9

Human Health Effects

Introduction

The authors of the Fourth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC) claimed to have "*very high* confidence" that "climate change currently contributes to the global burden of disease and premature deaths" (IPCC, 2007-II, p. 393, emphasis in the original). They also claim climate change will "increase malnutrition and consequent disorders … increase the number of people suffering from death, disease and injury from heatwaves, floods, storms, fires and droughts … continue to change the range of some infectious disease vectors … increase the burden of diarrhoeal diseases … increase cardio-respiratory morbidity and mortality associated with ground-level ozone … [and] increase the number of people at risk of dengue." The IPCC admits warming weather would "bring some benefits to health, including fewer deaths from cold," but says those benefits "will be outweighed by the negative effects of rising temperatures worldwide, especially in developing countries" (ibid.).

The 2009 report of the Nongovernmental International Panel on Climate Change (NIPCC) debunked many of those claims, starting with the simple fact that the modest warming that occurred in the twentieth century did not cause more "heatwaves, floods, storms, fires and droughts," and consequently these imagined phenomena could not have harmed human health or well-being. Readers of the current report are referred to Chapter 5, where they will find more, and more recent, evidence to that effect.

Idso and Singer (2009) went on to examine research on the relationships between temperature and CO_2 and diseases, heat-related mortality, nutrition, and human longevity, finding global warming is likely to improve rather than harm human health.

In the following pages we review new scientific research on these same matters, finding it supports the same conclusion. That analysis is followed by a brief discussion of viral and vector-borne diseases, after which we review papers that document CO_2-induced changes in certain of the medicinal and nutritional properties of plants, which should bode well for future human health gains.

References

Idso, C.D. and Singer, S.F. 2009. *Climate Change Reconsidered: 2009 Report of the Nongovernmental International Panel on Climate Change (NIPCC)*. Chicago, IL: The Heartland Institute.

IPCC. 2007-II. *Climate Change 2007: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*. Edited by M.L. Parry, O.F. Canziani, J.P. Palutikof, P.J. van der Linden and C.E. Hanson, Cambridge, UK: Cambridge University Press.

9.1. Temperature-Related Human Mortality

Christidis et al. (2010) report, "the IPCC AR4 states with very high confidence that climate change contributes to the global burden of disease and to increased mortality," citing the contribution of Confalonieri et al. (2007) to that document. Idso and Singer (2009), however, reported that rising temperatures lead to a greater reduction in winter deaths than the increase they cause in summer deaths, resulting in a large net decrease in human mortality, based on findings described in the peer-reviewed scientific literature through 2007. In this interim report we review studies of the subject published after that time.

Christidis et al. extracted the numbers of daily deaths from all causes reported on death registration data supplied by the U.K. Office of National Statistics for men and women 50 years of age or older in England and Wales for the period 1976–2005, which they divided by daily population estimates they obtained by fitting a fifth-order polynomial to midyear population data, yielding deaths per million people. They compared the results with surface air temperature data that showed a warming trend during the three-decade period of 0.47°C per decade. In addition, they employed a technique called optimal detection, which can be used to estimate the role of human adaptation in the temperature-related changes in mortality they observed.

As expected, during the hottest months of the year, warming led to increases in death rates, while during the coldest months of the year warming led to decreases in death rates. The three scientists reported, for example, that if no adaptation had taken place, there would have been 1.6 additional deaths per million people per year due to warming in the hottest part of the year over the period 1976–2005, but there would have been 47 fewer deaths per million people per year due to warming in the coldest part of the year, for a lives-saved to life-lost ratio of 29.4. That, of course, represents a substantial net benefit from the warming experienced in England and Wales during the three-decade period. When adaptation was included in the analysis, they found there was an increase of only 0.7 deaths per million people per year due to warming in the hottest part of the year, but a decrease of fully 85 deaths per million people per year due to warming in the coldest part of the year, for a lives-saved to life-lost ratio of 121.4.

Working in the Castile-Leon region of Spain—a plateau in the northwestern part of the country which includes nine provinces with a low population density that can be considered as aging—Fernandez-Raga et al. (2010) obtained (from the country's National Meteorological Institute) meteorological data from weather stations situated in eight of the provincial capitals for 1980–1998, and they obtained contemporary mortality data from the country's National Institute for Statistics for deaths associated with cardiovascular, respiratory, and digestive-system diseases.

Various analyses of the monthly averaged data revealed a number of interesting results. First, for all three of the disease types studied, the three researchers found "the death rate is about 15% higher on a winter's day than on a summer's day," which they describe as "a result often found in previous studies," citing the work of Fleming et al. (2000), Verlato et al. (2002), Grech et al. (2002), Law et al. (2002), and Eccles (2002). Second, in a finding that helps to explain the first finding, the three researchers discovered that when monthly averaged human death rates were plotted against monthly averages of daily mean, maximum, and minimum air temperature, the results nearly always took the form of a U-shaped concave parabola, as shown in Figure 9.1.1.

For all three disease types, Fernandez-Raga et al. found all three temperatures (daily mean, maximum, and minimum) at which minimum death rates occurred—which they refer to as *ideal* or *comfort* temperatures—were all within about 1°–7°C of the maximum values typically reached by those three types of temperature, whereas they were anywhere from 14° to 24°C away from their minimum values. Consequently, the ideal or comfort temperatures were always very close to (and sometimes nearly identical to) the maximum values reached by the mean, maximum, and minimum temperatures experienced in the region, and they were much more removed from the minimum values of those three temperature parameters, as illustrated in the figure.

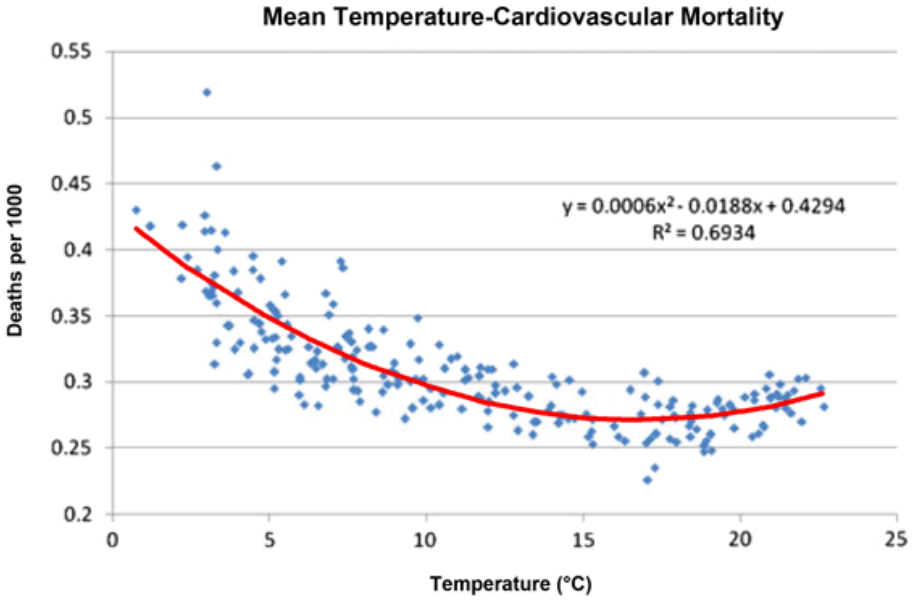

Figure 9.1.1. Monthly deaths in the Castile-Leon region of Spain attributable to cardiovascular disease vs. mean daily air temperature. Adapted from Fernandez-Raga et al. (2010).

The data clearly demonstrate the people of the Castile-Leon region of Spain are much more likely to die from a cardiovascular disease in the extreme cold of winter than in the extreme heat of summer. The same was found to hold true with respect to respiratory and digestive system diseases. Cold has been found to be a much greater killer of people than heat almost everywhere in the world, and in conjunction with almost any type of illness.

In a more broad-based study, Analitis et al. (2008) wrote, "in recent years, the effects of meteorologic factors on health have attracted renewed interest because of the observed and predicted climate change, which is expected to result in a general rise in temperature." This development, in their words, has led to a "recent focus on heat-wave episodes," which may have fostered the perception that cold-related mortality is not as important a public health concern as is heat-related mortality.

To rectify this situation, the 14 researchers analyzed short-term effects of cold weather on mortality in 15 European cities (Athens, Greece; Barcelona, Spain; Budapest, Hungary; Dublin, Ireland; Helsinki, Finland; Ljubljana, Slovenia; London, United Kingdom; Milan, Italy; Paris, France; Prague, Czech Republic; Rome, Italy; Stockholm, Sweden; Turin, Italy; Valencia, Spain; and Zurich, Switzerland). Specifically, they assessed the effects of minimum apparent temperature on cause- and age-specific daily mortality over the cold half of the year (October–March), using data from 1990–2000 analyzed via "Poisson regression and distributed lag models, controlling for potential confounders."

The international team of scientists—from Finland, Greece, Ireland, Italy, Slovenia, Spain, and Sweden—found "a 1°C decrease in temperature was associated with a 1.35% increase in the daily number of total natural deaths and a 1.72%, 3.30%, and 1.25% increase in cardiovascular, respiratory, and cerebrovascular deaths, respectively." In addition, they reported "the increase was greater for the older age groups," and the cold effect "persisted up to 23 days, with no evidence of mortality displacement." The latter finding is extremely important because in the case of heat-related deaths there is such a displacement, and its impact is substantial.

In Germany, for example, Laschewski and Jendritzky (2002) analyzed daily mortality rates in Baden-Wurttemberg (10.5 million inhabitants) over the 30-year period 1958–97 to determine the sensitivity of the population of this moderate climatic zone to long- and short-term episodes of heat and cold. Their research indicated mortality showed "a marked seasonal pattern with a minimum in summer

and a maximum in winter." With respect to short-term exposure to heat and cold, however, they found "cold spells lead to excess mortality to a relatively small degree, which lasts for weeks," and "the mortality increase during heat waves is more pronounced, but is followed by lower than average values in subsequent weeks." Thissuggests, in their words, that people who died from short-term exposure to heat "would have died in the short term anyway."

With respect to this short-term mortality displacement that occurs in conjunction with heat-related deaths, Laschewski and Jendritzky's data demonstrate it is precisely that: merely a displacement of deaths and not an overall increase. They found, for example, that the mean duration of above-normal mortality for the 51 heat episodes that occurred from 1968 to 1997 was ten days, with a mean increase in mortality of 3.9 percent, after which there was a mean decrease in mortality of 2.3 percent for 19 days. The net effect of the two perturbations was an overall decrease in mortality of 0.2 percent over the full 29-day period. Analitis et al. concluded their paper by stating their results "add evidence that cold-related mortality is an important public health problem across Europe and should not be overlooked by public health authorities because of the recent focus on heat-wave episodes."

