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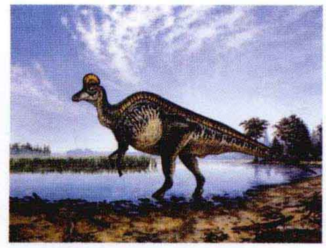

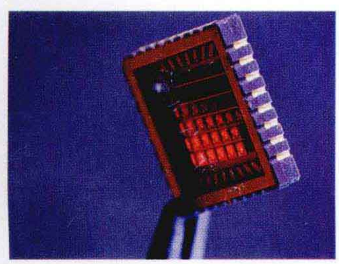

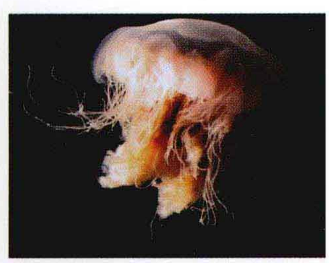

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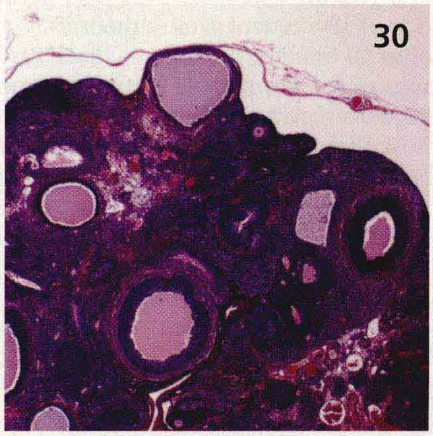
From Sigma Xi

Feature Articles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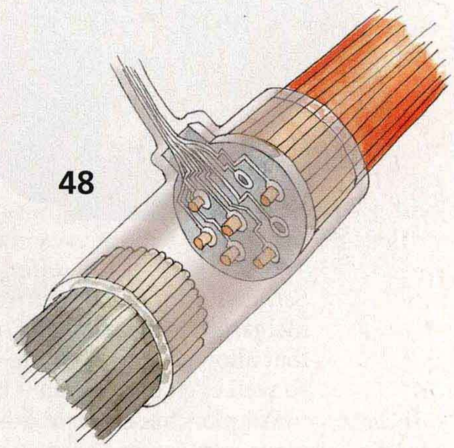
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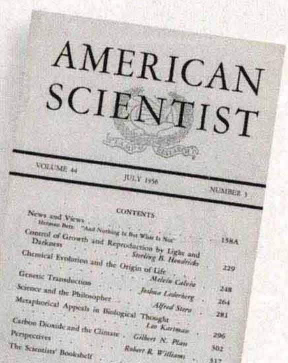

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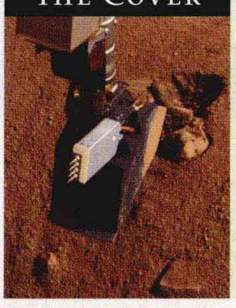
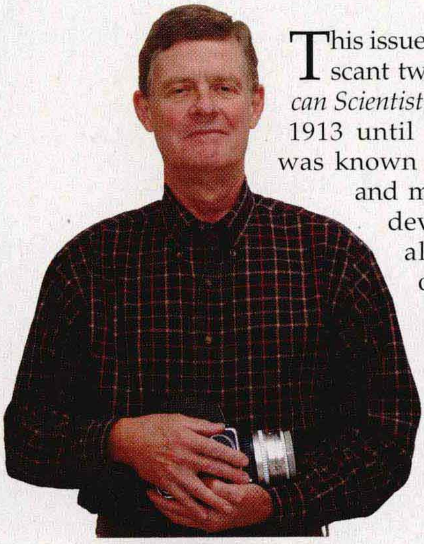
The Cover



More than a hundred exposures taken by the Phoenix lander's surface stereo imager camera were combined and projected as if the viewer is looking down from above to create this remarkably clear image of the spacecraft millions of miles away on the surface of Mars (cover). *The black circle is where the camera itself is mounted to the craft, an area that is out of the field of view of the camera. In "Phoenix on Mars" (pages 40–47), Walter Goetz describes the scientific studies that the lander has carried out on-site in the Martian polar region, including analyses of soil chemistry and water ice, often using its robotic arm* (left). *Phoenix has also made detailed observations of Martian weather and the complete water cycle on the red planet. (Images courtesy of NASA/JPL-Caltech/University of Arizona/Texas A&M University.)*

In with the Old; in with the New



This issue arrives in your hands a scant two years prior to *American Scientist*'s centennial year. From 1913 until 1943, the publication was known as *Sigma Xi Quarterly*, and much of its content was devoted to Society news, along with transcripts of lectures given by its most illustrious members. Since 1943, the publication has been known as *American Scientist* and has been largely devoted to describing the very best that science and engineering have had to offer. Starting in 1970, *American Scientist* adopted the current magazine format and increased its frequency to six times per year, changes that allowed it to do more of what it had been doing so well even better than it had before.

We plan to celebrate this milestone in a variety of ways, but one of the most important is to take a look back at some of the seminal articles the magazine has published over the years. A number of those are already included under the heading "Classics" at *American Scientist Online*, and we plan to add many more, but a few merit even more attention and will be republished in this and future issues. "Carbon Dioxide and the Climate," by Gilbert N. Plass, appeared in the July 1956 issue of *American Scientist*, and many would say that it, and a similar article by Plass that appeared later that year in *Telus*, marked the beginning of modern climate science. As the timeline that accompanies the article indicates, the notion of the so-called greenhouse effect goes back to the early 19th century, but it was Plass's work that placed carbon dioxide into the context that was then available about how climate was changing and concluded that its role accounted for the data better than competing theories.

Plass's article (see pages 58–67) could speak well for itself 54 years after the fact—indeed, I was taken aback by its prescience when Brian Hayes first pointed it out to me—but we thought it better to let people who know the topic put the work in perspective. We therefore asked James Rodger Fleming, a science historian at Colby College, and Gavin Schmidt, a climate modeller with NASA Goddard Institute for Space Studies, to comment on the place of Plass's work in both the history and science of climate research. I think you will agree that it was a remarkable achievement, but you'll also find out that he couldn't help it if he was lucky.

Along with the old revived, we have something entirely new to offer. Each month during the academic year, Sigma Xi and *American Scientist* host something we've come to call "Pizza Lunch" here at the Sigma Xi Center in Research Triangle Park, North Carolina. We invite scientists and engineers from the area's major research universities and institutions to give informal talks about their work. The audience is mainly science and technology communicators, so the content is accessible by the general public. Why not, we wondered, offer recordings (with slides, as appropriate) of the talks as podcasts? Indeed, and now—thanks to the efforts of Elsa Youngsteadt, Michael Heisel and Greg Ross—there are three to choose from. Just point your browser to www.americanscientist.org/science/page/pizza-lunch-podcasts and enjoy! Sorry, but we have yet to figure out how to deliver virtual pizza.—*David Schoonmaker*

In Defense of R. A. Fisher

To the Editors:

Together with A. W. F. Edwards, I was the last undergraduate student of R. A. Fisher (in genetics in Cambridge, 1956–57). The comment by Hari Dayal and Alok Kalia, and to a lesser extent, the reply by Andrew Gelman (November–December 2009) does a great injustice to Fisher. It is clear that none of the protagonists have read the paragraph in *Statistical Methods for Research Workers* in which Fisher introduced, in a delightful way, the $P < 0.05$ level of probability as the threshold that people, who do not understand tests of significance, religiously adhere to. Commenting on his new table of $\chi 2$ and probabilities, the two paragraphs on pages 79 and 80 of the first edition (1925) read:

> In preparing this table we have borne in mind that in practice we do not want to know the exact value of P for any observed $\chi 2$, but, in the first place, whether or not the observed value is open to suspicion. If P is between 0.1 and 0.9 there is certainly no reason to suspect the hypothesis tested. If it is below .02 it is strongly indicated that the hypothesis fails to account for the whole of the facts. We shall not often be astray if we draw a conventional line at .05, and consider that higher values of $\chi 2$ indicate a real discrepancy.
>
> To compare values of $\chi 2$, or of P, by means of a 'probable error' is merely to substitute an inexact (normal) distribution for the exact distribution given by the $\chi 2$ table.

Although relating directly to $\chi 2$, these comments are generally applicable. Fisher revolutionized experimental science at Rothamsted Experimental Station. By "tackling small sample problems on their merits," he introduced the concepts and techniques of degrees of freedom, null hypothesis, relevant subset, analysis of variance, an efficient statistic, sufficiency, likelihood, maximum likelihood, test of significance, information, the current standard table of $\chi 2$ (with the consequential layout of the other statistical tables that he worked out by pencil and paper methods) and others. Most have a direct application in almost every field of science, engineering, medicine and manufacturing. Thus the comment "To equate agricultural experiments with decisions regarding patients defies logic" is misleading and downright wrong.

