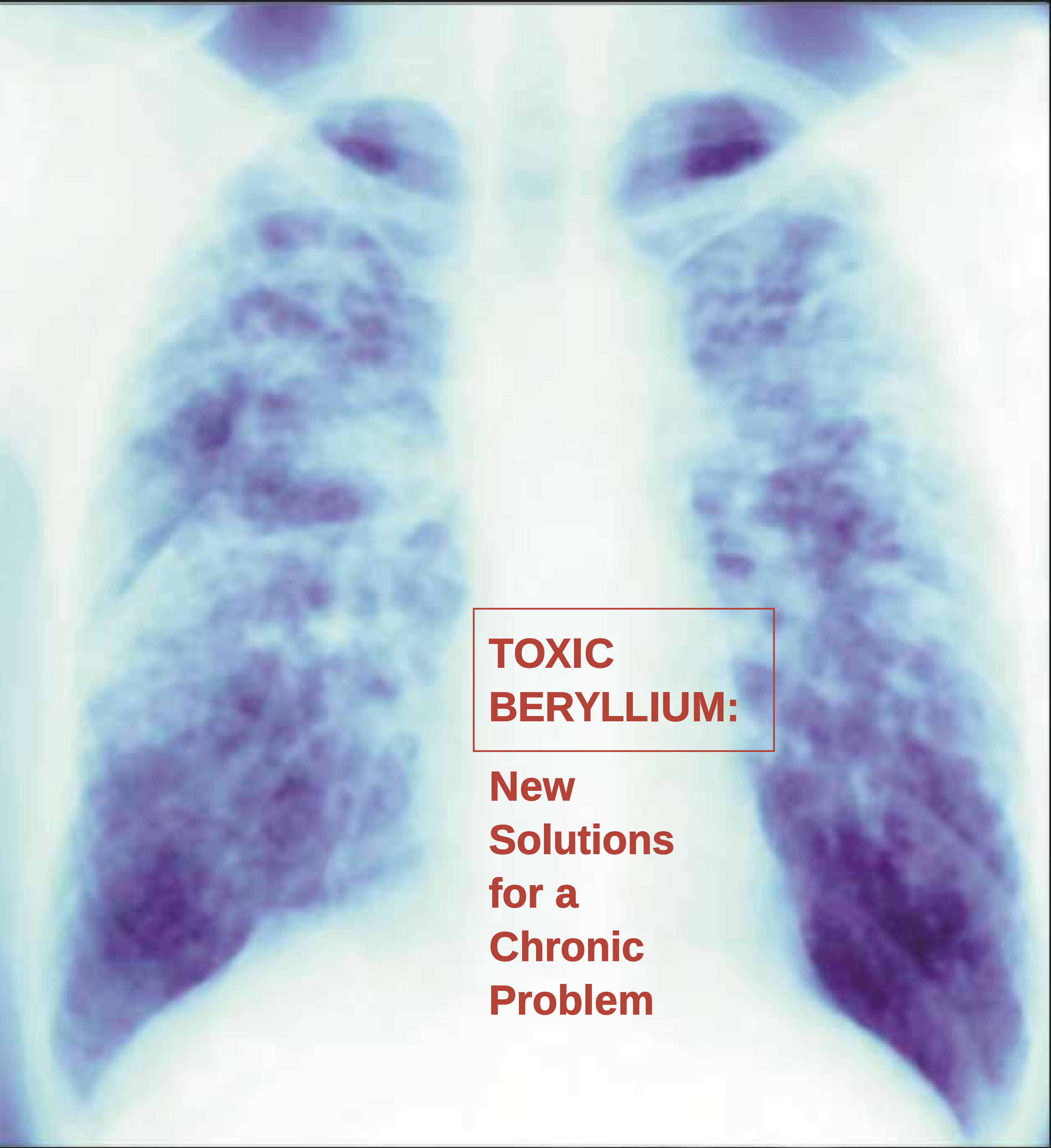

TOXIC BERYLLIUM: New Solutions for a Chronic Problem

The element beryllium was discovered more than 200 years ago, but it was not until 1927 that the first beryllium-containing materials were produced, and not until the 1940s—driven by the World War II demand for beryllium–copper alloys for use in weapons, radar, and other applications—that they were produced in significant quantities. Beryllium manufacturing during World War II and the Cold War that followed it resulted in the exposure of thousands of workers to beryllium dust, resulting in untold numbers of serious health effects including respiratory ailments, cancers, and death. Where once it was confined largely to defense applications, beryllium is now found in countless industrial and consumer products from satellites to toasters. Consequently, says Lee Newman, a professor of medicine at the University of Colorado School of Medicine in Denver and a pioneer in beryllium research, "Many more American workers are being placed at risk because these materials are being used very widely throughout industry instead of just [in] a narrow segment of industry." Legislation passed in December 2000 will compensate U.S. Department of Energy (DOE) employees, DOE contract employees, beryllium supplier employees, and their survivors for beryllium-related ailments. However, the problem remains of how to protect today's workers from the dangers of exposure to beryllium. An estimated 30,000 workers in the United States alone come into contact with beryllium daily, according to the National Institute for Occupational Safety and Health (NIOSH).

Scientists know that the current exposure limit for beryllium set by the Occupational Safety and Health Administration (OSHA) of 2 micrograms of airborne beryllium per cubic meter of air (µg/m^3) per 8-hour day leaves a significant percentage of workers at risk. But finding a safer limit presents numerous challenges. Simply reducing current exposure limits may not reduce the number of workers stricken with chronic beryllium disease (CBD), which results in death in about 30% of sufferers. Instead, researchers say, an entirely new type of exposure standard must be created that would take into account factors