In providing some background for another recent study of the subject, Young and Kakinen (2010) write, "Arctic populations, especially indigenous people, could be considered as 'vulnerable,' because their health status generally shows disparities when compared to the national or more southern populations," and they state "it is not known if the harsh climate, and especially cold temperatures, could be a contributing or causative factor of the observed health inequalities." To seek answers to this, the two researchers determined mean January and July temperatures for 27 Arctic regions, based on weather station data for the period 1961–1990, and their association with a variety of health outcomes assessed by correlation and multiple linear regression analyses.

The two researchers found mean January temperature correlated negatively with several health outcomes, including infant mortality rate, age-standardized mortality rates (all causes), perinatal mortality rate, and tuberculosis incidence rate, but it correlated positively with life expectancy. That is to say, as mean January temperature rose, the desirable metric of life expectancy at birth rose right along with it, while all of the undesirable health metrics (such as mortality and disease incidence) declined. For example, they report "for every 10°C increase in mean January temperature, the life expectancy at birth among males increased by about six years" and "infant mortality rate decreased by about four deaths per thousand live births."

Young and Kakinen concluded the cold climate of the Arctic is "significantly associated with higher mortality" and "should be recognized in public health planning," noting that "within a generally cold environment, colder climate results in worse health." For people living in these regions, therefore, a little global warming could go a long way toward improving their quality of life, as well as the length of time they have to enjoy it.

In another impressive study, Deschenes and Moretti (2009) analyzed the relationship between weather and mortality, based on data that included the universe of deaths in the United States over the period 1972–1988, wherein they matched each death to weather conditions on the day of death and in the county of occurrence. These high-frequency data and the fine geographical detail allowed them to estimate with precision the effect of cold and hot temperature shocks on mortality, as well as the dynamics of such effects—most notably, the existence or absence of a "harvesting effect" whereby the temperature-induced deaths either are or are not subsequently followed by a drop in the normal death rate that could either partially or fully compensate for the prior extreme temperature-induced deaths.

The two researchers state their results "point to widely different impacts of cold and hot temperatures on mortality." In the latter case, they discovered "hot temperature shocks are indeed associated with a large and immediate spike in mortality in the days of the heat wave," but "almost all of this excess mortality is explained by near-term displacement," so that "in the weeks that follow a heat wave, we find a marked decline in mortality hazard, which completely offsets the increase during the days of the heat wave," such that "there is virtually no lasting impact of heat waves on mortality."

In the case of cold temperature days, they also found "an immediate spike in mortality in the days of the cold wave," but "there is no offsetting decline in the weeks that follow," so "the cumulative effect of one day of extreme cold temperature during a thirty-day window is an increase in daily mortality by as much as 10%." In addition, they write, "this impact of cold weather on mortality is significantly larger for

females than for males," but "for both genders, the effect is mostly attributable to increased mortality due to cardiovascular and respiratory diseases."

In further discussing their findings, Deschenes and Moretti state, "the aggregate magnitude of the impact of extreme cold on mortality in the United States is large," noting it "roughly corresponds to 0.8% of average annual deaths in the United States during the sample period." They estimate "the average person who died because of cold temperature exposure lost in excess of ten years of potential life," whereas the average person who died because of hot temperature exposure likely lost no more than a few days or weeks of life.

Interestingly, the two scientists additionally report many people in the United States have taken advantage of these obvious facts by moving "from cold northeastern states to warm southwestern states." Based on their findings, they calculate "each year 4,600 deaths are delayed by the changing exposure to cold temperature due to mobility," and "3% to 7% of the gains in longevity experienced by the U.S. population over the past three decades are due to the secular movement toward warmer states in the West and the South, away from the colder states in the North."

Working in the Southern Hemisphere, Bi et al. (2008) used correlation and autoregressive integrated moving average regression analyses to derive relationships between various aspects of weather and mortality in the general population and elderly (65 years of age and older) of Brisbane, Australia—which they describe as having a subtropical climate—over the period 1986–1995. In doing so, they determined "death rates were around 50–80 per 100,000 in June, July, and August [winter], while they were around 30–50 per 100,000 in the rest of the year, including the summer." They state "this finding applied both to the general population and to the elderly population, and to deaths from various causes."

In discussing the fact that "more deaths occurred in the winter than during other seasons of the year, although winter in Brisbane is very mild," the researchers noted "it is understandable that more deaths would occur in winters in cold or temperate regions, but even in a subtropical region, as indicated in this study, a decrease in temperatures (in winters) may increase human mortality." Consequently, the evidence continues to grow that extremes of cold lead to the deaths of many more people than extremes of heat in both cold and warm climates.

In a study with a slightly different take on the subject, Tam et al. (2009) studied daily mortality data from 1997 to 2002, which they obtained from the Hong Kong Census and Statistics Department, examining the association between diurnal temperature range (DTR = daily maximum temperature minus daily minimum temperature), while focusing on cardiovascular disease among the elderly (people aged 65 and older). They discovered "a 1.7% increase in mortality for an increase of 1°C in DTR at lag days 0–3," and they describe these results as being "similar to those reported in Shanghai."

In discussing their findings, the four Hong Kong researchers stated, "a large fluctuation in the daily temperature—even in a tropical city like Hong Kong—has a significant impact on cardiovascular mortality among the elderly population." In addition, we note it has long been known that the DTR has declined significantly over many parts of the world as mean global temperature has risen over the past several decades (Easterling et al., 1997), which is perhaps another reason why colder temperatures are a much greater risk to human life than are warmer temperatures: As the planet warms, local DTRs tend to decline, which leads to a corresponding decline in human death rates.

Turning to the Shanghai study mentioned by Tam et al., we find that Cao et al. (2009)—working within the nine urban districts of Shanghai, China—used time-series and case-crossover approaches to assess the relationship between DTR and coronary heart disease (CHD) deaths between 1 January 2001 and 31 December 2004, based on mortality data for elderly people (66 years of age or older), obtained from the Shanghai Municipal Center of Disease Control and Prevention, plus temperature data they obtained from a fixed-site station in the Xuhui District of Shanghai, which they adjusted to account for the mortality impacts of long-term and seasonal trends in CHD mortality, day of week, temperature, relative humidity, and concomitant atmospheric concentrations of PM_{10}, SO_2, NO_2, and O_3, which they obtained from the Shanghai Environmental Monitoring Center.

This work revealed, in Cao et al.'s words, that "a 1°C increase in DTR (lag = 2) corresponded to a 2.46% increase in CHD mortality on time-series analysis, a 3.21% increase on unidirectional case-crossover analysis, and a 2.13% increase on bidirectional case-crossover analysis," and "the estimated effects of DTR on CHD mortality were

similar in the warm and cool seasons." Thus, the seven scientists concluded their data suggested even "a small increase in DTR is associated with a substantial increase in deaths due to CHD." And since the DTR has declined significantly over most of the world as mean global air temperature has risen over the past several decades, it can be appreciated that the global warming with which this DTR decrease is associated (which is driven by the fact that global warming is predominantly caused by an increase in daily minimum temperature) has likely helped to significantly reduce the CHD-induced mortality of elderly people worldwide.

In one final study dealing with the heart and employing a generalized additive statistical model that blends the properties of generalized linear models with additive models, Bayentin et al. (2010) analyzed the standardized daily hospitalization rates for ischemic heart disease (IHD) and their relationship with climatic conditions up to two weeks prior to the day of admission—controlling for time trends, day of the season, and gender—in order to determine the short-term effects of climate conditions on the incidence of IHD over the 1989–2006 time period for 18 different regions of Quebec. Perhaps the most interesting and important finding of this study was, as they describe it, that "a decline in the effects of meteorological variables on IHD daily admission rates was observed over the period of 1989–2006." This response, in their words, "can partly be explained by the changes in surface air temperature," which they describe as warming "over the last few decades," as is further described by Bonsal et al. (2001) and Zhang et al. (2000) for the twentieth-century portion of the study's duration. In addition, they note "winters have been steadily warmer," while "summers have yet to become hotter for most regions." This is another beneficial characteristic of the warming that was experienced over most of the planet throughout the latter part of the twentieth century: a gradual reduction in DTR, as confirmed by the work of Easterling et al. (1997).

In summation, the material presented in this chapter represents overwhelming evidence for a positive effect of global warming on human health.

References

Analitis, A., Katsouyanni, K., Biggeri, A., Baccini, M., Forsberg, B., Bisanti, L., Kirchmayer, U., Ballester, F., Cadum, E., Goodman, P.G., Hojs, A., Sunyer, J., Tiittanen, P., and Michelozzi, P. 2008. Effects of cold weather on mortality: Results from 15 European cities within the PHEWE project. *American Journal of Epidemiology* **168**: 1397–1408.

Bayentin, L., El Adlouni, S., Ouarda, T.B.M.J., Gosselin, P., Doyon, B., and Chebana, F. 2010. Spatial variability of climate effects on ischemic heart disease hospitalization rates for the period 1989-2006 in Quebec, Canada. *International Journal of Health Geographics* **9**:10.1186/1476-072X-9-5.

Bi, P., Parton, K.A., Wang, J., and Donald, K. 2008. Temperature and direct effects on population health in Brisbane, 1986–1995. *Journal of Environmental Health* **70** (8): 48–53.

Bonsal, B.R., Zhang, X., Vincent, L.A., and Hogg, W.D. 2001. Characteristics of daily and extreme temperatures over Canada. *Journal of Climate* **14**: 1959–1976.

Cao, J., Cheng, Y., Zhao, N., Song, W., Jiang, C., Chen, R., and Kan, H. 2009. Diurnal temperature range is a risk factor for coronary heart disease death. *Journal of Epidemiology* **19**: 328–332.

Christidis, N., Donaldson, G.C., and Stott, P.A. 2010. Causes for the recent changes in cold- and heat-related mortality in England and Wales. *Climatic Change* **102**: 539–553.

Confalonieri, U., Menne, B., Akhtar, R., Ebi, K.L., Hauengue, M., Kovats, R.S., Revich, B., and Woodward, A. 2007. Human health. In *Climate Change 2007: Impacts, Adaptation and Vulnerability*, edited by M.L. Parry, et al. Cambridge, UK: Cambridge University Press.