David A. Jones, Emeritus
Universities of Hull and Florida

Don't Forget the Scale

To the Editors:

William A. Shear's article "Harvestmen" (November–December 2009) on Opiliones is fascinating. It's no wonder that these insects enthrall the author. The photographs accompanying the text are most illuminating and beautiful. But why did neither author nor editor provide a scale for them? When searching for them, how can we find them without a clue as to their size?

Horst Roth
Montreal, QC

Dr. Shear responds:

In the case of Leiobunum species, the most common North American forms are so frequently seen that they are familiar to many people. Generally, their body lengths are in the range of 5 to 10 millimeters, with legs spanning much larger dimensions. In the cases of more exotic species, the dimensions

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range from around 2 millimeters in body length for some of the smaller cyphophthalmids to as much as 30 millimeters for a really big Brazilian Gonyleptid. Leg spans of these large species can be as wide as 25 centimeters.

A Little Context, Please

To the Editors:

The Feature Article by Keith A. Webster, "Mitochondrial Death Channels" (September–October 2009) beautifully illustrates the strength and weakness of much contemporary biomedical research: The strength is its exquisite description of the molecular, cellular and physiological details of a clinically important phenomenon, myocardial infarction, in the contexts of apoptosis, oxidative stress and ischemia-hypoxia. Its weakness is the absence of broader contexts, a common feature of contemporary biomedical research in papers and seminars.

The context here is the role of innate immunity in triggering acute myocardial infarction (AMI). Innate immunity, which is the initial response of the body to infectious, traumatic and toxic stresses comprises many pathways. One of them, the complement pathway, consists of some 30 serum and membrane-bound proteins that protect against infections, but also damage tissues such as the heart. This pathway is triggered by ischemia, hypoxia and oxidative stress and also mediates apoptosis and myocardial infarction. Knowledge of the participation of this pathway in infarction is important not only because it helps to explain how the heart is damaged but also suggests treatments such as antagonists of this pathway. Moreover, knowledge of this pathway may help to predict and evaluate the success of various treatments. For instance, drug-eluting stents employed to reduce the narrowing of blood vessels in the heart can trigger the complement pathway and thereby induce significant inflammation that impairs vascular healing and leads to renarrowing of the vessels.

The absence of broader context in much contemporary biomedical research reflects either the lack of knowledge of that context (for example, innate immunity and the complement pathway), or failure to consider the context germane. In either case, a by-product is failure to communicate the broader picture to graduate students, postdoctoral fellows and faculty. This failure is then reflected in the inadequate training that many of our graduate students and postdoctoral fellows receive and the eventual narrow teaching that they themselves do.

Abram B. Stavitsky
Cleveland, OH

Dr. Webster responds:

I appreciate Dr. Stavitsky's comments. Unlike innate immunity, however, the role of the mitochondrial death channels in necrotic and apoptotic death during AMI are now quite well understood. The mitochondrial permeability transition pore (mPTP) is a clear therapeutic target and there are a number of candidates of which, in my opinion, cyclosporine A (CsA), volatile anesthetics and Viagra are the most promising. Each of these agents target the mPTP—CsA directly through its binding to cyclophilin D (CypD), volatile anesthetics and Viagra indirectly by activating ischemic preconditioning and inhibiting GSK3-* upstream of CypD. Clinical trials are underway for these agents, each of which is already approved for other indications. And successful results have already been reported where volatile anesthetics are used during angioplasty or CABG.

Innate immunity is a much more difficult target. We are not sure whether it is injurious or protective. It is not clear to what extent innate immunity is a consequence rather than a cause of AMI. A central role of innate immunity in coronary artery disease has been recognized for many years, and an exaggerated role of inflammation within damaged vessel walls after angioplasty with or without coronary stenting is indeed a serious clinical concern and the focus of intense research. Activation of innate immunity during myocardial infarction and remodeling has also been recognized for many years and is supported both by animal and patient studies that have demonstrated increased levels of circulating inflammatory cells, cytokines, and complement factors in patients with unstable angina, pre- and post AMI, and post-AMI progressing to heart failure.

Support for a direct role of innate immunity in AMI also includes the presence of neutrophils, macrophages and elevated levels of inflammatory cytokines within the infarct and peri-infarct regions of the myocardium. In addition, over-expression of inflammatory cytokines in mouse models can reproduce multiple features of post-MI contractile dysfunction, negative remodeling and heart failure. Despite this, clinical trials targeting either complement or inflammatory cytokines have been largely unsuccessful. This may be because the overall role of innate immunity during human AMI is protective. So, whereas I agree with Dr. Stavitsky that graduate students and postdocs should be made aware of the roles of innate immunity in cardiovascular disease—at the University of Miami, they are—I am not sure that I have missed a broader context in my article by focusing on the death channels.

How to Write to *American Scientist*

Brief letters commenting on articles that have appeared in the magazine are welcomed. The editors reserve the right to edit submissions. Please include a phone number or e-mail address if possible. Address: Letters to the Editors, American Scientist, P.O. Box 13975, Research Triangle Park, NC 27709 or editors@amscionline.org.

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Page 8 adapted by Tom Dunne

Computing Science
Page 12 Barbara Aulicino

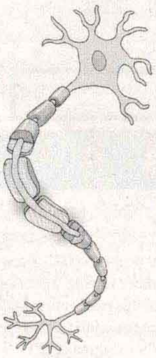
Engineering
Page 17 Tom Dunne

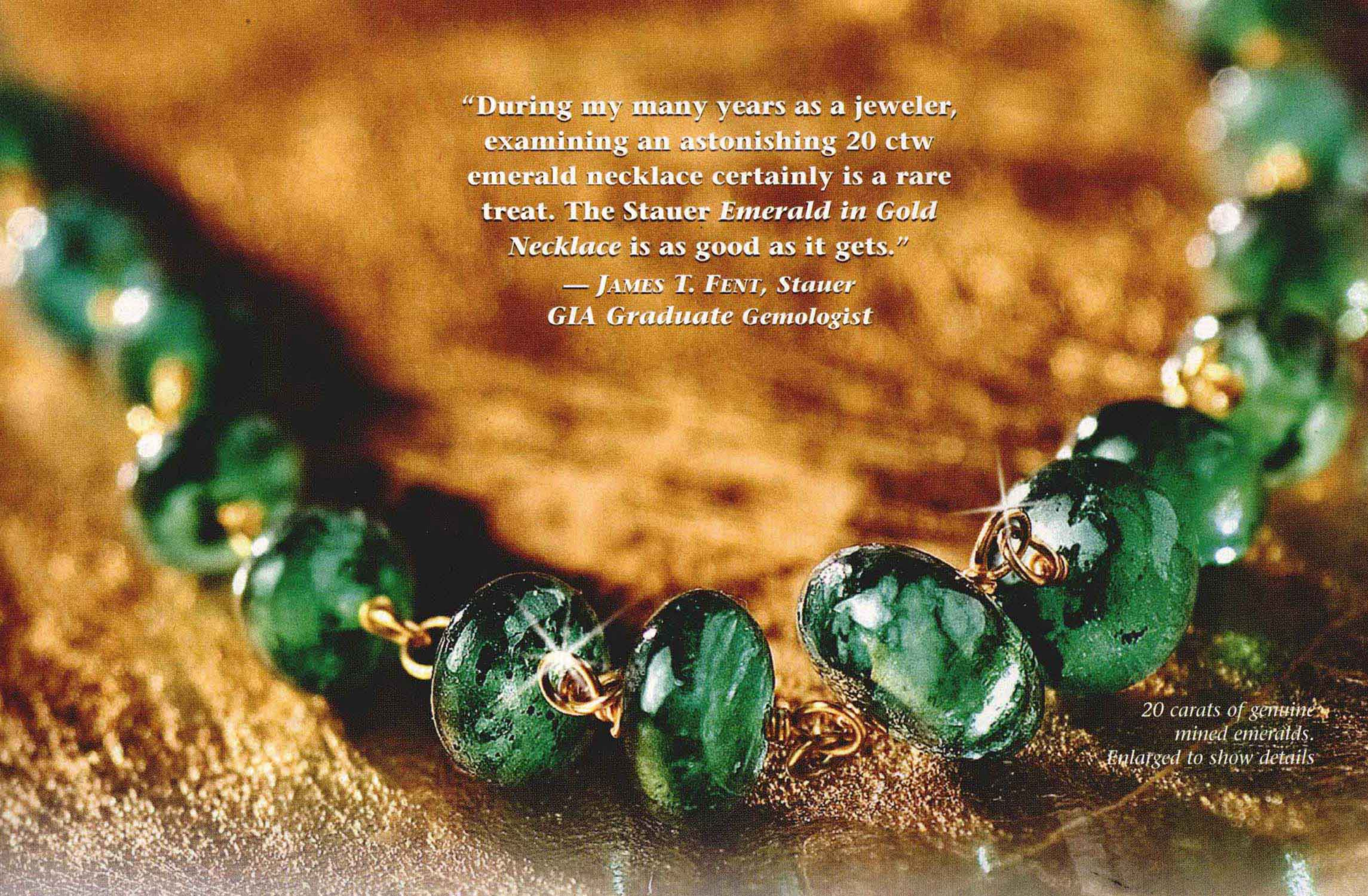
Assessing Risks from Bisphenol A
Figures 2–4, 6 *(right)*, 7 Barbara Aulicino

Phoenix on Mars
Figure 7 *(left)* Tom Dunne

Neural Interfaces
Figures 2–4, 6 *(right)*, 7 Tom Dunne

***American Scientist* Classics: Carbon Dioxide and the Climate**
Figure 2 Barbara Aulicino





The Curse of the Perfect Gift

20 carats of polished natural emeralds linked with 14K gold for under $200!

