CORRECTED 26 AUGUST 2005; SEE LAST PAGE

recognized. The data from Stan's group were compelling and incontrovertible, launching Bcl-2 as the founding member of a new class of oncogenes. The earlier proliferative paradigm of cancer pathogenesis was not wrong, but was simply incomplete. Dysregulated programmed cell death would soon be demonstrated in many tumors, and the word "apoptosis" would become part of the vernacular for all biomedical scientists.

For the rest of his life, Stan embraced the key scientific question posed by these studies: How does Bcl-2 block programmed cell death? He and his colleagues defined the physiological roles of Bcl-2 in B cell memory and T cell development, and showed that this protein was required for the survival of many cell types during normal development. Stan and his collaborators demonstrated that Bcl-2 is only one member of a large group of related proteins with conserved homology domains. Moreover, he and others showed that these proteins interact and subserve both pro- and antiapoptotic functions that regulate cell survival by affecting critical mitochondrial functions.

For these many remarkable observations, Stan was elected to the National Academy of Sciences at the age of 45. He proceeded to win the Bristol-Myers Squibb Award, the Mott Prize of the General Motors Cancer Research Foundation, the Pezcoller Foundation–American Association for Cancer Research International Prize, and the Stratton Medal from the American Society of Hematology, to name but a few of his many awards. David Nathan and the leadership at the Dana-Farber Cancer Institute recruited him to Harvard in 1998. There, he continued his extraordinary science and acted as a senior scientific leader of the institution until his untimely death.

Stan was one of the most highly cited scientists of our time. He published more than 250 peer-reviewed papers that were cited, in total, more than 40,000 times. Remarkably, 23 of his publications were cited at least 500 times; 11 were cited more than a thousand times. His papers reflect his experimental precision and creative genius; they were impeccably edited, understated, and a joy to read.

Stan's most enduring scientific legacy—and the one of which he was proudest—was that of his trainees. Forty of his former postdoctoral fellows now hold faculty positions at universities around the world. Stan never ran a mega-lab, because he worried too much about the well-being of every person that he mentored. When a graduate student told Stan that he was struggling, Stan smiled and replied, "Okay, let's struggle together," and he meant it. He brought out the best in every person he trained, and he served as a wonderful role model for future generations of physician-scientists. Most appropriately, he won the Barger Award for Excellence in Mentoring at Harvard last year.

A spirit of caring and humility pervaded all that Stan did. Despite his many scientific accolades, his source of greatest pride was his family. His wife of 25 years, Susan, and his sons, Jason and Evan, were the most important people in his life. The lessons of his parents and the farm in Beardstown, Illinois, were never far from his mind, and they kept him grounded. Although he was a visionary scientist and a natural leader, he was even more so a compassionate human being whose mission was to heal. He had an ever-optimistic view of life, and a broad, genuine smile that could light up a room. He embodied the spirit of Wordsworth, who wrote: "That best portion of a good man's life, his little, nameless, unremembered acts of kindness and of love." To Stan Korsmeyer, that was the best portion indeed.

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ATMOSPHERE

Air Pollution–Related Illness: Effects of Particles

André Nel

Worldwide epidemiological studies show a consistent increase in cardiac and respiratory morbidity and mortality from exposure to particulate matter (PM) (*1*–*3*). PM is a key ingredient of polluted air and is estimated to kill more than 500,000 people each year (*4*). To prevent this staggering loss of life we must understand the characteristics of the toxic particles and gain insight into how these characteristics are related to adverse health effects (*5*). As our understanding increases, we can use this knowledge to develop biomarkers in the hope of identifying susceptible individuals and reducing their exposure to PM.

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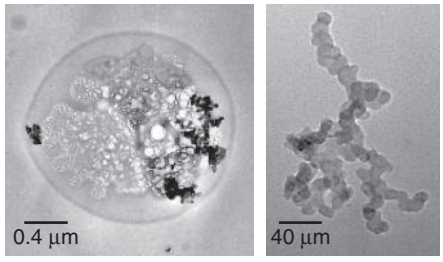
PM is composed of solid and liquid particles that come from sources such as vehicle exhaust, road dust, smokestacks, forest fires, windblown soil, volcanic emissions, and sea spray (*6*). Particle size, surface area, and chemical composition determine the health risk posed by PM (*7*). PM can be classified into coarse, fine, or ultrafine particles (*6*). Coarse particles, which have a diameter of more than 2.5 μm, are mostly derived from soil and sea salts. Fine particles (0.1 to 2.5 μm in diameter) and ultrafines (<0.1 μm in diameter) are predominantly derived from combustion of fossil fuel (see the first figure). Combustion particles have a core of elemental carbon that is coated with a layer of chemicals, including organic hydrocarbons, metals, nitrates, and sulfates. All of these components may play a role in particle toxicity (*7*).