Deschenes, O. and Moretti, E. 2009. Extreme weather events, mortality, and migration. *The Review of Economics and Statistics* **91**:659–681.

Easterling, D.R., Horton, B., Jones, P.D., Peterson, T.C., Karl, T.R., Parker, D.E., Salinger, M.J., Razuvayev, V., Plummer, N., Jamason, P., and Folland, C.K. 1997. Maximum and minimum temperature trends for the globe. *Science* **277**: 364–367.

Eccles, R. 2002. An explanation for the seasonality of acute upper respiratory tract viral infections. *Acta Oto-Laryngologica* **122**: 183–191.

Fernandez-Raga, M., Tomas, C., and Fraile, R. 2010. Human mortality seasonality in Castile-Leon, Spain, between 1980 and 1998: the influence of temperature, pressure and humidity. *International Journal of Biometeorology* **54**: 379–392.

Fleming, D.M., Cross, K.W., Sunderland, R., and Ross, A.M. 2000. Comparison of the seasonal patterns of asthma identified in general practitioner episodes, hospital admissions, and deaths. *Thorax* **55**: 662–665.

Grech, V., Balzan, M., Asciak, R.P., and Buhagiar, A. 2002. Seasonal variations in hospital admissions for asthma in Malta. *Journal of Asthma* **39**: 263–268.

Idso, C.D. and Singer, S.F. 2009. Climate Change Reconsidered: 2009 Report of the Nongovernmental International Panel on Climate Change (NIPCC). Chicago, IL: The Heartland Institute.

Laschewski, G. and Jendritzky, G. 2002. Effects of the thermal environment on human health: an investigation of 30 years of daily mortality data from SW Germany. *Climate Research* **21**: 91–103.

Law, B.J., Carbonell-Estrany, X., and Simoes, E.A.F. 2002. An update on respiratory syncytial virus epidemiology: a developed country perspective. *Respiratory Medicine Supplement B* **96**: S1–S2.

Tam, W.W.S., Wong, T.W., Chair, S.Y., and Wong, A.H.S. 2009. Diurnal temperature range and daily cardiovascular mortalities among the elderly in Hong Kong. *Archives of Environmental and Occupational Health* **64**: 202–206.

Verlato, G., Calabrese, R., and De Marco, R. 2002. Correlation between asthma and climate in the European Community Respiratory Health Survey. *Archives of Environmental Health* **57**: 48–52.

Young, T.K. and Kakinen, T.M. 2010. The health of Arctic populations: Does cold matter? *American Journal of Human Biology* **22**: 129–133.

Zhang, X.B., Vincent, L.A., Hogg, W.D., and Niitsoo, A. 2000. Temperature and precipitation trends in Canada during the 20th century. *Atmosphere-Ocean* **38**: 395–429.

9.2 Viral and Vector-borne Diseases

With respect to viral and vector-borne diseases, in a review of the pertinent literature that describes "those mechanisms that have led to an increase of virus activity in recent years," Zell et al. (2008) state "it is assumed that global warming is forced by the anthropogenic release of 'greenhouse gases'," and that a further "consistent assumption" has been a consequent "increased exposure of humans to tropical pathogens and their vectors." However, they note "there is dissent about this hypothesis (Taubes, 1997; Reiter, 2001; Hay et al., 2002; Reiter et al., 2003; Randolph, 2004; Zell, 2004; Halstead, 2008)," and they thus go on to explore the subject in more detail, ultimately concluding "only very few examples point toward global warming as a cause of excess viral activity." Instead, they find, "coupled ocean/atmosphere circulations and continuous anthropogenic disturbances (increased populations of humans and domestic animals, socioeconomic instability, armed conflicts, displaced populations, unbalanced ecosystems, dispersal of resistant pathogens etc.) appear to be the major drivers of disease variability," and global warming "at best" merely "contributes."

Similar sentiments were expressed that year by Wilder-Smith and Gubler (2008), who focused on the occurrence of dengue infections, reporting "climate has rarely been the principal determinant of [their] prevalence or range," and "human activities and their impact on local ecology have generally been much more significant." In this regard, they cite as contributing factors "urbanization, deforestation, new dams and irrigation systems, poor housing, sewage and waste management systems, and lack of reliable water systems that make it necessary to collect and store water." They further note "disruption of vector control programs, be it for reasons of political and social unrest or scientific reservations about the safety of DDT, has contributed to the resurgence of dengue around the world." In addition, they write, "large populations in which viruses circulate may also allow more co-infection of mosquitoes and humans with more than one serotype of virus," which would appear to be borne out by the fact that "the number of dengue lineages has been increasing roughly in parallel with the size of the human population over the last two centuries." Most important of all, perhaps, is "the impact of international travel." Wilder-Smith and Gubler note "humans, whether troops, migrant workers, tourists, business travelers, refugees, or others, carry the virus into new geographic areas." These movements, in their words, "can lead to epidemic waves." Given such findings, the two researchers conclude "population dynamics and viral evolution offer the most parsimonious explanation for the observed epidemic cycles of the disease, far more than climatic factors."

Also exploring this issue were Gage et al. (2008), who reviewed what was then known about it. The four researchers—all from the U.S. Centers for Disease Control's National Center for Zoonotic, Vector-Borne, and Enteric Diseases—concluded "the precise impacts" of the various climatic changes that are typically claimed to occur in response to rising atmospheric CO_2 concentrations "are difficult to predict." Indeed, they write, "in some areas, climate change could increase outbreaks and the spread of some vector-borne diseases while having quite the opposite effect on other vector-borne diseases."

In further discussing this complex situation, they note "the mere establishment of suitable vectors for a particular agent does not necessarily mean that spread to humans will commonly occur, as indicated by the limited transmission of dengue and malaria in the southern U.S.," because, as they continue, "local transmission has been limited by factors unrelated to the climatic suitability of the areas for the relevant vector species." In addition, they write, "in instances where a vector-borne disease is also zoonotic, the situation is even more complex, because not only must the vector and pathogen be present, but a competent vertebrate reservoir host other than humans must also be present."

So what are some of the non-climatic factors that affect the spread of vector-borne diseases among humans? Gage et al. list "many other global changes concurrently transforming the world, including increased economic globalization, the high speed of international travel and transport of commercial goods, increased population growth, urbanization, civil unrest, displaced refugee populations, water availability and management, and deforestation and other land-use changes," to which could be added the many different ways in which these phenomena are dealt with by different societies.

Kyle and Harris (2008) noted "dengue is a spectrum of disease caused by four serotypes of the most prevalent arthropod-borne virus affecting humans today," and "its incidence has increased dramatically in the past 50 years," such that "tens of millions of cases of dengue fever are estimated to occur annually, including up to 500,000 cases of the life-threatening dengue hemorrhagic fever/dengue shock syndrome." The researchers conducted a review of the pertinent scientific literature, exploring "the human, mosquito, and viral factors that contribute to the global spread and persistence of dengue, as well as the interaction between the three spheres, in the context of ecological and climate change."

The two researchers note "there has been a great deal of debate on the implications of global warming for human health," but "at the moment, there is no consensus." In the case of dengue, they write, "it is important to note that even if global warming does not cause the mosquito vectors to expand their geographic range, there could still be a significant impact on transmission in endemic regions," as they report that "a 2°C increase in temperature would simultaneously lengthen the lifespan of the mosquito and shorten the extrinsic incubation period of the dengue virus, resulting in more infected mosquitoes for a longer period of time." Nevertheless, they note there are "infrastructure and socioeconomic differences that exist today and already prevent the transmission of vector-borne diseases, including dengue, even in the continued presence of their vectors." Consequently, it would appear that whatever advantages rising temperatures might confer upon the dengue virus vector, they can be overcome by proper implementation of modern vector-control techniques.

One year later, Russell (2009)—a professor in the Department of Medicine of the University of Sydney and founding director of its Department of Medical Entomology—reported, "during the past 10 years, there has been increasing concern for health impacts of global warming in Australia, and continuing projections and predictions for increasing mosquito-borne disease as a result of climate change." However, he wrote, these claims "are relatively simplistic, and do not take adequate account of the current or historic situations of the vectors and pathogens, and the complex ecologies that might be involved." He then went on to review the consequences of these several inadequacies for malaria, dengue fever, the arboviral arthritides (Ross River and Barmah Forest viruses) and the arboviral encephalitides (Murray Valley encephalitis and Kunjin viruses). He did this within the context of predictions of projected climate changes as proposed and modeled by Australia's Commonwealth Scientific and Industrial Research Organization and the Intergovernmental Panel on Climate Change. He concluded "there might be some increases in mosquito-borne disease in Australia with a warming climate, but with which mosquitoes and which pathogens, and where and when, cannot be easily discerned." The strongest statement he could make was that "of itself, climate change as currently projected, is not likely to provide great cause for public health concern with mosquito-borne disease in Australia."

In another paper, Russell et al. (2009) wrote, "dengue has emerged as a leading cause of morbidity in many parts of the tropics," noting "Australia has had dengue outbreaks in northern Queensland." In addition, they reported, "substantial increases in distribution and incidence of the disease in Australia are projected with climate change," or, more specifically, "with increasing temperatures." They explored the soundness of these projections by

reviewing pertinent facts about the history of dengue in Australia, determining that the dengue vector (the *Aedes aegypti* mosquito) "was previously common in parts of Queensland, the Northern Territory, Western Australia and New South Wales," that it had "in the past, covered most of the climatic range theoretically available to it," and that "the distribution of local dengue transmission has [historically] nearly matched the geographic limits of the vector."

This being the case, the six scientists concluded the vector's current absence from much of Australia, as Russell et al. described it, "is not because of a lack of a favorable climate." Thus, they reasoned that "a temperature rise of a few degrees is not alone likely to be responsible for substantial increases in the southern distribution of *A. aegypti* or dengue, as has been recently proposed." Instead, they reminded everyone that "dengue activity is increasing in many parts of the tropical and subtropical world as a result of rapid urbanization in developing countries and increased international travel, which distributes the viruses between countries." Rather than attempts to limit dengue transmission by controlling the world's climate, therefore, the medical researchers recommend that "well resourced and functioning surveillance programs, and effective public health intervention capabilities, are essential to counter threats from dengue and other mosquito-borne diseases."