It happened on our last trip to South America. After visiting the "Lost City" of Machu Picchu in Peru, we ventured through the mountains and down the Amazon into Brazil. In an old village we met a merchant with an impressive collection of spectacular, iridescent emeralds. Each gem was tumbled smooth and glistened like a perfect rain forest dew drop. But the price was so unbelievable, I was sure our interpreter had made a mistake.

But there was no mistake. And after returning home, I had 20 carats of these exquisite emeralds strung up in 14k gold and wrapped as a gift for my wife's birthday. That's when my trouble began. She loved it. Absolutely adored it. In fact, she rarely goes anywhere without the necklace and has basked in compliments from total strangers for months now.

So what's the problem? I'm never going to find an emerald deal this good again. In giving her such a perfect gift, I've made it impossible to top myself.

To make matters worse, my wife's become obsessed with emeralds. She can't stop sharing stories about how Cleopatra cherished the green gem above all others and how emeralds were worshiped by the Incas and Mayans and prized by Spanish conquistadors and Indian maharajahs. She's even buying into ancient beliefs that emeralds bring intelligence, well-being and good luck to anyone who wears them. I don't have the heart to tell her that I'm never going to find another deal this lucky.

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A Short History of Hydrogen Sulfide

Roger P. Smith

From the sewers of Paris to physiological messenger

Early last year, reports began to emerge in the Southeastern United States of a strange illness. Homeowners reported nosebleeds, sinus irritation and respiratory problems that appeared to be associated with corrosion of copper pipes and air conditioner coils in their houses.

The culprit seems to be drywall imported from China and possibly contaminated with strontium sulfide, an unstable salt that releases hydrogen sulfide on exposure to moisture. It was used widely in the housing boom of 2004–2007, and in the rebuilding efforts after Hurricane Katrina in 2005, when domestic suppliers could not keep up with the demand. The Consumer Products Safety Commission is now investigating whether sulfide gases given off by the drywall, including hydrogen sulfide, are to blame. The Florida Department of Health maintains a Web site with information for consumers. Lawsuits abound, and many who are able to do so have moved out of their homes. Several estimates place the number of affected houses at 100,000.

To those experiencing or investigating this phenomenon early on, it seemed bizarre. But in fact, this is just the latest chapter in the history of a chemical whose effects were first noted in the 16th century. And there is still more to learn about its role in the human body. Recent research offers insights into its biochemical actions as well as some intriguing suggestions for medical uses.

Roger P. Smith is the Irene Heinz Given Professor of Pharmacology and Toxicology, Emeritus, at Dartmouth Medical School and former chair of the department. He served on the Associate Consulting Staff of Mary Hitchcock Memorial Hospital now in Lebanon, New Hampshire, and as a consultant to the V.A. Medical Center in White River Junction, Vermont. He received his Ph.D. from Purdue University. Address: Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, NH 03755. Email: roger.p.smith@dartmouth.edu

Occupational Exposures

In 1713, a remarkable Italian physician named Bernardino Ramazzini published *De Morbis Artificum*, or *Diseases of Workers*. In Chapter 14, titled "Diseases of Cleaners of Privies and Cesspits," he describes a painful inflammation of the eyes which was common among such workers. The inflammation often led to secondary bacterial invasion, and sometimes to total blindness. Displaying amazing insight, Ramazzini hypothesized that when the cleaners disturbed the excrement in the course of their work, an unknown volatile acid was produced, which was irritating to the eyes. It was also at least partially responsible for the odor of excrement, and it is now known to be generated wherever organic matter undergoes putrefaction.

Ramazzini further postulated that that same acid was causing copper and silver coins which the workers had in their pockets to turn black on their surfaces—an eerie resonance with the phenomena recently observed by U.S. homeowners. Around 1777, a series of accidents—some of them fatal—began to occur in Paris due to a gas emanating from its sewer system. The commission appointed to study the cases made its findings public in 1785. The report described two distinct types of poisonings: a mild form involving inflammation of the eyes and mucous membranes as already described by Ramazzini, and a severe form that was characterized by a fulminating (rapidly developing) asphyxia. It is little wonder that the French Romantic writer Victor Hugo (1802–1885) referred to the Parisian sewers as "the intestine of the Leviathan." Many years were to pass, however, before chemical analyses would establish the presence of hydrogen sulfide in the sewers and implicate it as the cause of the accidents.

The history of exposures has focused on sewers and the workplace, but the corrosive effects of hydrogen sulfide are common knowledge in Rotorua, New Zealand, which was built over centuries in a geothermally active area. The constant exposure to low, environmental levels of hydrogen sulfide produces such damage even as residents enjoy spas, indoor heating and cooking with the hot gases.

Today, the American Conference of Industrial Hygienists has set the so-called threshold limit value for its presence in the workplace at 10 parts per million (ppm) of hydrogen sulfide in air for eight hours a day, five days a week over a working lifetime. The U.S. National Institute for Occupational Safety and Health estimated in 1977—some 200 years after the Paris accidents—that 125,000 workers in at least 77 occupations, including drilling for petroleum, tanneries and the paper industry, may be at risk of exposure to hydrogen sulfide.

Chemical Discovery

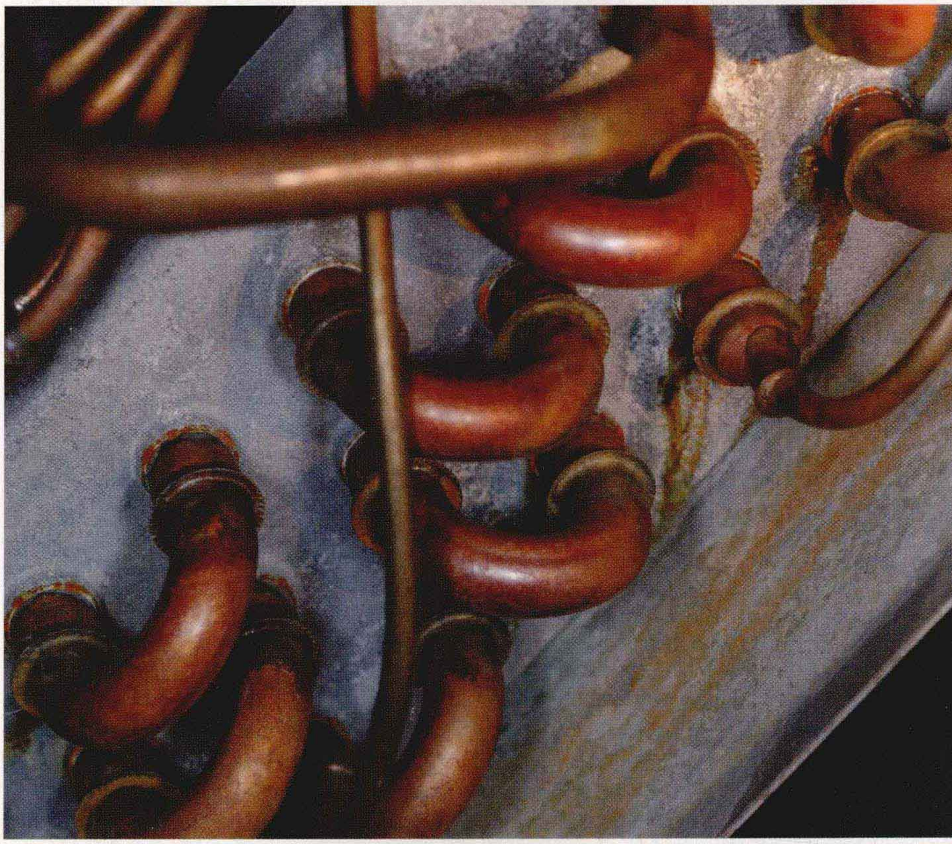
Around 1750, a humble young Swede beginning his career as an apothecary was fortunate to have a series of very understanding mentors who allowed him considerable free time for reading and experimentation. His name was Carl Wilhelm Scheele, and he turned out to be a gifted chemist. Like many chemists before and after him, Scheele seems to have given little thought to the biological effects of the materials with which he worked. One day while distilling potassium ferrocyanide with sulfuric acid, he noted a "strong, peculiar and not unpleasant odor." He brought himself to taste this gas and described it as "slightly on sweet [sic] and somewhat heating on the mouth." Today we describe the odor as that of bitter almonds and call the gas hydrogen cyanide. Scheele may have been fortunate to have escaped with his life.