that until recently have not been considered, including dust particle size, particle number, low dosage, chemical form, and possibly genetic predisposition of workers. Remarkably, says Dennis Paustenbach, corporate vice president and an environmental toxicologist for the scientific consulting firm Exponent, up until now standards have been based just on total airborne beryllium. "Form didn't make any difference," he says. "Particle size didn't make any difference. I think that probably was a real big mistake in the last 20 years." Or, says Lisa Maier, a professor of medicine at the University of Colorado Health Sciences Center in Denver, "The issue may be that we haven't looked at exposure in the right combinations."

To address the concerns about the current beryllium standard, officials at OSHA are in the process of setting new rules for workplace exposure to beryllium. In parallel, scientists at NIOSH are working with industry representatives and scientific consultants on a suite of research projects that they will use to develop a new NIOSH-recommended exposure limit (the current NIOSH recommended limit is 0.5 µg/m^3 per 8 hours). These results will also contribute data to OSHA's rule-making process, which will include a proposal that is based on data that OSHA collects from a variety of sources (including NIOSH), followed by public comments and additional fact-finding, a posthearing comment period, and then final recommendations. Meanwhile, the American Conference of Governmental Industrial Hygienists (ACGIH) has published a notice of intended change that would lower its threshold limit value of 2.0 µg/m^3 to 0.2 µg/m^3 averaged over an 8-hour work shift. Unlike the OSHA standard, which has the force of law behind it, the ACGIH and NIOSH recommendations are voluntary guidelines for industry and health professionals. The new OSHA standard should be proposed in 2001, according to Peter Infante, OSHA's director of standards review. "It will be an interesting standard," he says, "in that it will cover a lot of areas that we haven't gotten into before." In the interim, OSHA published a Hazard Information Bulletin in 1999 to inform employers and employees about the hazards of beryllium exposure below the current 2.0 µg/m^3 limit.