Studying dengue simultaneously in three other parts of the world, Johansson et al. (2009) wrote, "mosquito-borne dengue viruses are a major public health problem throughout the tropical and subtropical regions of the world," and "changes in temperature and precipitation have well-defined roles in the transmission cycle and may thus play a role in changing incidence levels." Therefore, as they continued, since "the El Niño Southern Oscillation (ENSO) is a multiyear climate driver of local temperature and precipitation world wide," and since "previous studies have reported varying degrees of association between ENSO and dengue incidence," as they describe it, they decided to analyze "the relationship between ENSO, local weather, and dengue incidence in Puerto Rico, Mexico, and Thailand." They did so by searching for relationships between ENSO, local weather, and dengue incidence in Puerto Rico (1986–2006), Mexico (1985–2006), and Thailand (1983–2006), using wavelet analysis as a tool to identify time- and frequency-specific associations.

The three researchers reported they "did not find evidence of a strong, consistent relationship in any of the study areas," and Rohani (2009), who wrote a Perspective piece on their study, stated they found "no systematic association between multi-annual dengue outbreaks and El Niño Southern Oscillation." Thus, as included in the Editors' Summary of Johansson et al.'s paper, their findings provided "little evidence for any relationship between ENSO, climate, and dengue incidence."

In another review paper dealing with the possible impacts of climate change on the spread of infectious diseases, Randolph (2009) noted it is generally tacitly assumed—and even explicitly stated—that climate change will result only in a worsening of the situation, with the expansion of vector-borne diseases into higher latitudes and an increased disease incidence. In fact, she states that implicit in almost all of the literature on this subject—both popular and scientific—"is an assumption that environmental change is more likely to strengthen the transmission potential and expand the range, rather than to disrupt the delicate balance between pathogen, vector and host upon which these systems depend."

The zoologist from the U.K.'s University of Oxford thus explores the evidence via an analysis of what the bulk of the accurately informed scientific literature on the subject seems to suggest. In doing so, she finds "the mercurial epidemiology of each vector-borne disease is the system-specific product of complex, commonly nonlinear, interactions between many disparate environmental factors." These include "not only climate but also other abiotic conditions (e.g., land cover) and the physical structure of the environment (e.g., water sources), and further biotic factors such as host abundance and diversity." She also indicates that a number of socioeconomic factors drive human living conditions and behaviors that determine the degree of exposure to the risk posed to them, and that nutritional status and concomitant immunity also determine the degree of resistance to infection.

In some interesting examples from the past, Randolph notes the upsurge of tick-borne diseases within preexisting endemic regions in central and Eastern Europe "appears to be an unforeseen consequence of the fall of the iron curtain and the end of the cold war," which she describes as "a sort of political global warming." Also noted is the fact that "the introduction of the mosquito *Aedes aegypti* to the Americas within water containers on board slave

ships from Africa was repeated four centuries later by the dispersal of the Asian tiger mosquito, *A. albopictus*, from Japan to the United States within water trapped in used car tires (Hawley et al., 1987; Reiter and Sprenger, 1987)."

This phenomenon, according to Randolph, continues today, augmented by trade in other water-carrying goods such as Asian Luck Bamboo plants. Such activities have allowed this mosquito species "to establish itself in almost all New World countries, a dozen European countries, parts of West Africa, and the Middle East." All of these disease expansions, in her words, have "nothing to do with climate change," which also holds true for such chance events as "the introduction of West Nile virus into New York in 1999, most probably by air from Israel (Lanciotti et al., 1999)," and the introduction "of the BTV-8 strain of bluetongue virus into the Netherlands in 2006 from South Africa (Saegerman et al., 2008)."

Contemporaneously, Harvell et al. (2009) stated that "in temperate climates, we might expect the range and activity of mosquitoes and the pathogens they vector, such as malaria and dengue, to increase with warmer temperatures." However, "from a later vantage point in 2009," they indicated that "surprisingly, insect-vectored diseases resoundingly do not show a net expansion in range or increase in prevalence." As for why this is so, the five scientists gave three explanations attributed to Lafferty (2009a): "(1) anthropogenic activities directly influence the distributions of vectors and infectious disease in ways unrelated to climate, (2) vectors and pathogens are limited by thermal maxima, so that temperature changes lead to shifts rather than expansions in distribution, and (3) other factors such as host acquired immunity and vector or parasite life history traits are linked to habitat suitability in addition to climate." In addition, they noted the important role that may be played by "evolutionary changes in properties of the host or pathogen," and in concluding their paper they therefore wrote, "ecologists need to consider how host biology, including movement behavior and acquired immunity, can mediate the impacts of global change on parasite/pathogen dynamics and disease severity," because, as they concluded, "at present, many of these mechanisms are poorly known."

Turning directly to the Lafferty (2009a) paper, we again read the projection that "global climate change will result in an expansion of tropical diseases, particularly vector-transmitted diseases, throughout temperate areas," examples of which include "schistosomiasis (bilharzia or snail fever), onchocerciasis (river blindness), dengue fever, lymphatic filariasis (elephantiasis), African trypanosomiasis (sleeping sickness), leishmaniasis, American trypanosomiasis (Chagas disease), yellow fever, and many less common mosquito and tick-transmitted diseases of humans," as well as many diseases of "nonhuman hosts." In a critique of this point of view, based on his review of the scientific literature, he concludes, "while climate has affected and will continue to affect habitat suitability for infectious diseases, climate change seems more likely to shift than to expand the geographic ranges of infectious diseases," and "many other factors affect the distribution of infectious disease, dampening the proposed role of climate." In fact, he concludes, "shifts in climate suitability might actually reduce the geographic distribution of some infectious diseases." And of perhaps even greater importance (because it is a real-world observation), he reports, "although the globe is significantly warmer than it was a century ago, there is little evidence that climate change has already favored infectious diseases."

In a companion paper (Lafferty, 2009b), the U.S. researcher lists several ways in which ecologists "can contribute substantially to the general theory of climate and infectious disease," some of the most important of which have to deal with "[1] multiple hosts and parasite species (Dobson, 2009), [2] nonhuman hosts (Harvell et al., 2009), [3] accounting for the effects of immunity (Dobson, 2009; Harvell et al., 2009; Ostfeld, 2009; Pascual and Bouma, 2009), [4] quality and details of [4a] climatic data and [4b] appropriate measures of disease response (Ostfeld, 2009; Pascual and Bouma, 2009; Randolph, 2009), [5] complex analyses to account for multiple, interdependent covariates (Dobson, 2009; Ostfeld, 2009; Pascual and Bouma, 2009; Randolph, 2009), [6] host movement in response to climate change (Harvell et al., 2009), and [7] geographic tools to account for distinctions between fundamental and realized niches (Ostfeld, 2009; Randolph, 2009)." These many and varied challenges confronting the scientific community in this emerging field of study show there is much unfinished business that must be conducted in researching the several potential relationships that may or may not exist between climatic change and the spread of infectious diseases.

In one additional study from 2009, Nabi and Qader (2009) analyze both sides of the global

warming/malaria incidence debate, considering the climatic conditions that affect the spread of the disease (temperature, rainfall, and humidity), as well as the host of pertinent non-climatic factors that play important roles in its epidemiology (the presence or absence of mosquito control programs, the availability or non-availability of malaria-fighting drugs, changing resistances to drugs, the quality of vector control, changes in land use, the availability of good health services, human population growth, human migrations, international travel, and standard of living).

According to the two researchers, their results indicate "global warming alone will not be of a great significance in the upsurge of malaria unless it is accompanied by a deterioration in other parameters like public health facilities, resistance to anti-malarial drugs, decreased mosquito control measures," etc. They write, "no accurate prediction about malaria can truly be made," because "it is very difficult to estimate what the other factors will be like in the future." The researchers do note, however, that mosquito-borne diseases were a major public health problem in the United States from the 1600s to the mid-1900s, "with occasional epidemics." By the middle of the twentieth century, however, "malaria disappeared from the country along with the other mosquito borne diseases like Dengue and Yellow fever," and "this decline was attributed to overall improvements in living conditions and better public health measures." The continuance of both of these has kept these diseases at bay throughout the latter half of the twentieth century as well, even though that period experienced what some have characterized as "unprecedented global warming."

In light of these several observations, plus many others from all around the world—which clearly establish the overriding importance of a country's standard of living and concomitant level of health-promoting services—Nabi and Qader conclude, "as public health workers, it would be more justifiable for us to exert our efforts on these other [non-climatic] parameters for the eradication and control of malaria."

Reiter (2010) notes the appearance of the West Nile virus in New York (USA) in 1999, plus the unprecedented panzootic that followed, "have stimulated a major research effort in the Western Hemisphere and a new interest in the presence of this virus in the Old World." These developments have been driven in part by the fact that "a great deal of attention has been paid to the potential impact of climate change on the prevalence and incidence of mosquito-borne disease."

Reiter reviews what researchers have learned about the subject and reports the worldwide implications for public health, summing things up in his final paragraph, where he states: "one point is clear: the importation and establishment of vector-borne pathogens that have a relatively low profile in their current habitat is a serious danger to Europe and throughout the world." This state of affairs, in his view, "is a direct result of the revolution of transport technologies and increasing global trade that has taken place in the past three decades," modern examples of which include "the global circulation of dengue virus serotypes (Gubler, 1998), the intercontinental dissemination of *Aedes albopictus* and other mosquitoes in used tires (Hawley et al., 1987; Reiter, 1998), the epidemic of chikungunya virus in Italy (Angelini et al., 2007), and the importation of bluetongue virus and trypanosomiasis into Europe (Meroc et al., 2008; Moretti, 1969)." In light of what his review reveals, he writes, "globalization is potentially a far greater challenge to public health in Europe than any future changes in climate (Tatem et al., 2006)."

In a study demonstrating the influence of globalization, Shang et al. (2010) used logistic and Poisson regression models to analyze bi-weekly, laboratory-confirmed dengue cases in Taiwan at their onset dates of illness from 1998 to 2007, in order to "identify correlations between indigenous dengue and imported dengue cases (in the context of local meteorological factors) across different time lags." They found "the occurrence of indigenous dengue was significantly correlated with temporally-lagged cases of imported dengue (2–14 weeks), higher temperatures (6–14 weeks), and lower relative humidity (6–20 weeks)," and that "imported and indigenous dengue cases had a significant quantitative relationship in the onset of local epidemics." Given these findings, the six Taiwanese researchers concluded, "imported dengue cases are able to initiate indigenous epidemics when appropriate weather conditions are present," or as they stated in another place, "imported dengue are able to serve as an initial facilitator, or spark, for domestic epidemics." Therefore, they suggest "early detection and case management of imported cases through timely surveillance and rapid laboratory-diagnosis may avert large scale epidemics of dengue/dengue hemorrhagic

fever," while noting "meteorology alone does not initiate an epidemic" and "an increase in viremic international travelers has caused global dengue hemorrhagic fever case numbers to surge in the past several decades." This surge is often erroneously claimed to be due to global warming.