Perhaps a guardian angel was with him again on the day that he treated ferrous sulfide (pyrite, or fool's gold) with a mineral acid. He called the rank odor that resulted *Schwefelluft* (sulfur air) and referred to it as *stinkende* (stinking or fetid). Today we refer to the odor as that of rotten eggs. His patron, the Swedish chemist and mineralogist Torbern Olof Bergman, also demonstrated its presence in some mineral springs. The publication date for these original observations was 1777—around the time of the Paris accidents. The fact that the same man discovered both hydrogen sulfide and hydrogen cyanide was the start of a long series of coincidences and discoveries about the two chemicals that would uncover their similarities.

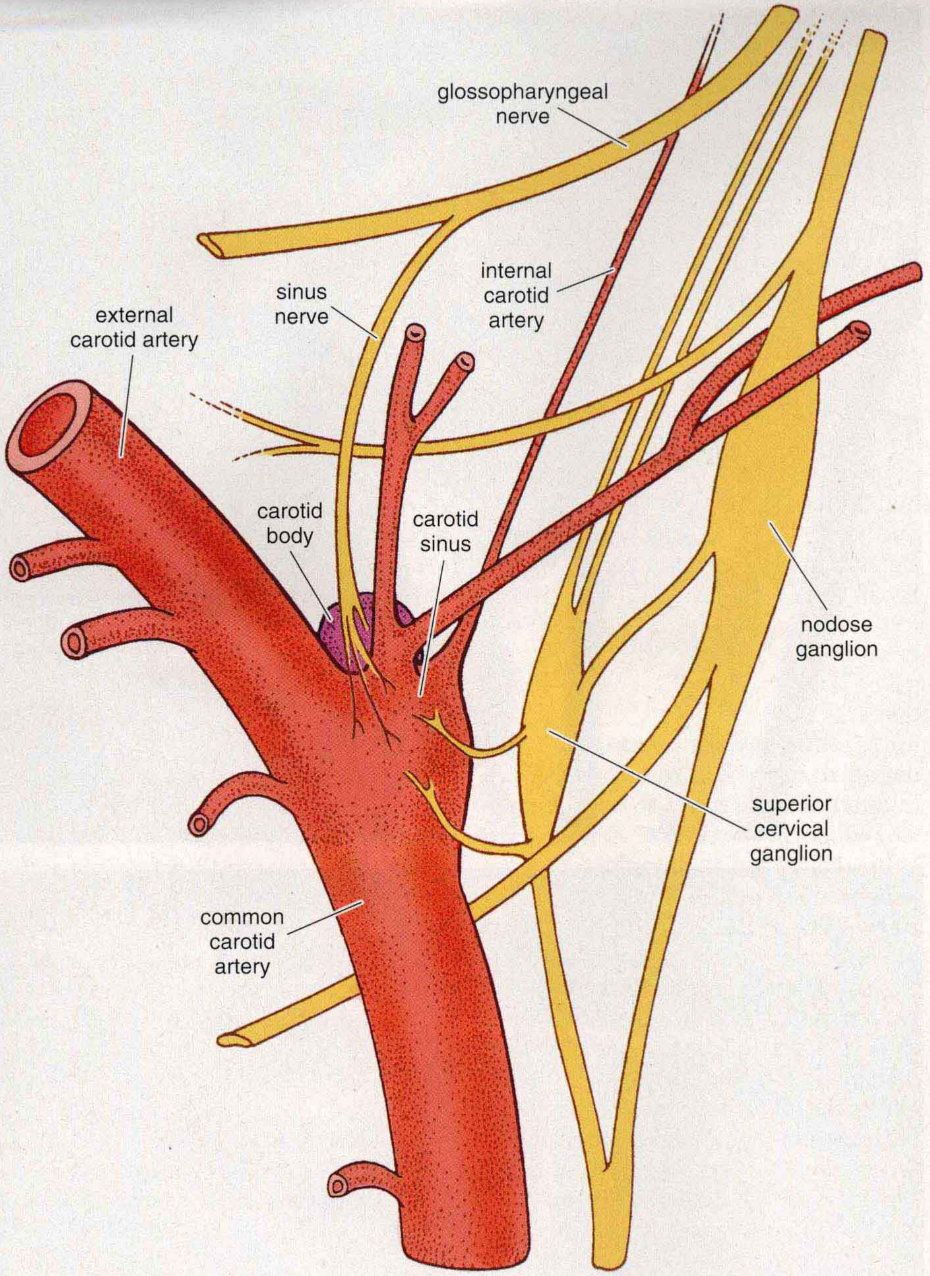
Biological Effects

Investigations on the biological effects of hydrogen sulfide began around the turn of the 20th century. François Chaussier, François Magendie, Claude Bernard and Felix Hoppe-Seyler were among the well-known scientists of the day who labored in that vineyard.

In experiments with dogs, marked differences in the effects of hydrogen sulfide were noted with only small changes in its concentration in the air they were breathing. Fifty ppm, which was considered a minimally lethal concentration at the time, resulted in a slight progressive depression in the rate and depth of respirations. After many hours of exposure, the dogs died from a type of pulmonary edema, acute respiratory distress syndrome (ARDS). When that concentration was doubled to 100 ppm, death resulted in 15 to 20 minutes. In these cases the respiration was stimulated almost immediately, this progressed to a pronounced hyperpnea (deep breathing), and death in apnea followed. At 300 ppm, respiratory arrest occurred after a few violent gasps. The same effects on respiration, with the exception of ARDS, were known to occur with injected or inhaled hydrogen cyanide. Mice may be more resistant to the effects of hydrogen sulfide. In a 1964 experiment,



Copper air-conditioner coils in some Florida homes have corroded so much that they have required replacing multiple times *(top)*. It is likely that the corrosion is the result of abnormally high levels of hydrogen sulfide in the air. The suspected source of the chemical is several brands of drywall imported from China. Drywall from China was also used in rebuilding efforts in Louisiana and Mississippi after Hurricane Katrina, when domestic supplies of drywall ran short. Coils from an air conditioner not exposed to hydrogen sulfide are shown for comparison *(bottom)*. (Photographs courtesy of the Florida Department of Health.)



The carotid body *(purple mass)* regulates respiration by sensing changes in the oxygen content of the blood as it flows through the carotid artery *(red)* to the brain. The carotid body contains chemoreceptors that bind hydrogen cyanide and hydrogen sulfide; when they do so, respiration is first stimulated and then depressed. In severe cases, breathing either of these gases can cause death. In experiments with dogs that were exposed to hydrogen sulfide in concentrations of 100 parts per million, the dogs died in 15 to 20 minutes. The carotid sinus and associated nerves of the cat are shown here; experiments with cats led to the discovery that severing the sinus nerve *(yellow)*, and thus denervating the carotid sinus, eliminated the effects of both chemicals on respiration.

they survived for 10 minutes in an atmosphere of 1,872 ppm and for 20 minutes at 985 ppm.

A more complete explanation of the respiratory stimulant effects of hydrogen cyanide and hydrogen sulfide had to await the discovery of the chemoreceptor function of the carotid body *(shown above)*, and the reflex effects that follow the activation of those receptors. The respiratory stimulant effects of cyanide and sulfide could be completely abolished by severing the sinus nerve and thus denervating the carotid sinus. In that case, larger doses of either chemical resulted only in respiratory depression, which was presumably mediated via the brainstem. Similarly, injections of sulfide or cyanide into the internal carotid or vertebral arteries also failed to stimulate respiration, since in those cases the chemicals reached the carotid sinus only after dilution in the general circulation. When innervation of the sinus was intact, the hyperpnea was accompanied by a fleeting rise in systemic blood pressure, and sometimes by a slowed heart rate (bradycardia). The cardiovascular effects varied with the injection site and the species and are still not adequately explained.

A Persistent False Trail

The great German biochemist Hoppe-Seyler became famous for his discovery of the abnormal form of hemoglobin known as methemoglobin, in which some or all of the heme irons have been oxidized to the ferric form. This reaction is readily mediated both in vivo and in vitro by sodium nitrite. Methemoglobin cannot reversibly combine with oxygen, and the disruption of the oxygen-transport function of the blood can result in hypoxia and death.

In 1863, Hoppe-Seyler passed a stream of pure hydrogen sulfide through a sample of human blood and claimed to have observed a greenish pigment that was associated with shifts in the visible absorption spectrum of hemoglobin. Although he was aware that he had probably produced a mixture containing unstable and denatured products, which resulted in turbidity and precipitation and made the absorption spectra suspect, he still thought that the mixture contained a new form of hemoglobin. He called it sulfhemoglobin and thereby launched one of the most confused areas in hematology. It led to the hypothesis some still subscribe to—namely, that hydrogen sulfide is a blood poison like sodium nitrite and carbon monoxide. No matter that animal experiments clearly demonstrated that it was a respiratory toxin, or that no such pigment has ever been identified in the blood of animals or humans fatally poisoned with hydrogen sulfide. Sulfhemoglobin generated by hydrogen sulfide appears to be a strictly in vitro phenomenon, and it has yet to be prepared in pure form.