Ubiquitous Beryllium

In 1999, the United States produced about 30 metric tons of beryllium, mostly as alloys with copper. Beryllium is widely used in spite of its relatively high cost of over $400 per pound (compared to $0.66 per pound for aluminum and $4.25 per pound for titanium) because for certain critical applications it performs better than alternatives. Some of beryllium's advantages are that it is light (one-third lighter than the next lightest metal, aluminum), strong (six times stronger than steel), less prone to expand and shrink, magnetically more transparent, and a better electrical and thermal conductor than alternative materials. Some beryllium is used as an unadulterated metal in components for satellites, aircraft, space optical systems, and guidance systems. Its nuclear characteristics (it produces neutrons when bombarded with alpha particles) allow it to serve critical roles in nuclear reactors and weapons. Because beryllium is transparent to X rays, it's used in X-ray tube windows. Some beryllium goes toward producing beryllium oxide, which is hard, strong, and an outstanding conductor of heat. Beryllium oxide is most often used in lasers and radar systems and as a substrate for electronic circuits that drive high-speed computers.

By far, however, most manufactured beryllium (about 75%) ends up in alloys, about 95% of which is copper alloy. Adding 0.5–2.0% beryllium to copper forms an alloy that is exceptionally strong and hard, an excellent electrical and thermal conductor, nonmagnetic, and resistant to corrosion and fatigue. Beryllium–copper springs, connectors, and switches are used in goods ranging from cars to computers, from satellites to home appliances. Beryllium–copper tubing is used in oil and gas drilling equipment and is made into

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Clogged lungs. A chest radiograph of a patient with CBD shows diffuse nodular and linear opacities that can aggregate to form masses that interfere with breathing. This worker was exposed to beryllium dust while machining beryllium ceramics.

bushings and bearings for heavy machinery and aircraft landing gear. Beryllium–copper is machined into nonsparking tools and such consumer items as golf clubs and bicycle components. Other beryllium alloys—typically a mixture of nickel, chromium, and beryllium—are even incorporated into dental devices such as crowns and bridges, prompting concern from some health professionals because the potential toxicity of such alloys is not known, although beryllium-related diseases have been identified in dental lab technicians.

A Chronic Problem

In the 1930s, just a few years after beryllium's emergence as a manufacturing material, researchers from the former Soviet Union and Europe began reporting beryllium-related lung diseases; the first American reports came in 1943. These early reports were of a rapidly appearing "chemical pneumonia," now called acute beryllium disease (ABD), that resulted from exposure to high concentrations of beryllium dust. Symptoms of ABD included shortness of breath, cough, chest pain, and rapid heart rate. Many workers who were exposed to 1,000 μg/m3 of airborne beryllium developed the disease, and about 15% of sufferers died. In response, the Atomic Energy Commission set the first limit for beryllium at a 2 μg standard for its workforce. Over the years, various federal agencies and industry organizations (including OSHA) have adopted and retained this standard, and there have been no reported cases of ABD where airborne concentrations of beryllium were kept below 100 μg/m^3. Reducing dust to manageable levels all but eliminated the appearance of the acute form of the disease (the last reported case of ABD in the United States was in 1967). And removing ABD sufferers from contact with beryllium dust allowed most patients to recover within a few weeks to several months, although some symptoms could persist.

Recovering from ABD, however, was no guarantee that a patient was free of beryllium-related illness. About 30% of ABD sufferers eventually developed CBD. And, Infante says, they demonstrated a significantly elevated risk of death from lung cancer. In fact, beryllium has long been thought to be a carcinogen. Studies in the early 1970s showed that beryllium causes lung cancer in lab animals, which was enough evidence for OSHA to propose in 1975—although not require—that workplace limits for beryllium be reduced to the lowest feasible levels, considered at the time to be 1 μg/m^3. In 1977, OSHA held a hearing that focused on lung cancer in exposed workers, but a final standard was never published due to concerns by the Departments of Energy and Defense that a reduced standard would not be economically feasible.

In all the familiar places. Beryllium's properties of strength, lightness, consistency, and conductivity make it an excellent choice for use in a variety of products from golf clubs to dental fixtures, electronics to aircraft, space technologies to nuclear weapons. The ubiquity of beryllium means greater numbers of workers are potentially exposed than ever before.