Gething et al. (2010) note that based on "model predictions," it is "reported widely in global climate policy debates that climate change is adding to the present-day burden of malaria and will increase both the future range and intensity of the disease," citing the IPCC (2007) and the U.S. Environmental Protection Agency (2010). Noting "it has long been known that the range of malaria has contracted through a century of economic development and disease control (Hay et al., 2009)," when "global temperature increases have been unequivocal," they go on to explore this apparent incongruity "for the first time" in another data-based study by comparing "an evidence-based map of contemporary malaria endemicity (Hay et al., 209)" with "the most reliable equivalent for the pre-intervention era, around 1900 (Lysenko et al., 1968)," when malaria was "at its assumed historical peak." This provides a comparison of "the magnitude of observed changes in range and endemicity to those proposed to occur in response to climate change."

The six scientists—from the Spatial Ecology and Epidemiology Group, the Malaria Public Health and Epidemiology Group, and the Centre for Tropical Medicine of the U.K.'s University of Oxford, plus the Departments of Biology and Geography and the Emerging Pathogens Institute of the University of Florida (USA)—report "comparison of the historical and contemporary maps revealed that endemic/stable malaria is likely to have covered 58% of the world's land surface around 1900 but only 30% by 2007," and "even more marked has been the decrease in prevalence within this greatly reduced range, with endemicity falling by one or more classes in over two-thirds of the current range of stable transmission." They state, "widespread claims that rising mean temperatures have already led to increases in worldwide malaria morbidity and mortality are largely at odds with observed decreasing global trends in both its endemicity and geographic extent." In fact, they report, "the combined natural and anthropogenic forces acting on the disease throughout the twentieth century have resulted in the great majority of locations undergoing a net reduction in transmission between one and three orders of magnitude larger than the maximum future increases proposed under temperature-based climate change scenarios."

Given such findings, Gething et al. conclude there has been "a decoupling of the geographical climate-malaria relationship over the twentieth century, indicating that non-climatic factors have profoundly confounded this relationship over time." They state "non-climatic factors, primarily direct disease control and the indirect effects of a century of urbanization and economic development, although spatially and temporally variable, have exerted a substantially greater influence on the geographic extent and intensity of malaria worldwide during the twentieth century than have climatic factors." As for the future, they write climate-induced effects "can be offset by moderate increases in coverage levels of currently available interventions."

Writing that "pathogens cause roughly one in five human deaths, are responsible for 51% of years of life lost globally, and have long affected human demographics," Dunn et al. (2010) note pathogens "have also been identified as drivers of human behavior, the politics and political stability of countries, human fertility, global economies, and more generally the course and dynamics of human history." And, somewhat ominously, they report "researchers have linked the presence and prevalence of some pathogens to climate, as has been highlighted in recent discussions of climate change and disease." They specifically mention malaria, plague, and dengue as examples. Thus, they conducted, as they describe it, "a global analysis of the relative influence of climate, alternative host diversity and spending on disease prevention on modern patterns in the richness and prevalence of human pathogens."

The U.S., Canadian, and New Zealand researchers found that "pathogen richness (number of kinds) is largely explained by the number of birds and mammal species in a region," and "the most diverse countries with respect to birds and mammals are also the most diverse with respect to pathogens." Noting "we are unlikely to be able to change patterns of pathogen richness dramatically," they observe that "pathogen richness, even when high, does not guarantee high prevalence, because of the potential impact of disease control effort." In fact, they found "pathogen prevalence is much more sensitive to variation in health spending among regions," and "importantly, for human health, the prevalence of key human pathogens is strongly influenced by disease

control efforts." Dunn et al. conclude, "even where disease richness is high, we might still control prevalence, particularly if we spend money in those regions where current spending is low, prevalence is high and populations are large."

Finally, in a brief review of the roles played by various factors that may influence the spread of tick-borne diseases, Sarah Randolph (2010) of the University of Oxford's Department of Zoology in the United Kingdom begins by noting many vector-borne diseases "have shown marked increases in both distribution and incidence during the past few decades, just as human-induced climate change is thought to have exceeded random fluctuations." She writes, "this coincidence has led to the general perception that climate change has driven disease emergence." However, after describing some of the outbreaks of tick-borne disease in Europe over the past couple of decades, Randolph states, "the inescapable conclusion is that the observed climate change alone cannot explain the full heterogeneity in the epidemiological change, either within the Baltic States or amongst Central and Eastern European countries," citing the work of Sumilo et al. (2007). Instead, she writes, "a nexus of interrelated causal factors—abiotic, biotic and human—has been identified," and "each factor appears to operate synergistically, but with differential force in space and time, which would inevitably generate the observed epidemiological heterogeneity."

Many of these factors, she continues, "were the unintended consequences of the fall of Soviet rule and the subsequent socio-economic transition (Sumilo et al., 2008b)." among these factors she cites "agricultural reforms resulting in changed land cover and land use, and an increased reliance on subsistence farming; reduction in the use of pesticides, and also in the emission of atmospheric pollution as industries collapsed; increased unemployment and poverty, but also wealth and leisure time in other sectors of the population as market forces took hold." In concluding, Randolph writes, "there is increasing evidence from detailed analyses that rapid changes in the incidence of tick-borne diseases are driven as much, if not more, by human behavior that determines exposure to infected ticks than by tick population biology that determines the abundance of infected ticks," as per the findings of Sumilo et al. (2008a) and Randolph et al. (2008). She ends her brief analysis by stating, "while nobody would deny the sensitivity of ticks and tick-borne disease systems to climatic factors that largely determine their geographical distributions, the evidence is that climate change has not been the most significant factor driving the recent temporal patterns in the epidemiology of tick-borne diseases."

The studies discussed above, coupled with numerous others referenced in the 2009 report of the Nongovernmental International Panel on Climate Change (Idso and Singer, 2009), suggest there is little of substance in the peer-reviewed scientific literature to support the contention that CO_2-induced global warming will elevate human mortality due to an enhanced spreading of vector-borne diseases. In fact, the great bulk of that research tends to refute those claims.

References

Angelini, R., Finarelli, A.C., Angelini, P., Po, C., Petropulacos, K., Macini, P., Fiorentini, C., Fortuna, C., Venturi, G., Romi, R., Majori, G., Nicoletti, L., Rezza, G., and Cassone, A. 2007. An outbreak of chikungunya fever in the province of Ravenna, Italy. *Eurosurveillance* **12**: eurosurveillance.org/ViewArticle.aspx?Articleid=3260.

Dobson, A.P. 2009. Climate variability, global change, immunity, and the dynamics of infectious diseases. *Ecology* **90**: 920–927.

Dunn, R.R., Davies, T.J., Harris, N.C., and Gavin, M.C. 2010. Global drivers of human pathogen richness and prevalence. *Proceedings of the Royal Society B* **277**: 2587–2595.

Gage, K.L., Burkot, T.R., Eisen, R.J., and Hayes, E.B. 2008. Climate and vector borne diseases. *American Journal of Preventive Medicine* **35**: 436–450.

Gething, P.W., Smith, D.L., Patil, A.P., Tatem, A.J., Snow, R.W., and Hay, S.I. 2010. Climate change and the global malaria recession. *Nature* **465**: 342–345.

Gubler, D.J. 1998. The global pandemic of dengue/dengue hemorrhagic fever: current status and prospects for the future. *Annals, Academy of Medicine, Singapore* **27**: 227–234.

Halstead, S.B. 2008. Dengue virus-mosquito interactions. *Annual Review of Entomology* **53**: 273–291.

Harvell, D., Altizer, S., Cattadori, I.M., Harrington, L., and Weil, E. 2009. Climate change and wildlife diseases: when does the host matter the most? *Ecology* **90**: 912–920.

Hawley, W.A., Reiter, P., Copeland, R.S., Pumpuni, C.B., and Craig Jr., G.B. 1987. *Aedes albopictus* in North

America: Probable introduction in used tires from northern Asia. *Science* **236**: 1114–1116.

Hay, S.I., Rogers, D.J., Randolph, S.E., Stern, D.I., Cox, J., Shanks, G.D., and Snow, R.W. 2002. Hot topic or hot air? Climate change and malaria resurgence in East African highlands. *Trends in Parasitology* **18**: 530–534.

Idso, C.D. and Singer, S.F. 2009. *Climate Change Reconsidered: 2009 Report of the Nongovernmental International Panel on Climate Change (NIPCC)*. Chicago, IL: The Heartland Institute.

Intergovernmental Panel on Climate Change. 2007. *Climate Change 2007: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change*, edited by M.L. Parry, et al. Cambridge, UK: Cambridge University Press.

Johansson, M.A., Cummings, D.A.T., and Glass, G.E. 2009. Multiyear climate variability and dengue-El Niño Southern Oscillation, weather and dengue incidence in Puerto Rico, Mexico, and Thailand: a longitudinal data analysis. *PLoS Medicine* **6**: e1000168.

Kyle, J.L. and Harris, E. 2008. Global spread and persistence of dengue. *Annual Review of Microbiology* **62**: 71–92.

Lafferty, K.D. 2009a. The ecology of climate change and infectious diseases. *Ecology* **90**: 888–900.

Lafferty, K.D. 2009b. Calling for an ecological approach to studying climate change and infectious diseases. *Ecology* **90**: 932–933.

Lanciotti, R.S., Roehrig, J.T., Deubel, V., Smith, J., Parker, M., Steele, K., Crise, B., Volpe, K.E., Crabtree, M.B., Scherret, J.H., Hall, R.A., MacKenzie, J.S., Cropp, C.B., Panigrahy, B., Ostlund, E., Schmitt, B., Malkinson, M., Banet, C., Weissman, J., Komar, N., Savage, H.M., Stone, W., McNamara, T., and Gubler, D.J. 1999. Origin of the West Nile virus responsible for an outbreak of encephalitis in the northeastern United States. *Science* **286**: 2333–2337.