Sulfmethemoglobin

No less a scientist than Linus Pauling and his associates described the magnetic properties of another blood pigment, which they called sulfmethemoglobin. This pigment is easily prepared in pure form by mixing hydrogen sulfide with methemoglobin, and it is chemically analogous to cyanmethemoglobin, in which the cyanide ion is bound to ferric irons of heme. The hydrosulfide anion (HS^-) also binds to ferric heme, albeit not quite so tenaciously as cyanide. Indeed, this reaction has been exploited medically as an antidote to cyanide poisoning. One can deliberately inject sodium nitrite intravenously to generate a tolerable level of methemoglobin. The methemoglobin will temporarily bind free cyanide as the inactive complex cyanmethemoglobin. Over time the cyanide is slowly released, at a rate at which the body's natural detoxification mechanisms can deal with it.

At least three laboratories have demonstrated that the same principles can be applied to hydrogen sulfide poisoning and that induced methemoglobinemia can indeed be lifesaving. At least a half dozen successful human resuscitations have been reported in the literature. The odds against its successful application, however, are high. Few poisons are more rapidly acting than inhaled hydrogen sulfide, and inhalation is invariably the route of exposure. Sulfide poisoning tends to occur in remote locations, and there is seldom a medically qualified individual on the scene who is prepared with a parenteral form of nitrite and trained to make intravenous injections. Most successful resuscitations from cyanide poisoning have occurred in individuals who ingested soluble salts of cyanide, where absorption is delayed.

Chemical Similarities Between Cyanide and Sulfide

In addition to the similarities in their physiological effects, cyanide and sulfide have chemical similarities. The undissociated forms of both hydrogen cyanide and hydrogen sulfide are flammable, volatile gases. Hydrogen sulfide (whose vapor density, or d, is 1.19) is heavier than air ($d = 1.0$) whereas hydrogen cyanide ($d = 0.941$) is lighter. Both are weak acids with acid dissociation constants (pK_a) that are of some physiological significance: hydrogen cyanide 9.2–9.3 and hydrogen sulfide 7.04. Both form salts with sodium and potassium as well as with some alkaline earths. Both anions bind to methemoglobin as noted above, and each of those complexes has its distinct visible absorption spectrum. And both are inhibitors of cytochrome *c* oxidase, the terminal enzyme in the electron transport chain that reacts with molecular oxygen in aerobic organisms. Blockage of that key enzyme is believed to be the mechanism of action in the rapidly lethal form of cyanide and sulfide poisonings.

New Biological Roles

Inhibition of cytochrome *c* oxidase results in a decrease in oxidative phosphorylation (the metabolic pathway that produces ATP). This in turn lowers the metabolic rate and body temperature in mice. These phenomena accompany states of suspended animation. When mice were exposed to hydrogen sulfide at concentrations of 80 ppm, dramatic effects were observed in the first 5 minutes. By 6 hours, their metabolic rate had dropped by 90 percent and body temperature to 2 degrees Celsius above ambient temperature. When the mice were then returned to room air, the metabolic rate and temperature returned to normal with no detectable behavioral or functional deficits. As already noted, lethal levels for hydrogen sulfide in mice are much higher than for dogs, but this state in mice must also occur over a fairly narrow range of concentrations.

Finally, and most astonishingly of all, experimental evidence contributed in 2008 indicates that like carbon monoxide and nitric oxide, hydrogen sulfide is an important signaling molecule in biology, and it may find a role in medicine. It is physiologically generated in mice by cystathionine γ-lyase, and genetic deletion of that enzyme markedly reduces hydrogen sulfide levels in the serum, heart, aorta and other tissues. Mutant mice lacking the enzyme have marked hypertension and diminished endothelium-dependent vasorelaxation, consistent with an important vasodilator role for hydrogen sulfide. The enzyme is physiologically activated by the calcium-binding protein calmodulin, which is a mechanism for hydrogen sulfide formation in response to vascular activation. Thus, hydrogen sulfide appears to be a physiologic vasodilator and regulator of blood pressure. Its relative contribution vis-à-vis the similar nitric oxide is not yet clear.

What a strange and wondrous journey this odiferous and violently toxic chemical, associated with the excrement of humanity, has led us on for five centuries. It's a history that could fill a book, one that covers a vast range of territory, from the search to determine the cause of workplace injuries to fascinating discoveries about how hydrogen sulfide interacts with chemoreceptors in the body. And for all the false leads, in the end it may yet turn out to have some useful applications in medicine—even if only a new Viagra.

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A Tisket, a Tasket, an Apollonian Gasket

Dana Mackenzie

In the spring of 2007 I had the good fortune to spend a semester at the Mathematical Sciences Research Institute in Berkeley, an institution of higher learning that takes "higher" to a whole new extreme. Perched precariously on a ridge far above the University of California at Berkeley campus, the building offers postcard-perfect vistas of the San Francisco Bay, 1,200 feet below. That's on the west side. Rather sensibly, the institute assigned me an office on the east side, with a view of nothing much but my computer screen. Otherwise I might not have gotten any work done.

However, there was one flaw in the plan: Someone installed a screen-saver program on the computer. Of course, it had to be mathematical. The program drew an endless assortment of fractals of varying shapes and ingenuity. Every couple minutes the screen would go blank and refresh itself with a completely different fractal. I have to confess that I spent a few idle minutes watching the fractals instead of writing.

One day, a new design popped up on the screen *(see the first figure)*. It was different from all the other fractals. It was made up of simple shapes—circles, in fact—and unlike all the other screen-savers, it had numbers! My attention was immediately drawn to the sequence of numbers running along the bottom edge: 1, 4, 9, 16 … They were the perfect squares! The sequence was 1-squared, 2-squared, 3-squared, and so on.

Fractals made of circles do funny things to mathematicians

Before I became a full-time writer, I used to be a mathematician. Seeing those numbers awakened the math geek in me. What did they mean? And what did they have to do with the fractal on the screen? Quickly, before the screen-saver image vanished into the ether, I sketched it on my notepad, making a resolution to find out someday.

As it turned out, the picture on the screen was a special case of a more general construction. Start with three circles of any size, with each one touching the other two. Draw a new circle that fits snugly into the space between them, and another around the outside enclosing all the circles. Now you have four roughly triangular spaces between the circles. In each of those spaces, draw a new circle that just touches each side. This creates 12 triangular pores; insert a new circle into each one of them, just touching each side. Keep on going forever, or at least until the circles become too small to see. The resulting foam-like structure is called an Apollonian gasket *(see the second figure)*.

Something about the Apollonian gasket makes ordinary, sensible mathematicians get a little bit giddy. It inspired a Nobel laureate to write a poem and publish it in the journal *Nature*. An 18th-century Japanese samurai painted a similar picture on a tablet and hung it in front of a Buddhist temple. Researchers at AT&T Labs printed it onto T-shirts. And in a book about fractals with the lovely title *Indra's Pearls*, mathematician David Wright compared the gasket to Dr. Seuss's *The Cat in the Hat*:

> The cat takes off his hat to reveal Little Cat A, who then removes his hat and releases Little Cat B, who then uncovers Little Cat C, and so on. Now imagine there are not one but three cats inside each cat's hat. That gives a good impression of the explosive proliferation of these tiny ideal triangles.

Getting the Bends

Even the first step of drawing an Apollonian gasket is far from straightforward. Given three circles, how do you draw a fourth circle that is exactly tangent to all three?

Apparently the first mathematician to seriously consider this question was Apollonius of Perga, a Greek geometer who lived in the third century B.C. He has been somewhat overshadowed by his predecessor Euclid, in part because most of his books have been lost. However, Apollonius's surviving book *Conic Sections* was the first to systematically study ellipses, hyperbolas and parabolas—curves that have remained central to mathematics ever since.

One of Apollonius's lost manuscripts was called *Tangencies*. According to later commentators, Apollonius apparently solved the problem of drawing circles that are simultaneously tangent to three lines, or two lines and a circle, or two circles and a line, or three circles. The hardest case of all was the case where the three circles are tangent.