Despite the elevated lung cancer risk seen among ABD sufferers, the low relative risk of lung cancer observed among former beryllium workers made it difficult to establish a link to lung cancer in humans. Unlike CBD, which can surface just months after exposure, lung cancer rarely develops earlier than 12 years after exposure and often takes longer, Infante explains. By 1992, however, epidemiologic studies convinced the International Agency for Research on Cancer (an expert cancer agency of the World Health Organization) and more recently the National Institutes of Health to declare that beryllium is indeed a human carcinogen. The National Toxicology Program's *Report on Carcinogens, Ninth Edition*, lists beryllium as a probable carcinogen, and it is expected that the tenth *Report* will list it as a known human carcinogen. And although current OSHA limits are based on preventing CBD rather than lung cancer, new standards will consider cancer risks. "Beryllium disease is the major disease that's going to drive the standard, but I'm not downplaying the cancer because beryllium is clearly a human lung carcinogen," Infante says.

Top row (l–r): Digital Stock; PhotoDisc; PhotoDisc; Digital Stock. Center: Lee S. Newman. Bottom row (l–r): Digital Stock; PhotoDisc; PhotoDisc; PhotoDisc

Cases of CBD began to appear in 1946. CBD is incurable, although when caught early, symptoms can be suppressed with steroids. Unlike the acute form, CBD continues to appear in new workers who work in areas that appear to adhere to OSHA's beryllium limit. In fact, CBD eventually occurs in as much as 17% of workers in particularly risky occupations, such as those who work in machine shops or in construction where beryllium is used [see *EHP* 104(Suppl 5):937–943 (1996)]. Confusing matters is the fact that many people are able to work with beryllium for years with no apparent adverse health affects, occasionally even surviving high doses from industrial accidents, while even in facilities that adhere to current safety guidelines other workers become sensitized to beryllium or develop CBD. And, on occasion, people who have never worked directly with beryllium and so are thought to have had very little exposure to the metal—such as spouses of workers or secretaries in the offices of companies that use beryllium—have developed CBD. Setting a protective exposure limit may require understanding why the relationship between dose and disease seems to vary so much from person to person.

"The dose–response relationship does not seem to be all that straightforward," says Babetta Marrone, a principal investigator on the Beryllium Health Effects Project at Los Alamos National Laboratory in New Mexico. "In occupations with greater exposure to beryllium, you see more disease, but the disease does not occur in everyone with a high exposure, and on the flip side you see disease in people who have almost [undetectable levels of] exposure."

Some of this difference in response may be attributable to an individual worker's genetics. It's possible, Maier says, that genetic susceptibility may explain why very low levels of exposure can trigger CBD in some people, while others tolerate much higher exposures. "This paradox appears to be explained by a genetic predisposition," Marrone says, "in which case there may be no real measurable or enforceable lower limit to beryllium exposure [that will protect] some of these folks."

Infante disagrees. "In spite of the lack of knowledge in some areas of scientific investigation for beryllium," he says, "it would appear that there is sufficient information to set a permissible limit for beryllium in the workplace." He says that's why more than two years ago the ACGIH proposed lowering its recommended limits to 0.2 $\mu g/m^3$. Also, he points out, a paper by Tsutomu Yoshida and colleagues from Japan's Fujita Health University School of Medicine, published in the July 1997 issue of *Industrial Health*, concluded that if exposure is kept below 0.01$\mu g/m^3$, workers don't become sensitized to beryllium.

A Sensitive Issue

CBD results when beryllium particles are inhaled and come into contact with specialized helper T (or $CD4^+$) lymphocytes in the lungs, thus triggering the cells to become sensitized and then proliferate. "Presumably, beryllium binds to some sort of cell protein or peptide, making them now seem foreign, and that is what is initiating a hypersensitivity reaction," says Milton Rossman, a professor of medicine at the University of Pennsylvania Medical Center in Philadelphia. As the cells react to the particles they form clumps, or granulomas, that rob the lungs of their elasticity and make it difficult to breathe.

