Dr. Frank Caldwell Garland, June 20, 1950–August 17, 2010

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Frank Caldwell Garland, Ph.D., died August 17, 2010 after a year-long battle with cancer. He will be remembered for his seminal work with his brother Cedric F. Garland in proposing the ultraviolet-B (UVB)-vitamin D-cancer hypothesis to explain the geographical variation of colon cancer mortality rates in the United States in 1980. This hypothesis has been extended to about 20 types of cancer using the ecological approach, and supported strongly by observational studies of prediagnostic serum 25-hydroxyvitamin D [25(OH)D] for incidence of breast, colorectal and ovarian cancer, and a randomized controlled trial that used sufficient vitamin D (1,150 IU/day) to and found a strongly beneficial effect on cancer incidence. The UVB-vitamin D-cancer hypothesis is also supported by studies that used as the index of solar UVB irradiance the amount of sunlight exposure in childhood or incidence of non-melanoma skin cancer. Survival after diagnosis was increased for individuals with higher serum 25(OH)D levels at the time of cancer diagnosis for six types of cancer: breast, colorectal, lung and prostate cancer; melanoma and non-Hodgkin's lymphoma. The ecological study approach is ideally suited to studying cancer risk-modifying factors since the lag between cancer initiation and detection or death can be 20–40 years or more, making ordinary observational studies difficult. The impact on vitamin D research by both Frank Garland and Cedric Garland has been immense. Health policy leaders will realize this in the near future, providing a rich legacy for humanity.

Dr. Frank Caldwell Garland died Tuesday, August 17, 2010, in La Jolla, California, after a year-long battle with cancer. He was Professor of Family and Preventive Medicine at the University of California, San Diego School of Medicine, and Technical Director and former Scientific Director of the Naval Health Research Center in San Diego. Born June 20, 1950, in San Diego, Garland received his Ph.D. in epidemiology from Johns Hopkins University and began a distinguished career in vitamin D research for cancer and other disease prevention, along with research on several other diseases.

Garland's brother and coinvestigator, Cedric Garland, also a professor of family and preventive medicine at UC-San Diego, said their interest in vitamin D began in July 1974. At a seminar, the Garland brothers noticed from mortality rate maps that breast and colon cancer rates were twice as high in many counties of the northern tier of states than in the southwest. These geographic differences led to their hypothesis that vitamin D and calcium were preventing adenocarcinoma of the colon and breast in the sunnier parts of the United States. This theory broke away from the conventional belief that sunlight was a dangerous cause of skin cancer that everyone should avoid.

First published in 1980 in the *International Journal of Epidemiology*,¹ the Garlands' hypothesis proposed that vitamin D and calcium can prevent cancer, setting the course for a three-decade-long career devoted to vitamin D research.

Frank Garland's descriptive study of sunlight and cancer mortality initiated two well-known studies that members of the Garland team and other colleagues

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published in the medical journal *The Lancet*. The first was a 19-year historical cohort study in Chicago, that found that people whose vitamin D and/or calcium intakes were in the top fifth of the population had half the incidence of colon cancer of those in the bottom fifth.² This was the first study to find an effect of oral intake of vitamin D or calcium on cancer risk. The second key paper by Garland and his colleagues analyzed vitamin D concentrations in volunteers in Washington County, Maryland. This cohort study collected blood from 25,000 volunteers and showed for the first time that people with high concentrations of 25(OH)D in the blood had very low risk of colon cancer.³ They also extended the UVB-vitamin D-cancer hypothesis to breast cancer, in collaboration with Edward Gorham⁴ and ovarian⁵ cancer.

In 2006, their landmark study was reprinted⁶ along with favorable commentaries by distinguished cancer researchers.⁷⁻¹¹ Other ecological studies extended the ultraviolet B (UVB)-vitamin D-cancer hypothesis to 20 types of cancer.¹²⁻¹⁶

The Garlands and their colleagues, including Edward Gorham, Sharif Mohr and William Grant, also examined the role of UVB and vitamin D in reducing the risk of cancer using cancer incidence data from over 100 countries for each type of cancer with respect to solar UVB indices based on stratospheric ozone levels, cloud cover and latitude, and including other important risk-modifying factors such as diet and smoking. The first type of cancer studied in this series of studies was ovarian cancer.¹⁷ By now, eight types of cancer have been studied this way: bladder, brain, breast, endometrial, lung, ovarian, pancreatic and renal cancers as well as type 1 diabetes mellitus.¹⁸ The regression fit to the scatter plot of cancer incidence with respect to latitude is lightheartedly called a "smiley curve." Such ecological study findings are generally quite consistent, as recently (reviewed in refs. 19, 20).

Several articles using other approaches offered more support for the UVB-vitamin D-cancer hypothesis. A paper from the Health Professionals Follow-Up Study found that six types of cancer had significant inverse correlations with a vitamin D index, and another six had nonsignificant

inverse correlations.²¹ Also, an important randomized controlled trial of vitamin D and calcium supplementation found a 77% reduction in all-cancer incidence between the ends of the first and fourth years.²² This was a serendipitous result of a trial originally intended to study the association of vitamin D and calcium supplementation with incidence of fractures.