No one knows, of course, what Apollonius' solution was, or whether it was correct. After many of the writings of the ancient Greeks became available again to European scholars of the Renaissance, the unsolved "problem of

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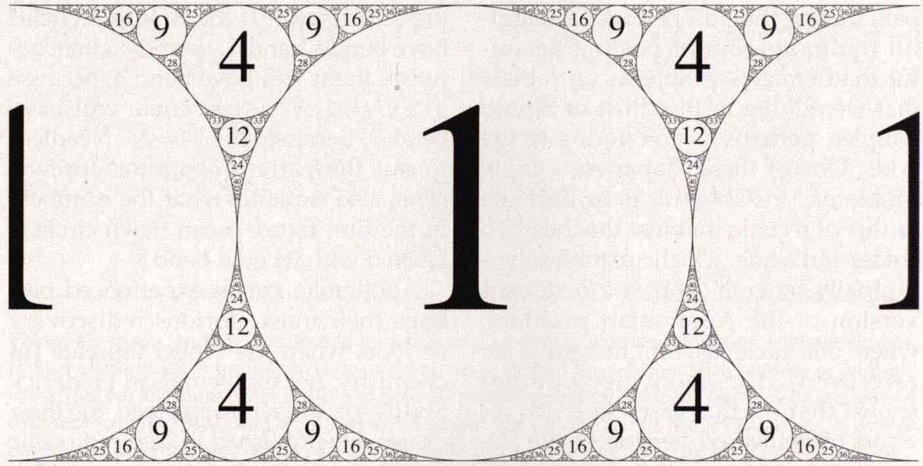


Numbers in an Apollonian gasket correspond to the curvatures or "bends" of the circles, with larger bends corresponding to smaller circles. The entire gasket is determined by the first four mutually tangent circles; in this case, two circles with bend 1 and two "circles" with bend *0* (and therefore infinite radius). The circles with a bend of zero look, of course, like straight lines. (Image courtesy of Alex Kontorovich.)

Apollonius" became a great challenge. In 1643, in a letter to Princess Elizabeth of Bohemia, the French philosopher and mathematician René Descartes correctly stated (but incorrectly proved) a beautiful formula concerning the radii of four mutually touching circles. If the radii are r, s, t and u, then Descartes's formula looks like this:

$$1/r^2+1/s^2+1/t^2+1/u^2=1/2\,(1/r+1/s+1/t+1/u)^2.$$

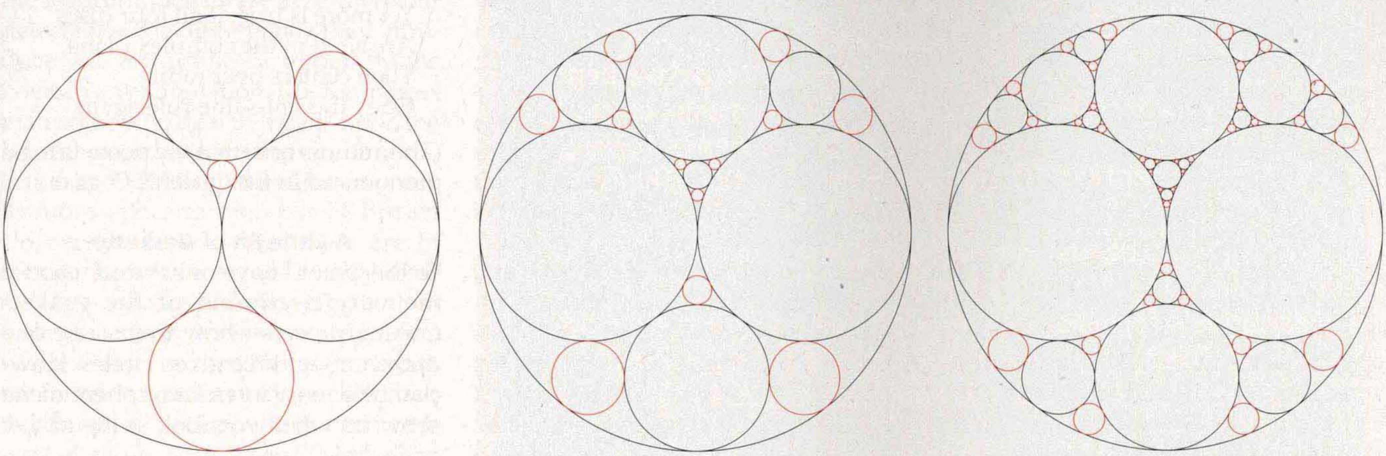
All of these reciprocals look a little bit extravagant, so the formula is usually simplified by writing it in terms of the *curvatures* or the *bends* of the circles. The curvature is simply defined as the reciprocal of the radius. Thus, if the curvatures are denoted by a, b, c and d, then Descartes's formula reads as follows:

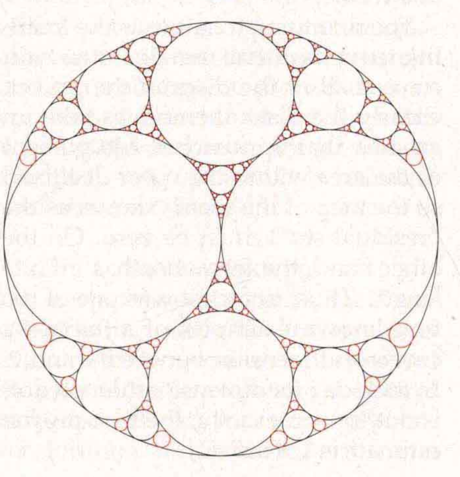
$$a^2+b^2+c^2+d^2=(a+b+c+d)^2/2.$$

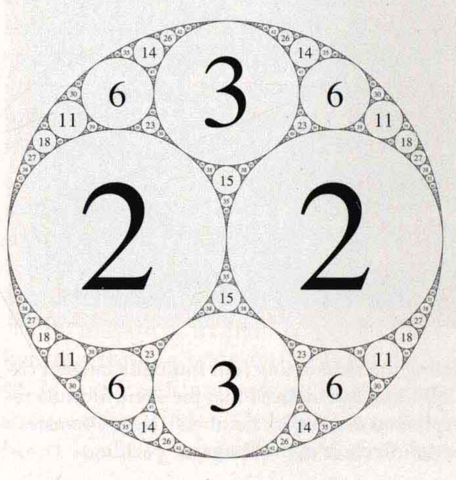
As the third figure shows, Descartes's formula greatly simplifies the task of finding the *size* of the fourth circle, assuming the sizes of the first three are known. It is much less obvious that the very same equation can be used to compute the *location* of the fourth circle as well, and thus completely solve the drawing problem. This fact was discovered in the late 1990s by Allan Wilks and Colin Mallows of AT&T Labs, and Wilks used it to write a very efficient computer program for plotting Apollonian gaskets. One such plot went on his office door and eventually got made into the aforementioned T-shirt.

Descartes himself could not have discovered this procedure, because it involves treating the coordinates of the circle centers as complex numbers. Imaginary and complex numbers were not widely accepted by mathematicians until a century and a half after Descartes died.

In spite of its relative simplicity, Descartes's formula has never become widely known, even among mathematicians. Thus, it has been rediscovered over and over through the years. In Ja-







An Apollonian gasket is built up through successive "generations." For instance, in generation 1 *(top left)*, each of the red circles is inscribed in one of the four triangular pores formed by the black circles. The final gasket shown here, whimsically named "bugeye" by Katherine Sanden, an undergraduate student of Peter Sarnak at Princeton University, has circles with bends –1 (for the largest circle that encloses the rest), 2, 2 and 3. The list of bends that appears in a given gasket (here, 2, 3, 6, 11, etc.) form a number sequence whose properties Sarnak would like to explain—but, he says, "the necessary mathematics has not been invented yet." (Image courtesy of Katherine Sanden.)

pan, during the Edo period, a delightful tradition arose of posting beautiful mathematics problems on tablets that were hung in Buddhist or Shinto temples, perhaps as an offering to the gods. One of these "Japanese temple problems," or *sangaku,* is to find the radius of a circle that just touches two circles and a line, which are themselves mutually tangent. This is a restricted version of the Apollonian problem, where one circle has infinite radius (or zero bend). The anonymous author shows that, in this case, $\sqrt{a}+\sqrt{b}=\sqrt{c}$, a sort of demented version of the Pythagorean theorem. This formula, by the way, explains the pattern I saw in the screensaver. If the first two circles have bends 1 and 1, then the circle between them will have bend 4, because $\sqrt{1}+\sqrt{1}=\sqrt{4}$. The next circle will have bend 9, because $\sqrt{1}+\sqrt{4}=\sqrt{9}$. Needless to say, the pattern continues forever. (This also explains what the numbers in the first figure mean. Each circle is labeled with its own bend.)

Apollonian circles experienced perhaps their most glorious rediscovery in 1936, when the Nobel laureate (in chemistry, not mathematics) Frederick Soddy became mesmerized by their charm. He published in *Nature* a poetic version of Descartes' theorem, which he called "The Kiss Precise":

Four circles to the kissing come
The smaller are the benter.
The bend is just the inverse of
The distance from the center.
Though their intrigue left
  Euclid dumb,
There's now no need for rule
  of thumb.
Since zero bend's a dead
  straight line,
And concave bends have
  minus sign,
The sum of the squares of all
  four bends
Is half the square of their sum.

Soddy went on to state a version for three-dimensional spheres (which he was also not the first to discover) in the final stanza of his poem.