Currently, government and air-quality monitoring agencies track and regulate 10-μm-diameter (PM10) and 2.5-μm-diameter (PM2.5) particles. Unfortunately, the unregulated ultrafine particles are potentially the most dangerous. Ultrafines are the major component in vehicle emissions—the largest source of air pollution in urban areas (*8*)—and they have the largest surface area and highest content of potentially toxic hydrocarbons among all PM sources. They can also penetrate deeper into lung tissue than fine or coarse particles (*8*).

Pulmonary effects of PM include the triggering of inflammation in the smaller airways, which can lead to the exacerbation



Dangerous dirt. (**Left**) Electron micrograph of a fine mode particle collected by an impactor from air outside an engineering laboratory at the University of California, Los Angeles. A halo surrounds residues of what are probably inorganic salts and polar organic compounds dissolved in the original aqueous droplet. Sootlike particles are also present. (**Right**) Aggregates of ultrafine particles collected on the last stage of an eight-stage impactor. These are soot particles emitted from diesel engine sources such as buses. More volatile particles may have evaporated in the electron microscope.

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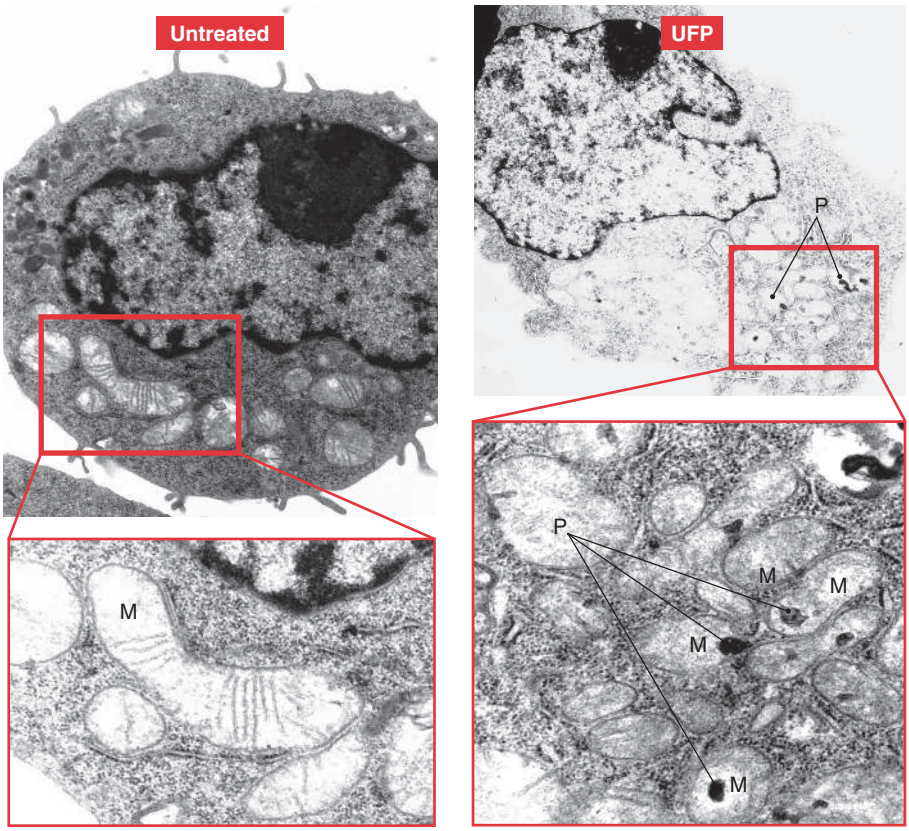

Toxic particles. The effect of ultrafine particles (UFP) in a macrophage cell line. (**Left**) An untreated macrophage with healthy mitochondria (M). (**Right**) The same cell type treated with ambient ultrafine particles, collected in the Los Angeles basin. The enlarged images show that the untreated cell has healthy mitochondria with cristae, whereas the treated cell has damaged mitochondria that lack cristae. The vacuolar structures in the treated cell each represent a mitochondrion with included particles (P). Whether the particles gain access to and then damage the mitochondria or gain access to already damaged mitochondria is unknown. [Modified from (*15*)]

of asthma and chronic bronchitis, airway obstruction, and decreased gas exchange (*1*, *2*, *9*). PM can also interfere with the clearance and inactivation of bacteria in lung tissue. More recently, there has been a growing awareness that PM is a cardiovascular risk factor that is associated with heart attacks, stroke, heart rhythm disturbances, and sudden death (*3*).