Lysenko, A.J. and Semashko, I.N. 1968. In *Itogi Nauki: Medicinskaja Geografija*, edited by A.W. Lebedew, 25–126. Moscow, Russia: Academy of Sciences.

Meroc, E., Faes, C., Herr, C., Staubach, C., Verheyden, B., Vanbinst, T., Vandenbussche, F., Hooyberghs, J., Aerts, M., De Clercq, K., and Mintiens, K. 2008. Establishing the spread of bluetongue virus at the end of the 2006 epidemic in Belgium. *Veterinary Microbiology* **131**: 133–144.

Moretti, G. 1969. African trypanosomiasis detected in France: difficulties of diagnosis. *Presse Medicale* **77**(41):1404.

Nabi, S.A. and Qader, S.S. 2009. Is global warming likely to cause an increased incidence of malaria? *Libyan Journal of Medicine* **4**: 18–22.

Ostfeld, R.S. 2009. Climate change and the distribution and intensity of infectious diseases. *Ecology* **90**: 903–905.

Pascual, M. and Bouma, M.J. 2009. Do rising temperatures matter? *Ecology* **90**: 906–931.

Randolph, S.E. 2004. Evidence that climate change has caused 'emergence' of tick-borne diseases in Europe? *International Journal of Medical Microbiology* **293**, Suppl. **37**: 5–15.

Randolph, S.E. 2009. Perspectives on climate change impacts on infectious diseases. *Ecology* **90**: 927–931.

Randolph, S.E. 2010. To what extent has climate change contributed to the recent epidemiology of tick-borne diseases? *Veterinary Parasitology* **167**: 92–94.

Randolph, S.E., Asokliene, L., Avsic-Zupanc, T., Bormane, A., Burri, C., Golovljova, I., Hubalek, Z., Knap, N., Kondrusik, M., Kupca, A., Pejcoch, M., Vasilenko, V., and Zygutiene, M. 2008. Variable spikes in TBE incidence in 2006 independent of variable tick abundance but related to weather. *Parasites and Vectors* **1**: e44.

Reiter, P. 1998. *Aedes albopictus* and the world trade in used tires, 1988–1995: The shape of things to come? *Journal of the American Mosquito Control Association* **14**: 83–94.

Reiter, P. 2001. Climate change and mosquito-borne disease. *Environmental Health Perspectives* **109**: 141–161.

Reiter, P. 2010. West Nile virus in Europe: understanding the present to gauge the future. *Eurosurveillance* **15**: eurosurveillance.org/ViewArticle.aspx?Articleid=19508.

Reiter, P., Lathrop, S., Bunning, M., Biggerstaff, B., Singer, D., Tiwari, T., Baber, L., Amador, M., Thirion, J., Hayes, J., Seca, C., Mendez, J., Ramirez, B., Robinson, J., Rawlings, J., Vorndam, V., Waterman, S., Gubler, D., Clark, G., and Hayes, E. 2003. Texas lifestyle limits transmission of dengue virus. *Emerging Infectious Diseases* **9**: 86–89.

Reiter, P. and Sprenger, D. 1987. The used tire trade: a mechanism for the worldwide dispersal of container breeding mosquitoes. *Journal of the American Mosquito Control Association* **3**: 494–501.

Rohani, P. 2009. The link between dengue incidence and El Niño Southern Oscillation. *PLoS Medicine* **6**: e1000185.

Russell, R.C. 2009. Mosquito-borne disease and climate change in Australia: time for a reality check. *Australian Journal of Entomology* **48**: 1–7.

Russell, R.C., Currie, B.J., Lindsay, M.D., Mackenzie, J.S., Ritchie, S.A., and Whelan, P.I. 2009. Dengue and climate change in Australia: predictions for the future should incorporate knowledge from the past. *Medical Journal of Australia* **190**: 265–268.

Saegerman, C., Berkvens, D., and Mellor, P.S. 2008. Bluetongue epidemiology in the European Union. *Emerging Infectious Diseases* **14**: 539–544.

Shang, C.-S., Fang, C.-T., Liu, C.-M., Wen, T.-H., Tsai, K.-H., and King, C.-C. 2010. The role of imported cases and favorable meteorological conditions in the onset of dengue epidemics. *PLoS* **4**: e775.

Sumilo, D., Asokliene, L., Avsic-Zupanc, T., Bormane, A., Vasilenko, V., Lucenko, I., Golovljova, I., and Randolph, S.E. 2008a. Behavioral responses to perceived risk of tick-borne encephalitis: vaccination and avoidance in the Baltics and Slovenia. *Vaccine* **26**: 2580–2588.

Sumilo, D., Asokliene, L., Bormane, A., Vasilenko, V., Golovljova, I., and Randolph, S.E. 2007. Climate change cannot explain the upsurge of tick-borne encephalitis in the Baltics. *PLos ONE* **2**: e500.

Sumilo, D., Bormane, A., Asokliene, L., Vasilenko, V., Golovljova, I., Avsic-Zupanc, T., Hubalek, Z., and Randolph, S.E. 2008b. Socio-economic factors in the differential upsurge of tick-borne encephalitis in Central and Eastern Europe. *Reviews in Medical Virology* **18**: 81–95.

Tatem, A.J., Hay, S.I., and Rogers, D.J. 2006. Global traffic and disease vector dispersal. *Proceedings of the National Academy of Sciences, USA* **103**: 6242–6247.

Taubes, G. 1997. Global warming: apocalypse not. *Science* **278**: 1004–1006.

U.S. Environmental Protection Agency. 2010. Endangerment and Cause or Contribute Findings for Greenhouse Gases Under Section 202(a) of the Clean air Act (Technical Support Document). Washington, DC: U.S. Environmental Protection Agency.

Wilder-Smith, A. and Gubler, D.J. 2008. Geographic expansion of Dengue: the impact of international travel. *Medical Clinics of North America* **92**: 1377–1390.

Zell, R. 2004. Global climate change and the emergence/re-emergence of infectious diseases. *International Journal of Medical Microbiology* **293**, Suppl. **37**: 16–26.

Zell, R., Krumbholz, A., and Wutzler, P. 2008. Impact of global warming on viral diseases: what is the evidence? *Current Opinion in Biotechnology* **19**: 652–660.

9.3. Plant Nutrient and Medicinal Properties

In this section, we survey the peer-reviewed scientific literature pertaining to the effects of higher atmospheric CO_2 concentrations on plant nutrient content and on specific plant compounds of direct medicinal value, such as antioxidants that inhibit oxidation, some of which (vitamins E, C, and beta carotene) are found in the human body and are thought to protect its cells from the damaging effects of oxidation.

Reactive oxygen species (ROS) generated during cellular metabolism or peroxidation of lipids and proteins play a causative role in the pathogenesis of cancer and coronary heart disease (CHD), as demonstrated by Slaga et al. (1987), Frenkel (1992), Marnett (2000), and Zhao et al. (2000). However, Yu et al. (2004) have noted "antioxidant treatments may terminate ROS attacks and reduce the risks of CHD and cancer, as well as other ROS-related diseases such as Parkinson's disease (Neff, 1997; Chung et al., 1999; Wong et al., 1999; Espin et al., 2000; Merken and Beecher, 2000)," and they therefore state, "developing functional foods rich in natural antioxidants may improve human nutrition and reduce the risks of ROS-associated health problems."

Spurred on by these findings and thoughts, Levine et al. (2008) grew well-watered and -fertilized wheat plants (*Triticum aestivum*, cv Yocoro roho) from seed in custom-designed root modules—"consisting of a porous tube embedded in Turface (1-2 mm particle size) substrate containing 5 g Osmocote time release fertilizer per liter"—which were housed in Plexiglas chambers kept at atmospheric CO_2 concentrations of 400, 1,500, or 10,000 ppm for periods of 14, 21, and 28 days, while measurements were made of a number of plant metabolic properties, including the leaf concentrations of several flavonoids capable of scavenging ROS.

According to the 13 researchers, their results indicated "elevated CO_2 promoted the accumulation of secondary metabolites (flavonoids) progressively to a greater extent as plants became mature." And as best as can be determined from the bar graphs of their results, the percentage increase in total wheat leaf flavonoid concentration in going from an atmospheric CO_2 concentration of 400 to 1,500 ppm was 22 percent, 38 percent, and 27 percent (the one exception to this general rule) at 14, 21, and 28 days after planting, respectively, and in going from a CO_2

concentration of 400 to 10,000 ppm, the percentage increase in total flavonoid concentration was 38 percent, 56 percent, and 86 percent, respectively, at 14, 21, and 28 days after planting. In addition, they found "both elevated CO_2 levels resulted in an overall 25% increase in biomass over the control plants."

In addition to the potential for the types of benefits described at the beginning of this section, the U.S., Japanese, and German scientists write, "the increased accumulation of secondary metabolites in plants grown under elevated CO_2 may have implications regarding plant-herbivore interactions, decomposition rates for inedible biomass, and potential beneficial effects on plant tolerance to water stress (Idso, 1988) and cold stress (Solecka and Kacperska, 2003) due to their potentials for the scavenging of reactive oxygen species (ROS)."

In another study published in 2008, Stutte et al. (2008) wrote, as background for their plant CO_2-enrichment experiment, that "many *Scutellaria* species are rich in physiologically active flavonoids that have a wide spectrum of pharmacological activity." They note leaf extracts of *Scutellaria barbata* "have been used in traditional Chinese medicine to treat liver and digestive disorders and cancers (Molony and Molony, 1998)," and "recent research has shown extracts of *S. barbata* to be limiting to the growth of cell lines associated with lung, liver, prostate and brain tumors (Yin et al., 2004)."

Stutte et al. grew *S. barbata* and *S. lateriflora* plants from seed in large, walk-in, controlled environment chambers—which were maintained at atmospheric CO_2 concentrations of either 400, 1,200, or 3,000 ppm—to the time of flowering (35 days after planting) and to the time of seed drop (49 days after planting). The plants were then harvested, their fresh and dry weights were determined, and the concentrations of a host of plant flavonoids within their tissues were measured.