It's generally thought that before CBD can develop as a full-blown, symptomatic disease, a person must become sensitized, or develop an allergic reaction, to beryllium. The relationship between sensitization and development of CBD, however, is not completely understood. Experts disagree on the strength of the relationship between sensitization and CBD, the exact rate at which sensitized people may develop CBD, and even how to define sensitization and CBD.

The question is, if sensitization precedes CBD, does that mean that everyone who becomes hypersensitive will develop CBD? "That's the hypothesis, that people who are sensitized have already started down this path," says Marrone. But Rossman says it is possible to become sensitized and never develop CBD. "In the screening studies that have been done in industry, we find a lot of people who have hypersensitivity to beryllium but no evidence of disease, and we don't know for sure if all these people will develop beryllium disease or only some of them will," he says. Maier adds that for any group of people that becomes sensitized to beryllium, 10% of the group per year will develop CBD. For example, in a group of 100 newly sensitized individuals, the first year 10 of 100 would develop CBD. The next year 9 of the remaining 90 would, and so on. At some point, she says, there may be a plateau after which CBD would be less likely to surface.

Researchers are investigating the processes that lead to sensitization: whether people must inhale beryllium to become sensitized or if touching or ingesting beryllium is enough to induce the allergic reaction.

Recent animal models demonstrate that sensitization can occur by exposure through the skin. If these findings apply to humans, Paustenbach says, and in fact workers can become sensitized without breathing beryllium dust, that may explain why reducing airborne beryllium may not eliminate sensitization and why air concentrations may not correlate closely with disease rates. New standards, says Infante, are likely to minimize skin contact and ingestion.

In the early 1990s, a test for sensitization called the beryllium lymphocyte proliferation test (BeLPT) was developed. This test measures how lymphocytes react to beryllium. But the BeLPT can produce both false positives and false negatives, even on repeated tests. "The standard lymphocyte proliferation test has a lot of 'noise' in it," Rossman says. The test requires live cells, so blood must be transported immediately to special centers. Sometimes not enough cells survive the trip, and factors such as medications and illness can affect the way cells respond to the test. Medications such as steroids, for example, suppress the immune system, preventing lymphocytes from proliferating. This lack of cell multiplication can result in a negative response, even if the subject is in fact sensitized. Even common medicines such as aspirin can produce false results, Rossman says. Similarly, Infante says, "Cells of immunologically compromised cancer patients may not respond [to the test]."

"We are working on how we can improve the accuracy of that test and make it a better predictor for the disease so you get more of a one-to-one relationship between sensitization to detect," Marrone says. A new test called the Immuno-LPT uses flow cytometry, a laser-based technique, to detect proliferation of $CD4^+$ cells as they respond to beryllium. Most people with CBD show a $CD4^+$ cell response to beryllium. But people who are sensitized but don't have CBD may instead show a different cell response. Marrone believes that sensitized people who have the same reaction as people with CBD would have a greater likelihood of developing CBD.

Tests that detect beryllium sensitization don't address the underlying goal: preventing sensitization in the first place. Preventing exposures might be accomplished through engineering controls, use of respirators, and good housekeeping procedures. In addition, tests that look for genetic characteristics that may predispose individuals to becoming sensitized might also play a role in reducing CBD in the workplace. Researchers suggest that with such tests individuals with genetic susceptibility could be determined and discouraged or prevented from working with beryllium. Such a scenario is fraught with ethical dilemmas, however.

One dilemma is whether relying on genetic screens would allow companies to eliminate employees who might be able to remain healthy in pristine—albeit expensive—work environments. "In general," says Rossman, "we think that the industry should be safe for the individual and not vice versa." Privacy advocates also fear that opening the door to one genetic test could unleash a flood of genetic information that, for example, companies or their insurance carriers could use to screen out potential employees with any number of genetic "flaws."

The source of the problem. Beryllium is extracted from beryl ore.