Several observational studies of breast and colorectal cancer found 40–60% reductions for individuals with serum 25(OH)D levels above 100 nmol/L compared with less than 20 nmol/L.²³⁻²⁶ A recent observational study also found an inverse correlation for ovarian cancer with respect to prediagnostic serum 25(OH)D.²⁷ A review of the evidence for UVB and vitamin D in reducing the risk of cancer based on A.B. Hill's criteria for causality in epidemiology concluded that the criteria were largely satisfied for breast and colorectal cancer, but there is also good evidence that other cancers meet these criteria as well, including bladder, esophageal, gallbladder, gastric, ovarian, rectal, renal and uterine corpus cancer, as well as Hodgkin's and non-Hodgkin's lymphoma.²⁸ A recent review from the Netherlands concluded that the evidence for a beneficial effect of UVB included reduction in incidence of colon and breast cancers and non-Hodgkin's lymphoma.²⁹

Two bibliographic means have been used to assess the impact of the work of the Garlands and their colleagues. One is the number of scientific papers that have cited their work. According to the ISI citation index, seven of their vitamin D papers^{1-4,30-32} have been cited more than 100 times, placing them in the top 1%–5% of health and medicine journal articles for the year of publication. Another way is to look at the number of papers with the terms *vitamin D* and *cancer* in the title or abstract. As of 2 December 2010, the PubMed database indicates 2277 such reports. Their seminal paper was the first to look at the role of vitamin D at the population level.

Several reasons explain the lack of acceptance of the UVB-vitamin D-cancer hypothesis:³³

(1) Selling vitamin D yields little profit.

(2) Health care systems around the world would lose money if everyone had serum 25(OH)D levels above 100 nmol/L rather than near 50–60 nmol/L, because maintaining the higher levels would reduce mortality rates by 15–20%.³⁴⁻³⁸

(3) Some dermatologists emphasize the importance of avoiding the sun and consider the UVB-vitamin D-cancer hypothesis as a threat to their message.³⁹⁻⁴²

Recognizing that the health systems of the world are slow to accept the rising tide of evidence that vitamin D has many health benefits and that most people do not have optimal serum 25(OH)D levels,⁴³ several nonprofit organizations have formed to educate the public directly. Two prominent examples are the Vitamin D Council, directed by John J. Cannell, MD (www.VitaminDSociety.org), and Grassroots Health, directed by Carole Baggerly (www.GrassrootsHealth.net). Both organizations have information about the health benefits of vitamin D, and both offer a serum 25(OH)D test kit that involves placing spots of blood on a card and mailing it in for analysis.

It is prophetic to consider German philosopher Arthur Schopenhauer's quote about truth: "All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident." The status for vitamin D findings appears to be in stage 2. A few investigators occasionally publish papers that could be regarded as opposing the UVB-vitamin D-cancer hypothesis. Some of this research magnifies minor variations found among observational studies without realizing that the effects of vitamin D are important starting in early life, and that observational studies that begin to collect data late in life may not be optimally suited to assessing the lifelong role of vitamin D in cancer prevention.

The resolution of the 1854 Broad Street cholera epidemic has many aspects in common with the UVB-vitamin D-cancer hypothesis. Dr. John Snow's investigation by interviewing relatives and neighbors of those who died from cholera, then mapping of the residences of those who died and doing some statistical analysis, concluded that the water drawn from the Broad Street pump was the source of cholera, even though the mechanism

was not fully understood for decades, as a scientific germ theory of cholera was not then accepted. (An Italian, Filippo Pacini, described the cholera bacterium in the same year, but his discovery was ignored until the cholera bacterium was again discovered independently by Robert Koch, in 1883).⁴⁴ John Snow's work is a foundation stone of modern epidemiology—it ultimately caused scientific thinking to evolve and incorporate the then-unknown role of microorganisms in disease.

To be a great scientist is to be curious, and Frank was curious about everything in the scientific and natural world. A gifted naturalist, Frank could recognize a bird simply from its flight pattern or song, and he could identify a plant from only a berry or leaf. On a camping trip in the Anza Borrego Desert, I (EDG) once asked Frank what birds he thought we'd see that day. He named a dozen birds—including a crested black cardinal-like bird called a *Phainopepla*, a spotted cactus wren and a small green verdin—all of which we saw within 30 minutes. When I asked him how he knew what we would see, he told me that he'd heard their singing that morning as he lay in his tent and identified them by their songs.

Frank also appreciated history, understanding the potential of a few dedicated people to shape the future. He would give exciting accounts of the actions of the small Army of the West in the historic Battle of San Pasqual that contributed to California's independence in 1846.

Another place that Frank loved and often visited was a desert cactus region located on a high, isolated windblown ridge above the San Diego Wild Animal Park. The saguaro, senita and ocotillo cactus there are spectacular and the long and panoramic view across the San Pasqual Valley laying below appealed to Frank's sense of history.

Dr. Frank Garland enjoyed taking the long view across time and across that historic valley and took a long view in his own life. He often reminded his colleagues that distinguishing the urgent from the important is crucial. He reminded us to deal with whatever is urgent but to never neglect what is important. Defining and establishing the crucial role of vitamin D in the prevention of many types of cancer

and other devastating diseases, was of pre-eminent importance to him. His accomplishments on this topic are his most outstanding and lasting scientific legacy and contribution to the well-being of humankind.

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