The results of this project indicated that at 49 days after planting, the shoot dry weight of *S. barbata* increased by 54 percent at 1,200 ppm CO_2 and by 57 percent at 3,000 ppm CO_2, and that of *S. lateriflora* increased by 44 percent and 70 percent, respectively, under the same CO_2 concentrations. In addition, the average concentration of the six flavonoids the researchers measured was increased by 48 percent at 1,200 ppm CO_2 and by 81 percent at 3,000 ppm CO_2 in the vegetative tissues of *S. barbata*, and it was increased by more than 2.4-fold at 1,200 and 4.9-fold at 3,000 ppm CO_2 in *S. lateriflora*. Stutte et al. reported that in the case of *S. lateriflora*, "there was a 4.2-fold increase in total flavonoid content when enriching from 400 to 1200 ppm CO_2, and a 13.7-fold increase at 3000 ppm." They state "these results are generally consistent with those of B. Schmidt, W.D. Clark and S.B. Idso (unpublished data) who grew *S. baicalensis* at 700 ppm CO_2" and found "total dry biomass was increased significantly" and "the overall antioxidant capacity, based on the ferric reducing antioxidant power assay, was increased."

The three researchers concluded their results "clearly demonstrate the potential to use controlled environments to increase the production and quality of *Scutellaria* species ... because the practice has the potential to increase the value of the product by reducing the time to harvest, increasing yield per unit area, and increasing bioactivity per gram of dry matter." Likewise, their extremely positive results hint at the likelihood that the active ingredients of many other medicinal plants may also be similarly enhanced by atmospheric CO_2 enrichment and that the historical rise in the air's CO_2 content may have already done much the same thing for many of the plants that people include in their everyday diets.

La et al. (2009) took up the challenge to explore the subject further, writing by way of background, "epidemiological studies show that there is a negative relationship between vegetable intake and the risk of a number of cancers (Wattenberg, 1993; Kohlmeier and Su, 1997; Price et al., 1998)," and "it has been widely recognized that some of the cancer-chemoprotective activities in these vegetables are attributable to their contents of glucosinolates (GSs) (Zhao et al., 1992; Wattenberg, 1993; Tawfiq et al., 1995; Fahey et al., 1997; Rosa et al., 1997; Holst and Williamson, 2004)." They decided to see what effect the ongoing rise in the air's CO_2 content might have on the production of these important cancer-fighting agents.

The five scientists placed seedlings of Chinese broccoli (*Brassica alboglabra* L. var. *Sijicutiao*), in pairs in 1.8-L pots within growth chambers maintained at either 350 or 800 ppm CO_2, where the plant's roots were immersed in culture solutions treated with either low, medium, or high nitrogen and allowed to grow for 35 days, after which the plants were separated into their primary morphological parts and weighed, while their bolting stems were ground into powder for glucosinolate (GS) analyses.

"Regardless of N concentration," state the researchers in describing their findings, the elevated CO_2 treatment "significantly increased plant height [15.64 percent], stem thickness [11.79 percent], dry weights of the total aerial parts [11.91 percent], bolting stems [15.03 percent], and roots [16.34 percent]." In addition, they report the elevated CO_2 increased the total GS concentrations of the bolting stems in the low and medium N treatments by 15.59 percent and 18.01 percent, respectively, compared with those at ambient CO_2, although there was no such effect in the high N treatment. Thus, in terms of the total amount of GS production within the bolting stems of Chinese broccoli, these results suggest increases of 33 to 36 percent may be obtained for plants growing in low to medium N conditions in response to a 450 ppm increase in the air's CO_2 concentration. Such results bode well for people who eat broccoli—and, in all likelihood, other cruciferous vegetables as well—especially for those who will live in the CO_2-enriched world of the future.

Jin et al. (2009) grew well-watered and fertilized spinach (*Spinacia oleracea* cv. Huangjia) plants from seed for approximately three weeks in controlled-environment chambers containing ambient air of 350 ppm CO_2 or enriched air of 800 ppm CO_2, after which they harvested the plants, weighed them, and measured the concentrations of several of the nutritive or health-promoting substances contained in their leaves. As best as can be determined from Jin et al.'s graphs of their results, the extra 450 ppm of CO_2 increased the fresh weight of the spinach shoots by about 67 percent and their dry weight by approximately 57 percent. In addition, it boosted the soluble sugar concentrations of their leaves by approximately 29 percent and their soluble protein concentrations by about 52 percent. As an added bonus, the extra CO_2 also increased spinach leaf concentrations of ascorbate, glutathione, and total flavonoids by 21 percent, 16 percent, and 3 percent, respectively, suggesting that as time progresses and the air's CO_2 content continues its upward climb, spinach should become more nutritious.

Turning our attention to fruit, Bindi et al. (2001), working near Rapolano, Siena (Italy), conducted a two-year free-air CO_2 enrichment (FACE) study of 21-year-old grapevines (*Vitis vinifera* L., cv Sangiovese), where they enriched the air around the plants to 550 and 700 ppm CO_2 while measuring numerous plant parameters, including—after the fermentation process was completed—"the principal chemical compounds that determine the basic red wine quality."

Their results indicated "elevated atmospheric CO_2 levels had a significant effect on biomass components (total and fruit dry weight) with increases that ranged from 40 to 45% in the 550 ppm treatment and from 45 to 50% in the 700 ppm treatment." In addition, they report "acid and sugar contents were also stimulated by rising CO_2 levels up to a maximum increase in the middle of the ripening season (8–14%)," but as the grapes reached the maturity stage, the CO_2 effect on these parameters gradually disappeared. In terms of the primary pigments contained in the wine itself, however, it can be calculated from the bar graphs of their results that in response to the ~50 percent increase in atmospheric CO_2 concentration experienced in going from ambient to 550 ppm CO_2, the concentrations of total polyphenols, total flavonoids, total anthocyanins and non-anthocyanin flavonoids in the wine rose by approximately 19 percent, 33 percent, 31 percent, and 38 percent, respectively. Given these findings, Bindi et al. concluded, "the expected rise in CO_2 concentrations may strongly stimulate grapevine production without causing negative repercussions on quality of grapes and wine."

Similar results have been reported by Goncalves et al. (2009). Working with a native grape variety (Touriga Franca, *Vitis vinifera* L.) in the Demarcated Region of Douro, northern Portugal, the six Portuguese researchers investigated "the impact of elevated carbon dioxide concentration on the quality of berries, must, and red wine (with special reference to volatile composition, phenolic content, and antioxidant activity)" in an experiment in which grapevines were grown in open-top chambers maintained at either 365 or 550 ppm CO_2. As they describe their findings, "in general, the increase of CO_2 did not affect berry characteristics" and "did not significantly change the total antioxidant capacity of the red wines." In fact, "thirty-five volatile compounds belonging to seven chemical groups were identified," and "generally, the same volatile compounds were present in all of the wines." Although some of these compounds were "slightly affected," they state "the red wine quality remained almost unaffected."

In considering these findings, Goncalves et al. state their study showed "the predicted rise in CO_2 might strongly stimulate grapevine photosynthesis and yield (data not shown) without causing negative

impacts on the quality of grapes and red wine." Putting their personal stamp of approval on their findings, they add that "the informal sensorial analysis carried out by the researchers" also showed "wine quality remained almost unaffected."

Vurro et al. (2009) examined the effect of atmospheric CO_2 enrichment on thyme (*Thymus vulgaris* L.), noting thyme has "a considerable economic value in the nutraceutical and pharmaceutical industry (Vardar-Uenlue et al., 2003; Konyalioglu et al., 2006)," and "thyme essential oil possesses per se considerable antioxidant capacity (Economou et al., 1991), and may therefore contribute towards the control of antioxidant status in the leaves."

Against this backdrop, Vurro et al. grew well-watered one-year-old thyme plants for three additional months out-of-doors within a mini-FACE system at Ravenna, Italy, where the air's CO_2 concentration was maintained at approximately 500 ppm (during daylight hours only), and where control plants were continuously exposed to air of approximately 370 ppm CO_2, and they measured several plant parameters at the end of each of the three months of the study.

In analyzing their results, the four researchers report "none of the plants grown under high levels of CO_2 for 90 days presented either significant differences in fresh weight and dry weight compared with controls, or macroscopic alteration of morphogenesis (number and length of nodes/internodes, branching, leaf area and chlorosis, etc.), at any of the sampling times." However, they did find that "in plants grown under elevated CO_2, a relative increase in oil yield of 32, 34 and 32 percent was, respectively, recorded in the first, second and third sampling-time (July, August and September)," and they observed a "general depression of the oxidative stress under elevated CO_2" that led to a "down-regulation of leaf reactive oxygen species-scavenging enzymes under elevated CO_2." Such findings, in the words of the Italian scientists, point to "a 'low cost' life strategy for growth under elevated CO_2, not requiring synthesis/activation of energy-intensive and expensive metabolic processes," which thus allows the plants to invest more energy in the production of essential plant oils of nutritional and pharmaceutical value.

In another study conducted with pharmaceutical considerations in mind, Ziska et al. (2008) evaluated "the growth and production of opiates for a broad range of recent and projected atmospheric carbon dioxide concentrations using wild poppy (*P. setigerum*) as a surrogate for *P. somniferum*," noting that "among medicinal plants, the therapeutic uses of opiate alkaloids from poppy (*Papaver* spp.) have long been recognized."

Specifically, Ziska et al. grew well-watered and fertilized plants from seed within growth chambers maintained at four different atmospheric CO_2 concentrations—300, 400, 500, and 600 ppm—for 90 to 100 days, while quantifying plant growth and the production of secondary compounds including the alkaloids morphine, codeine, papaverine, and noscapine, which were derived from latex obtained from capsules produced by the plants.

The three researchers' data indicate that relative to the plants grown at 300 ppm CO_2, those grown at 400, 500, and 600 ppm produced approximately 200, 275, and 390 percent more aboveground biomass, respectively, as best as can be determined from their bar graphs. In addition, they report, "reproductively, increasing CO_2 from 300 to 600 ppm increased the number of capsules, capsule weight and latex production by 3.6, 3.0 and 3.7 times, respectively, on a per plant basis," with the ultimate result that "all alkaloids increased significantly on a per plant basis." Based on these findings, Ziska et al. conclude, "as atmospheric CO_2 continues to increase, significant effects on the production of secondary plant compounds of pharmacological interest (i.e. opiates) could be expected." These effects, in their words, "are commonly accepted as having both negative (e.g. heroin) and positive (e.g. codeine) interactions with respect to public health."