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What once may have seemed like a distant possibility has become reality overseas. Recently England became the first country to allow insurance companies to use the results of a genetic test—in this case for Huntington disease—to refuse coverage to applicants. To allay such concerns, any successful beryllium-susceptibility testing program would have to keep its results tightly under cover, says Timothy Takaro, an assistant professor of medicine and environmental health at the University of Washington in Seattle who has worked on beryllium health issues at the DOE's Hanford Nuclear Site in eastern Washington. "We strongly advocate that workers get such information but that it be withheld from management," he says. Similarly, Marrone says that any screening program at Los Alamos would also provide genetic test results only to the person who was tested.

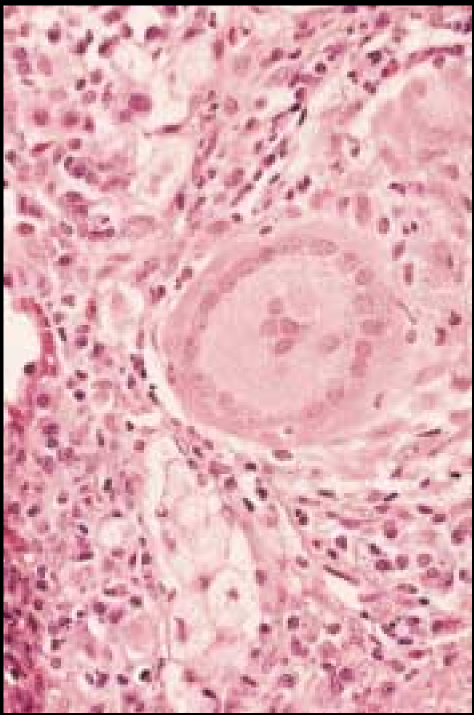
In an 8 October 1993 *Science* article, Italian scientists Luca Richeldi, Rosa Sorrentino, and Cesare Saltini announced that Glu^{69} (a glutamic acid in position 69 of the *HLA-DPB1* gene) appeared more than three times as often in CBD sufferers that they tested as in a control group of beryllium workers. This difference suggested that the presence of the Glu^{69} genetic marker increases the risk of CBD significantly for workers who are exposed to beryllium. According to Maier, however, the difference is not great enough to reliably predict who will or won't develop CBD. "When you have a low-prevalence disease with a test that has not great sensitivity and specificity, then you're going to have more problems with predictive value," she says.

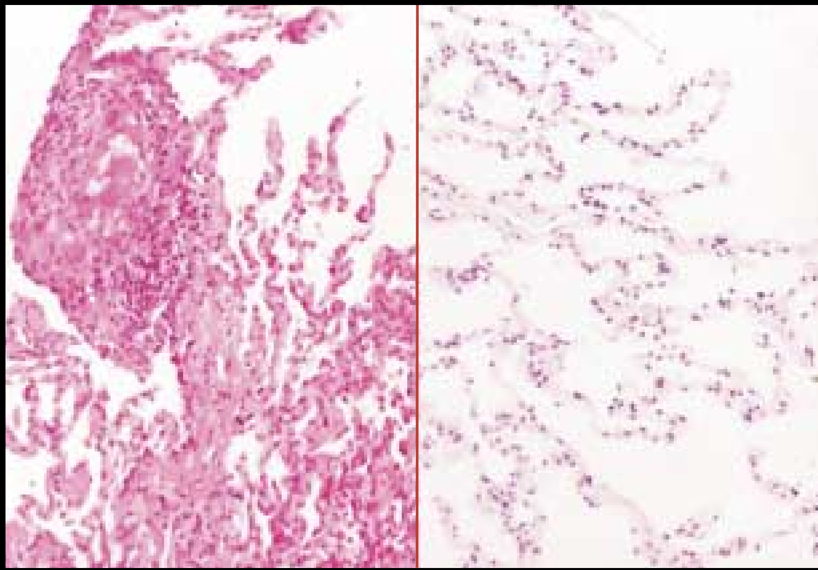
Rossman is using DNA analysis to attempt to identify peptides that may stimulate the immune response. If it turns out that only certain people have such peptides, then identifying the peptides could result in an effective screening tool, Rossman says. "Or if it's an interaction between beryllium and [a] protein," he says, "maybe you could figure out a way to block that interaction."