A number of mechanisms have been proposed to explain the adverse health impact of PM (*5*). Effects of PM that have experimental support are inflammation, cytokine and chemokine release, production of white blood cells, oxygen free-radical production in the lungs, endotoxin-mediated cellular and tissue responses, stimulation of irritant receptors, and covalent modification of key cellular enzymes (*5*, *9*). Best characterized in humans are the effects of PM on airway inflammation (*10*). In human and animal studies, inhalation of particles elicits proinflammatory effects, cytokine production, and enhancement of allergic responses in the upper and lower airways (*9*–*11*). PM exposure is likely linked to inflammation through the generation of reactive oxygen species and oxidative stress (*9*, *12*–*14*). Although there is still debate about which particle components are responsible for producing reactive oxygen species, there is accumulating evidence that pro-oxidative organic hydrocarbons, such as polycyclic aromatic hydrocarbons and quinones, and transition metals, such as copper, vanadium, chromium, nickel, cobalt, and iron, play a role (*15*, *16*). The particle provides a template for electron transfer to molecular oxygen in these reduction and oxidation (redox) cycling events (*7*). In addition, target cells, such as airway epithelial cells and macrophages, generate reactive oxygen species in response to particle uptake by biologically catalyzed redox reactions that occur in the cell membrane and mitochondria (*9*, *13*, *15*). The second figure shows mitochondrial damage to a macrophage caused by ultrafine particles.

Reactive oxygen species can damage cellular proteins, lipids, membranes, and DNA. To defend against this damage, cells use up their stores of a key antioxidant, glutathione. The glutathione depletion can induce a state of cellular stress, called oxidative stress, that triggers an increase in the production of antioxidant enzymes through activation of a transcription factor Nrf2 (*17*). Failure to overcome oxidative stress leads to the activation of additional intracellular signaling cascades that regulate the expression of cytokine and chemokine genes (*14*, *16*). These products are produced locally in target tissues as well as systemically, and lead to widespread proinflammatory effects remote from the site of damage.

Some individuals may be more prone to the development of inflammation, asthma, and allergic responses, because of mutations in the genes involved in the induction of the antioxidant defense (*18*). Other conditions that predispose to PM susceptibility include old age, preexisting chronic heart and lung disease, and diabetes mellitus, all of which are associated with oxidative stress and inflammation.

Although oxidative stress and inflammation may explain aspects of cardiovascular disease such as the growth of atherosclerotic plaques, other adverse outcomes, such as sudden death, may result from altered autonomic regulation of heart rate and changes in the clotting abilities of the blood (*3*). Although the cause of altered autonomic nervous activity is unknown, the systemic release of cytokines from the lung and vasculature may affect the production of clotting factors and anticoagulant enzymes in the liver. This could lead to the formation of a dense clot on top of a ruptured atherosclerotic plaque, the pathological hallmark of fatal heart attacks. The role of adsorbed particle chemicals in these cardiovascular events is uncertain. However, it is noteworthy that the ultrafine particles may gain access to the systemic circulation by penetrating alveolar membranes in lung tissue (*19*).

Public concern about the adverse health impact of PM should drive future research. We need to determine which chemical components are most important and whether, in addition to the PM mass, we also need to monitor particle number when considering the effects of ultrafine particles. Products of oxidative stress, inflammation, or tissue damage can be used as biomarkers for early indication of adverse effects of PM exposure. These biomarkers could be monitored in population studies to find susceptible subsets and to determine whether regulatory efforts are sufficient to protect against PM-induced or PM-exacerbated disease.

