promote degradation of colonic 1,25-dihydroxyvitamin D3 by elevating expression of CYP24.²⁰ An interaction between vitamin D and calcium with respect to colon cancer prevention had been postulated by Garland *et al.*² already two decades ago and has been confirmed recently in several studies.^{12,21-23} From our data in a mouse model it is quite clear that lack of both substances will lead to connected events: in the colon, low dietary calcium causes hyperproliferation and elevation of vitamin D degradation. This in turn will cause further hyperproliferation.

While I could only mention a few of our own studies concerning colorectal cancer it is clear that the Garland papers were seminal also in other areas of cancer research. In fact it has to be acknowledged that all of the research on extrarenal vitamin D synthesis for tumour prevention, be it in the prostate, mammary gland, or pancreas, originated from the 'Garland Hypothesis' in the early 1980s. I had been in e-mail contact with Cedric Garland already for several years. In April 2005, I had the chance to actually visit him at UCSD. For me, it was a homecoming to my old Alma Mater, and I finally was able to meet the person who had strongly influenced 15 years of my research.

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Commentary: Sunlight, vitamin D, and the cancer connection revisited

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This discussion commemorates the 25th anniversary of the publication in this journal of the report by Cedric and Frank Garland that first raised the hypothesis that vitamin D—the so-called ‘sunlight vitamin’—might have a protective influence on colon cancer.¹ As research in this area has accelerated, most rapidly in only the last few years, the Garlands’ insights can now

be fully recognized. Experimental, clinical, and epidemiological data is pointing to a beneficial role of vitamin D, not only for colorectal malignancy but also potentially for many of the most common and lethal forms of cancer in temperate climates. Vitamin D is a fat-soluble vitamin that is essential as a positive regulator of calcium homeostasis. The term ‘vitamin D’ is something of a misnomer as all of the human requirement can be obtained from a non-nutritive source: ultraviolet radiation (UVR) in sunlight. In the skin, 7-dehydrocholesterol (pro-vitamin D3) is photolysed by ultraviolet light (UVR, 280–320 nm) to pre-vitaminD3, which spontaneously isomerizes to vitamin

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