Ever since Soddy's prosodic effort, it has become something of a tradition to publish any extension of his theorem in poetic form as well. The following year, Thorold Gosset published an n-dimensional version, also in *Nature.* In 2002, when Wilks, Mallows and Jeff Lagarias published a long article in the *American Mathematical Monthly,* they ended it with a continuation of Soddy's poem entitled "The Complex Kiss Precise":

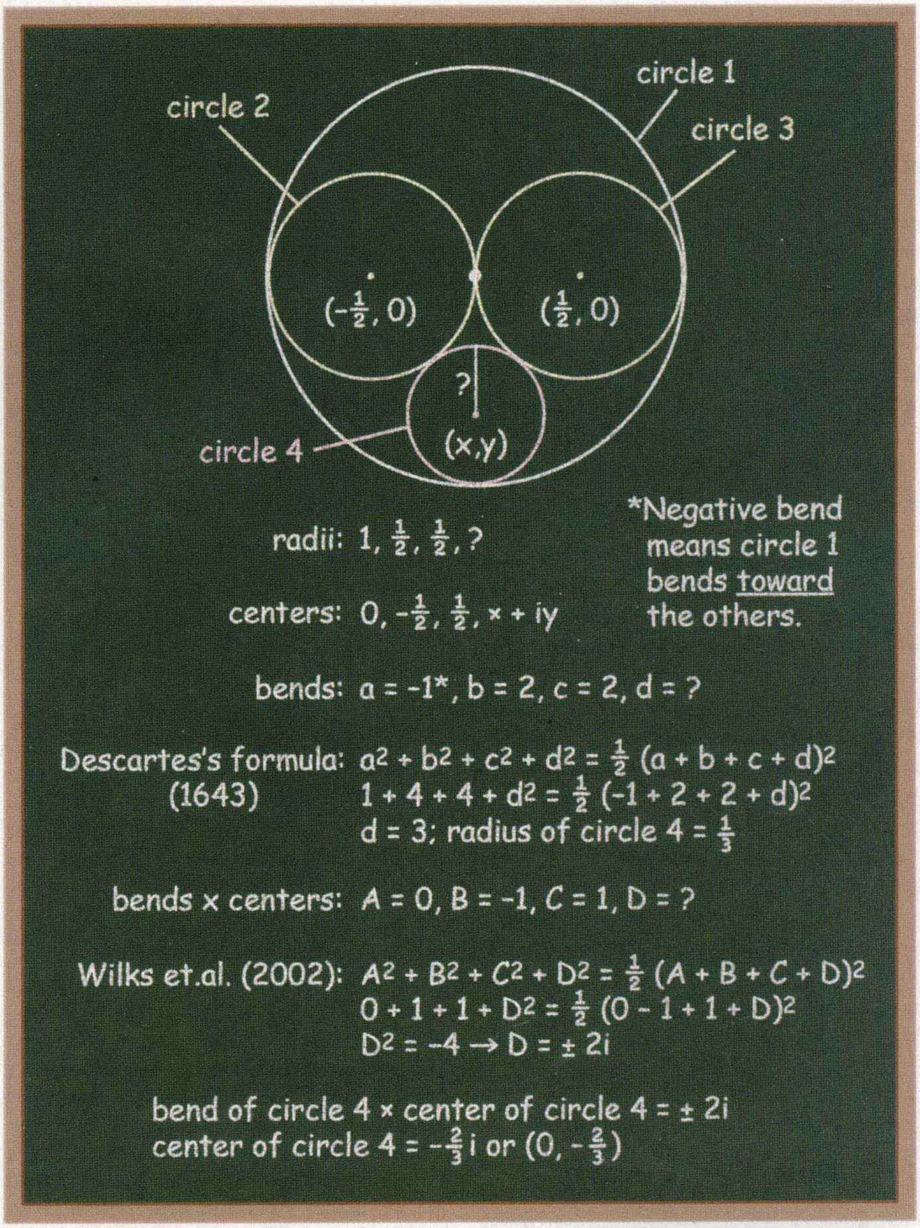
Yet more is true: if all four discs
Are sited in the complex plane,
Then centers over radii
Obey the self-same rule again.

(The authors note that the poem is to be pronounced in the Queen's English.)

A Little Bit of Gasketry

To this point I have only written about the very beginning of the gasket-making process—how to inscribe one circle among three given circles. However, the most interesting phenomena show up when you look at the gasket as a whole.

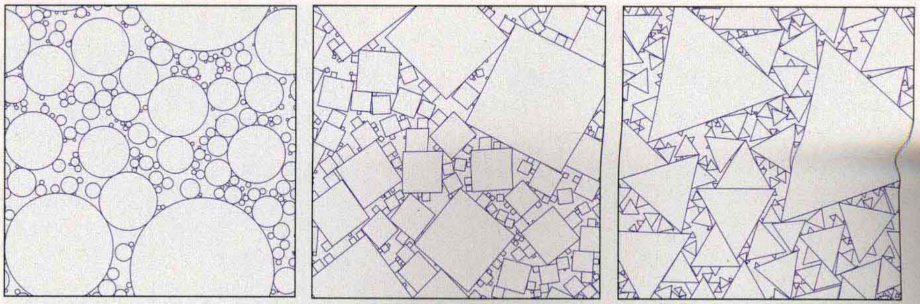
The first thing to notice is the foam-like structure that remains after you cut out all of the discs in the gasket. Clearly the disks themselves take up an area that approaches 100 percent of the area within the outer disk, and so the area of the foam (known as the "residual set") must be zero. On the other hand, the foam also has infinite length. Thus, in fact, it was one of the first known examples of a *fractal*—a curve of dimension between 1 and 2. Even today its dimension (denoted δ) is not known exactly; the best-proven estimate is 1.30568.



In 1643 René Descartes gave a simple formula relating the radii of any four mutually tangent circles. More than 350 years later, Allan Wilks and Colin Mallows noticed that the same formula relates the coordinates of the centers of the circles (expressed as complex numbers). Here Descartes's formula is used to find the radius and center of the fourth circle in the "bugeye" packing.

The concept of fractional dimension was popularized by Benoît Mandelbrot in his enormously influential book *The Fractal Geometry of Nature*. Although the meaning of dimension 1.30568 is somewhat opaque, this number is related to other properties of the foam that have direct physical meaning. For instance, if you pick any cutoff radius r, how many bubbles in the foam have radius larger than r? The answer, denoted $N(r)$, is roughly proportional to r^{δ}. Or if you pick the n largest bubbles, what is the remaining pore space between those bubbles? The answer is roughly proportional to $n^{1-2/\delta}$.

Physicists are very familiar with this sort of rule, which is called a *power law*. As I read the literature on Apollonian packings, an interesting cultural difference emerged between physicists and mathematicians. In the physics literature, a fractional dimension δ is *de facto* equivalent to a power law r^{δ}. However, mathematicians look at things through a sharper lens, and they realize that there can be additional, slowly increasing or slowly decreasing terms. For instance, $N(r)$ could be proportional to $r^{\delta}\log(r)$ or $r^{\delta}/\log(r)$. For physicists, who study foams empirically (or semi-empirically, via computer simulation), the logarithm terms are absolutely undetectable. The discrepancy they introduce will always be swamped by the noise in any simulation. But for mathematicians, who deal in logical rigor, the logarithm terms are where most of the action is. In 2008, mathematicians Alex Kontorovich and Hee Oh of Brown University showed that there are in fact no logarithm terms in $N(r)$. The number of circles of radius greater than r obeys a strict power law, $N(r) \sim Cr^{\delta}$, where C is a constant that depends on the first three circles of the packing. For the "bugeye" packing illustrated in the second figure, C is about 0.201. (The tilde (~) means that this is not an *equation* but an *estimate* that becomes more and more accurate as the radius r decreases to 0.) For mathematicians, this was a major advance. For physicists, the likely reaction would be, "Didn't we know that already?"



Physicists study random Apollonian packings as a model for foams or powders. In these simulations, new bubbles or grains nucleate in a random place and grow, either with rotation or without, until they encounter another bubble or grain. Different geometries for the bubbles or grains, and different growth rules, lead to different values for the dimension of the residual set—a way of measuring the efficiency of the packing. (Image courtesy of Stefan Hutzler and Gary Delaney.)

Random Packing

For many physical problems, the classical definition of the Apollonian gasket is too restrictive, and a random model may be more appropriate. A bubble may start growing in a randomly chosen location and expand until it hits an existing bubble, and then stop. Or a tree in a forest may grow until its canopy touches another tree, and then stop. In this case, the new circles do not touch three circles at a time, but only one. Computer simulations show that these "random Apollonian packings" still behave like a fractal, but with a different dimension. The empirically observed dimension is 1.56. (This means the residual set is larger, and the packing is less efficient, than in a deterministic Apollonian gasket.) More recently, Stefan Hutzler of Trinity College Dublin, along with Gary Delaney and Tomaso Aste of the University of Canberra, studied the effect of bubbles with different shapes in a random Apollonian packing. They found, for example, that squares become much more efficient packers than circles if they are allowed to rotate as they grow, but surprisingly, triangles become only slightly more efficient. As far as I know, all of these results are begging for a theoretical explanation.