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ATMOSPHERIC SCIENCE

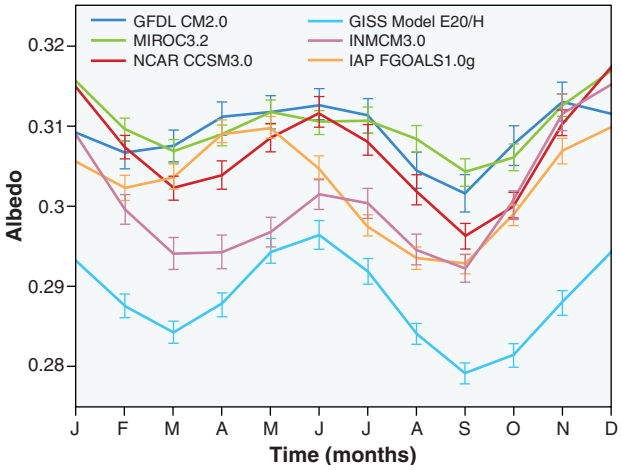
In Search of Balance

Robert J. Charlson, Francisco P. J. Valero, John H. Seinfeld

The climate of Earth and its global mean surface temperature are the consequence of a balance between the amount of solar radiation absorbed by Earth's surface and atmosphere and the amount of outgoing longwave radiation emitted by the system. The former is governed by the albedo (reflectivity) of the system, whereas the latter depends strongly on the atmospheric content of gases and particles (such as clouds and dust). Although the theory of absorption of infrared radiation by gases in the atmosphere (*1*) is well accepted and embodied in climate models, the observational and theoretical treatments of albedo, aerosols, and clouds are still under development. One brevium (*2*) and two reports (*3*, *4*) in this issue report estimates of Earth's albedo and of solar radiation reaching the surface, but the uncertainties remain large.

The buildup of CO_2 (*5*), CH_4, and other greenhouse gases during the past century has led to an increased absorption of infrared radiation in the atmosphere (enhanced greenhouse effect) and a consequent warming ("positive forcing") of the climate. But human-made changes in aerosols and clouds can cause enhanced albedo and hence cooling ("negative forcing"), and they may already have offset a substantial part of the enhanced greenhouse effect. Present trends suggest that by 2050, the magnitude of the enhanced greenhouse effect will be so large that the net anthropogenic forcing will be unequivocally positive and substantial in magnitude (*6*).

Changes in energy balance affect a host of climatic factors, such as temperature, sea level, meteorological patterns, and precipitation. To understand and quantify these effects, the enhanced greenhouse effect and all other forcings must be known accurately. To complicate matters further, the enhanced greenhouse effect is suspected of causing changes in clouds and hence albedo, resulting in feedbacks on both incoming and outgoing radiation (*7*).



Apparent agreement. Monthly mean annual cycle and standard deviation (vertical bars) of albedo from six models (*12*, *15*). These and other models are used by the Intergovernmental Panel on Climate Change (IPCC) for preindustrial control simulations.

Increased albedo could counteract the enhanced greenhouse effect on a global scale. However, the spatial and temporal characteristics of aerosols, clouds, and greenhouse gases differ widely. Clouds change rapidly, and atmospheric residence times for aerosols are short relative to those for the key greenhouse gases (which remain in the atmosphere for centuries). Albedo therefore changes rapidly, whereas the enhanced greenhouse effect simply increases as a result of the slow accumulation of greenhouse gases. Local and regional changes in energy balance would occur even if the albedo change could offset the enhanced greenhouse effect globally. Light-absorbing aerosols further complicate the picture by cooling Earth's surface, heating the atmosphere, and making clouds more absorbing; they may even reduce cloud cover, thereby decreasing albedo further.

These considerations underscore the importance of understanding the natural and anthropogenic changes in Earth's albedo and the need for sustained, direct, and simultaneous observations of albedo with all methods that are currently available. Albedo changes may be as important as changes in greenhouse gases for determining changes in global climate.

Many methods have been used to estimate albedo, which cannot be measured directly. These methods differ in their scattering geometries, calibration accuracy, and in spectral, space, and time coverage. The different modes of observation include measurements of earthshine reflected from the Moon (*8*, *9*), broadband radiometer data from low orbits around Earth [Wielicki *et al.* on page 825 (*2*)], geostationary cloud-cover observations (*10*), deep space radiometry (*11*), and surface radiometry [Pinker *et al.* on page 850 (*3*), Wild *et al.* on page 847 (*4*)]. All these methods require a theoretical model for relating the measured parameters to albedo, and they all rely on different assumptions. It is critical to compare the results from different approaches to test the consistency among them.

The scientific community has recognized this essential need for years, but major impediments have developed. For example, the broadband data collected by the ERBS (Earth Radiation Budget Satellite) between 2000 and 2004 are not being analyzed for budgetary reasons. The DSCOVR (Deep Space Climate Observatory) satellite has been built but has since fallen victim to the delayed space shuttle program and is now in storage awaiting a launch opportunity. The CALIPSO (Cloud-Aerosol Lidar and Infrared Pathfinder Satellite Observation) and CloudSat satellites have been built and have scheduled launches, but recent budget cuts imposed on the Earth sciences in NASA will severely constrain the analysis and interpretation of the data. Inasmuch as

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Perspectives: "Air pollution-related illness: effects of particles" by A. Nel (6 May 2005, p. 804). In the right-hand panel of the figure on page 804, the scale bar should be 40 nm, not 40 μm.