In one final study, we report the work of Oliveira et al. (2010). Writing as background for their investigation, the five Brazilian researchers state, "presently, there is a growing interest in the use of inulin as a health food ingredient, as an alternative for low-calorie sweeteners, and as a dietary fiber and fat substitute (Ritsema and Smeekens, 2003)." In addition, they note "it is suggested" that a daily intake of low amounts of inulin or its derivatives generate certain bifidogenic effects that promote the growth of beneficial bacteria in the intestinal tract, as well as anti-tumor effects, citing the writings of Roberfroid (2005). They explain that their experimental subject, *Vernonia herbacea* (Vell.) Rusby, is an Asteraceae from the Brazilian Cerrado that accumulates inulin-type fructans in certain underground organs called rhizophores.

In conducting their experiment, Oliveira et al. grew well-watered and fertilized *V. herbacea* plants in open-top chambers within a glasshouse for 120 days at atmospheric CO_2 concentrations of either 380 or 760 ppm, during which period they measured plant net photosynthetic rates, water use efficiencies, and fructan concentrations after 15, 30, 60, 90, and 120 days of treatment, as well as above- and below-ground biomass at the end of the experiment. Results indicated that "plants under elevated CO_2 presented increases in height (40%), photosynthesis (63%) and biomass of aerial (32%) and underground (47%) organs when compared with control plants." In addition, they state, "water use efficiency was significantly higher in treated plants, presenting a 177% increase at day 60." Finally, they report that although fructan concentration remained unchanged, the significant CO_2-induced increase in underground organ biomass caused "a 24% increase in total fructan yield."

Because of the significant enhancement of inulin-type fructan production by *V. herbacea* under conditions of atmospheric CO_2 enrichment, the positive health effects of those compounds, and the great increase in water-use efficiency displayed by the plants while producing them, a CO_2-enriched future would appear to bode well for their commercial production throughout much of the central fifth—the Cerrado—of Brazil.

References

Bindi, M., Fibbi, L., and Miglietta, F. 2001. Free Air CO_2 Enrichment (FACE) of grapevine (*Vitis vinifera* L.): growth and quality of grape and wine in response to elevated CO_2 concentrations. *European Journal of Agronomy* **14**: 145–155.

Chung, H.S., Chang, L.C., Lee, S.K., Shamon, L.A., Breemen, R.B.V., Mehta, R.G., Farnsworth, N.R., Pezzuto, J.M., and Kinghorn, A.D. 1999. Flavonoid constituents of chorizanthe diffusa with potential cancer chemopreventive activity. *Journal of Agricultural and Food Chemistry* **47**: 36–41.

Economou, K.D., Oreopoulou, V., and Thomopoulos, C.D. 1991. Antioxidant activity of some plant extracts of the family Labiatae. *Journal of the American Oil Chemists' Society* **68**: 109–113.

Espin, J.C., Soler-Rivas, C., and Wichers, H.J. 2000. Characterization of the total free radical scavenger capacity of vegetable oils and oil fractions using 2,2-diphenyl-1-picryhydrazyl radical. *Journal of Agricultural and Food Chemistry* **48**: 648–656.

Fahey, J.W., Zhang, Y., and Talalay, P. 1997. Broccoli sprouts: an exceptionally rich source of inducers of enzymes that protect against chemical carcinogens. *Proceedings of the National Academy of Sciences, USA* **94**: 10,367–10,372.

Frenkel, K. 1992. Carcinogen-mediated oxidant formation and oxidative DNA damage. *Pharmacology and Therapeutics* **53**: 127–166.

Goncalves, B., Falco, V., Moutinho-Pereira, J., Bacelar, E., Peixoto, F., and Correia, C. 2009. Effects of elevated CO_2 on grapevine (*Vitis vinifera* L.): Volatile composition, phenolic content, and *in vitro* antioxidant activity of red wine. *Journal of Agricultural and Food Chemistry* **57**: 265–273.

Holst, B. and Williamson, G. 2004. A critical review of the bioavailability of glucosinolates and related compounds. *Natural Product Reports* **21**: 425–447.

Idso, S.B. 1988. Three phases of plant response to atmospheric CO_2 enrichment. *Plant Physiology* **87**: 5–7.

Jin, C.W., Du, S.T., Zhang, Y.S., Tang, C., and Lin, X.Y. 2009. Atmospheric nitric oxide stimulates plant growth and improves the quality of spinach (*Spinacia oleracea*). *Annals of Applied Biology* **155**: 113–120.

Kohlmeier L. and Su, L. 1997. Cruciferous vegetable consumption and colorectal cancer risk: meta-analysis of the epidemiological evidence. *FASEB Journal* **11**: 2141.

Konyalioglu, S., Ozturk, B., and Meral, G.E. 2006. Comparison of chemical compositions and antioxidant activities of the essential oils of two *Ziziphora* taxa from Anatolia. *Pharmaceutical Biology* **44**: 121–126.

La, G.-X, Fang, P., Teng, Y.-B, Li, Y.-J, and Lin, X.-Y. 2009. Effect of CO_2 enrichment on the glucosinolate contents under different nitrogen levels in bolting stem of Chinese kale (*Brassica alboglabra* L.). *Journal of Zhejiang University Science B* **10**: 454–464.

Levine, L.H., Kasahara, H., Kopka, J., Erban, A., Fehrl, I., Kaplan, F., Zhao, W., Littell, R.C., Guy, C., Wheeler, R., Sager, J., Mills, A., and Levine, H.G. 2008. Physiologic and metabolic responses of wheat seedlings to elevated and super-elevated carbon dioxide. *Advances in Space Research* **42**: 1917–1928.

Marnett, L.J. 2000. Oxyradicals and DNA damage. *Carcinogenesis* **21**: 361–370.

Merken, H.M. and Beecher, G.R. 2000. Measurement of food flavonoids by high-performance liquid chromatography: a review. *Journal of Agricultural and Food Chemistry* **48**: 577–599.

Molony, D. and Molony, M.M.P. 1998. The American Association of Oriental Medicines Complete Guide to Chinese Herbal Medicine. New York, NY: Berkley Publishing Group.

Neff, J. 1997. Big companies take nutraceuticals to heart. *Food Processing* **58**(10): 37–42.

Oliveira, V.F., Zaidan, L.B.P., Braga, M.R., Aidar, M.P.M., and Carvalho, M.A.M. 2010. Elevated CO_2 atmosphere promotes plant growth and inulin production in the cerrado species *Vernonia herbacea*. *Functional Plant Biology* **37**: 223–231.

Price, K.R., Casuscelli, F., Colquhoun, I.J., and Rhodes, M.J.C. 1998. Composition and content of flavonol glycosides in broccoli florets (*Brassica oleracea*) and their fate during cooking. *Journal of the Science of Food and Agriculture* **77**: 468–472.

Ritsema, T. and Smeekens, S. 2003. Fructans: beneficial for plants and humans. *Current Opinion in Plant Biology* **6**: 223–230.

Roberfroid, M.B. 2005. Introducing inulin-type fructans. *British Journal of Nutrition* **93**: S13–S25.

Rosa, E., Heaney, R.K., Fenwick, G.R., and Portas, C.A.M. 1997. Glucosinolates in crop plants. *Horticultural Reviews* **19**: 99–215.

Slaga, T.J., O'Connell, J., Rotstein, J., Patskan, G., Morris, R., Aldaz, M., and Conti, C. 1987. Critical genetic determinants and molecular events in multistage skin carcinogenesis. *Symposium on Fundamental Cancer Research* **39**: 31–34.

Solecka, D. and Kacperska, A. 2003. Phenylpropanoid deficiency affects the course of plant acclimation to cold. *Physiologia Plantarum* **119**: 253–262.

Stutte, G.W., Eraso, I., and Rimando, A.M. 2008. Carbon dioxide enrichment enhances growth and flavonoid content of two *Scutellaria* species. *Journal of the American Society for Horticultural Science* **133**: 631–638.

Tawfiq, N., Heaney, R.K., Pulumb, J.A., Fenwick, G.R., Musk, S.R., and Williamson, G. 1995. Dietary glucosinolates as blocking agents against carcinogenesis: glucosinolate breakdown products assessed by induction of quinine reductase activity in murine hepa1c1c7 cells. *Carcinogenesis* **16**: 1191–1194.

Vardar-Uenlue, G., Candan, F., Soekmen, A., Daferera, D., Polissiou, M., Soekmen, M., Doenmez, E., and Tepe, B. 2003. Antimicrobial and antioxidant activity of the essential oil and methanol extracts of *Thymus pectinatus* Fisch. et Mey var. pectinatus (Lamiaceae). *Journal of Agricultural and Food Chemistry* **51**: 63–67.

Vurro, E, Bruni, R., Bianchi, A., and di Toppi, L.S. 2009. Elevated atmospheric CO_2 decreases oxidative stress and increases essential oil yield in leaves of *Thymus vulgaris* grown in a mini-FACE system. *Environmental and Experimental Botany* **65**: 99–106.

Wattenberg, L.W. 1993. *Food and Cancer Prevention: Chemical and Biological Aspects.* London, UK: Royal Society of Chemistry.

Wong, S.S., Li, R.H.Y., and Stadlin, A. 1999. Oxidative stress induced by MPTP and MPP+: selective vulnerability of cultured mouse astocytes. *Brain Research* **836**: 237–244.

Yin, X., Zhou, J., Jie, C., Xing, D., and Zhang, Y. 2004. Anticancer activity and mechanism of *Scutellaria barbata* extract on human lung cancer cell line A549. *Life Sciences* **75**: 2233–2244.

Yu, L., Haley, S., Perret, J., and Harris, M. 2004. Comparison of wheat flours grown at different locations for their antioxidant properties. *Food Chemistry* **86**: 11–16.

Zhao, F., Evans, E.J., Bilsborrow, P.E., Schnug, E., and Syers, J.K. 1992. Correction for protein content in the determination of the glucosinolate content of rapeseed by the XRF method. *Journal of the Science of Food and Agriculture* **58**: 431–433.

Zhao, J., Lahiri-Chatterjee, M., Sharma, Y., and Agarwal, R. 2000. Inhibitory effect of a flavonoid antioxidant silymarin on benzoyl peroxide-induced tumor promotion, oxidative stress and inflammatory responses in SENCAR mouse skin. *Carcinogenesis* **21**: 811–816.

Ziska, L.H., Panicker, S., and Wojno, H.L. 2008. Recent and projected increases in atmospheric carbon dioxide and the potential impacts on growth and alkaloid production in wild poppy (*Papaver setigerum* DC.). *Climatic Change* **91**: 395–403.