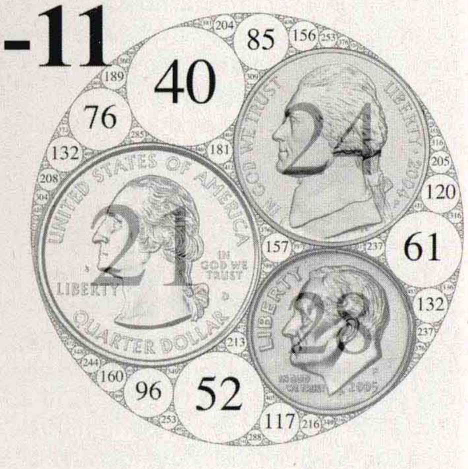
For mathematicians, however, the classical, deterministic Apollonian gasket still offers more than enough challenging problems. Perhaps the most astounding fact about the Apollonian gasket is that if the first four circles have integer bends, then *every other circle* in the packing does too. If you are given the first three circles of an Apollonian gasket, the bend of the fourth is found (as explained above) by solving a quadratic equation. However, every *subsequent* bend can be found by solving a *linear* equation:

$$d+d'=2(a+b+c)$$

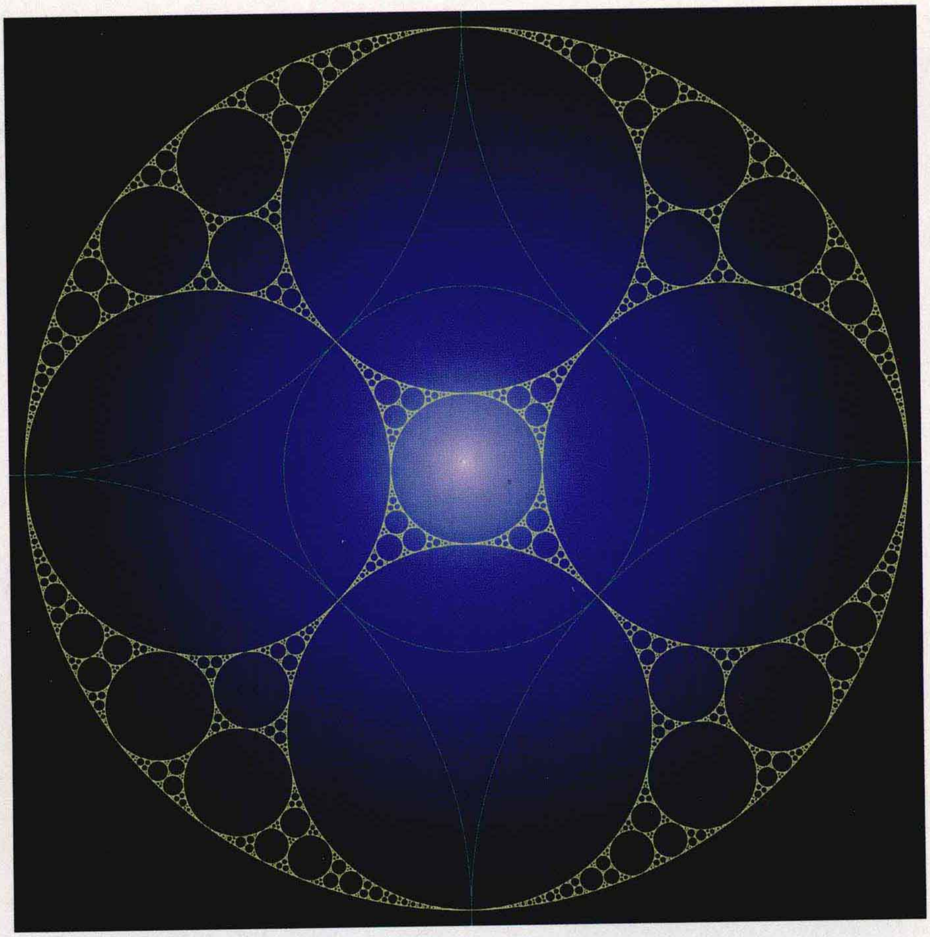
For instance, in the "bugeye" gasket, the three circles with bends $a=2$, $b=3$, and $c=15$ are mutually tangent to two other circles. One of them, with bend $d=2$, is already given in the first generation. The other has bend $d'=38$, as predicted by the formula, $2+38=2(2+3+15)$. More importantly, even if we did not know d', we would still be guaranteed that it was an integer, because a, b, c and d are.

Hidden behind this "baby Descartes equation" is an important fact about Apollonian gaskets: They have a very high degree of symmetry. Circles a, b and c actually form a sort of curved mirror that reflects circle d to circle d' and vice versa. Thus the whole gasket is like a kaleidoscopic image of the first four circles, reflected again and again through an infinite collection of curved mirrors.

Kontorovich and Oh exploited this symmetry in an extraordinary and amusing way to prove their estimate of the function $N(r)$. Remember that $N(r)$ simply counts how many circles in the gasket have radius larger than r. Kontorovich and Oh modified the function $N(r)$ by introducing an extra variable of position—roughly equivalent to put-



A favorite example of Sarnak's is the "coins" gasket, so called because three of the four generating circles are in proportion to the sizes of a quarter, nickel and dime, respectively. (Image courtesy of Alex Kontorovich.)



Many variations on the Apollonian gasket construction are possible. In this beautiful example, each pore is occupied by three inscribed circles rather than by one. Light blue arcs represent five "curved mirrors." Reflections in these curved mirrors—known technically as circle inversions—create a kaleidoscopic effect. Every circle in the gasket is generated by repeated inversions of the first six circles through these curved mirrors. (Image courtesy of Jos Leys.)

ting a lightbulb at a point x and asking how many circles illuminated by that lightbulb have radius larger than r. The count will fluctuate, depending on exactly where the bulb is placed. But it fluctuates in a very predictable way. For instance, the count is unchanged if you move the bulb to the location of any of its kaleidoscopic reflections.

This property makes the "lightbulb counting function" a very special kind of function, one which is invariant under the same symmetries as the Apollonian gasket itself. It can be broken down into a spectrum of similarly symmetric functions, just as a sound wave can be decomposed into a fundamental frequency and a series of overtones. From this spectrum, you can in theory find out everything you want to know about the lightbulb counting function, including its value at any particular location of the lightbulb.

For a musical instrument, the fundamental frequency or lowest overtone is the most important one. Similarly, it turned out that the first symmetric function was all that Kontorovich and Oh needed to figure out what happens to $N(r)$ as r approaches 0.

In this way, a simple problem in geometry connects up with some of the most fundamental concepts of modern mathematics. Functions that have a kaleidoscopic set of symmetries are rare and wonderful. Kontorovich calls them "the Holy Grail of number theory." Such functions were, for instance, used by Andrew Wiles in his proof of Fermat's Last Theorem. An interesting new kaleidoscope is enough to keep mathematicians happy for years.

Gaskets Galore

Kontorovich learned about the Apollonian kaleidoscope from his mentor, Peter Sarnak of Princeton University, who learned about it from Lagarias, who learned about it from Wilks and Mallows. For Sarnak, the Apollonian gasket is wonderful because it has neither too few nor too many mirrors. If there were too few, you would not get enough information from the spectral decomposition. If there were too many, then previously known methods, such as the ones Wiles used, would already answer all your questions.

Because Apollonian gaskets fall right in the middle, they generate a host of unsolved number-theoretic problems. For example, which numbers actually appear as bends in a given gasket? These numbers must satisfy certain "congruence restrictions." For example, in the bugeye gasket, the only legal bends have a remainder of 2, 3, 6 or 11 when divided by 12. So far, it seems that every number that satisfies this congruence restriction does indeed appear in the figure somewhere. (The reader may find it amusing to hunt for 2, 3, 6, 11, 14, 15, 18, 23, etc.) "Computation indicates that every number occurs, but we can't prove that even 1 percent of them actually occur!" says Ron Graham of the University of California at San Diego. For other Apollonian gaskets, such as the "coins" gasket in the fifth figure, there are some absentees—numbers that obey the congruence restrictions but don't appear in the gasket. Sarnak believes, however, that the number of absentees is always finite, and beyond a certain point any number that obeys the congruence restrictions does appear somewhere in the gasket. At this point, though, he is far from proving this conjecture—the necessary math just doesn't exist yet.

And even if all the problems concerning the classic Apollonian gaskets are solved, there are still gaskets galore for mathematicians to work on. As mentioned before, they could study random Apollonian gaskets. Another modification is the gasket shown in the last figure, where each pore is filled by three circles instead of one. Mallows and Gerhard Guettler have shown that such gaskets behave similarly to the original Apollonian gaskets—if the first six bends are integers, then all the rest of the bends are as well. Ambitious readers might want to work out the "Descartes formula" and the "baby Descartes formula" for these configurations, and investigate whether there are congruence restrictions on the bends.

Perhaps you, too, will be inspired to write a poem or paint a tablet in honor of Apollonius' ingenious legagy. "For me, what's attractive about Apollonian gaskets is that even my 14-year-old daughter finds them interesting," says Sarnak. "It's truly a god-given problem—or perhaps a Greek-given problem."