Marrone says that a more useful genetic marker for CBD would appear in virtually all workers who develop the disease and in as few people who do not as possible. To that end, her group is looking at variations within the alleles in the region of the genome around the Glu^{69} marker. "Variations of that marker seem to be more highly correlated, or maybe even only found, in the diseased than in the general population," she explains. "When you look in more detail, what you find is that very rare variations of this Glu^{69} marker are found in higher frequency in the diseased, at least to the extent to which we've looked at it." Marrone's group at Los Alamos is confident enough in the predictive value of their results that they've started a genetic testing program for their own beryllium workers, a step other researchers have been loath to take. "We really believe that we have identified variations that would be useful as genetic markers," Marrone says, "and that we should at this point correctly and responsibly communicate the genetic risk factors to the worker population." But Infante cautions that identifying specific genetic risks associated with Glu^{69} is not enough to ensure the safety of workers whose genes do not exhibit these variations. That's because some CBD-stricken workers do not have these genetic markers of susceptibility.

Alloying Suspicions

The scientific community has long understood that CBD could result from contact with beryllium metal and its more toxic cousin, beryllium oxide. Less clear is whether working with low-beryllium-content alloys also can cause the disease. However, recent work, including two 1999 case studies by Newman and Ron Balkissoon published in the April 1999 issue of the *Journal of Occupational and Environmental Medicine*, suggests that people who work with 2% beryllium–copper





Immune response gone awry. A normal lung (right) has a typically thin, lacelike appearance. In a lung with CBD (center), clusters of immune cells form thousands of granulomas or ball-like structures (left) that attempt to surround the inhaled beryllium dust particles. The lung tissue can also become diffusely infiltrated by these beryllium-reactive cells, interfering with the exchange of oxygen.

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alloys do indeed run a significant risk of developing CBD.

CBD has been diagnosed previously in people who worked with beryllium alloys. But what separates the two new cases from earlier studies is that these workers had no opportunity for contact with purer forms of beryllium. "I think we're as confident as you can be about that," Newman says. "Neither worker has prior employment in any beryllium-related industry. And we have no reason to think they had any incidental or environmental exposure out of the ordinary." Less confident is Marc Kolanz, director of environmental health and safety for Brush Wellman, the company that processes and produces most of the world's beryllium. Kolanz says that the workers studied were exposed to higher doses and more toxic forms of beryllium than the study asserts.

According to Balkissoon and Newman, periodic air samples in the areas of the plant where the patients worked had tested as being within OSHA's 2 $\mu g/m^3$ per 8-hour day standard for all forms of beryllium, although other areas exceeded the limit on at least two occasions. But the patients themselves reported working without respirators in an environment where alloy dust was plentiful and where they sometimes breathed fumes from heated alloy. Such conditions, Newman says, are typical of facilities that work only with low-percentage beryllium alloys. "In the past 15 years, virtually everywhere that I've gone I've found that companies have been casual, even cavalier, about the use of beryllium–copper. That's largely because they've received information from their beryllium supplier implying that beryllium–copper is safe to use, that you can grind it and polish it and do other operations with it without the fear of beryllium disease."

Workers in beryllium-related industries who have been studied have so far worked with either pure or high-content forms of beryllium or in environments where they might be exposed to those forms. This has made it difficult to isolate the effects of exposure to particles of low-percentage alloys. "I think there is still the perception that 2% beryllium–copper is really safe and you don't have to worry about developing chronic beryllium disease," says Balkissoon.

According to NIOSH epidemiologist Kathleen Kreiss, even working within regulatory limits is no guarantee of a safe workplace. Current standards, she says, are flawed because they rely on just the total weight of particles in a given area. "We should be looking at respirable beryllium and particle count," she says. A better standard, according to Kreiss, would be one that considers particle size and perhaps other factors such as solubility, particle count, whether the beryllium was fired at a low or high temperature, and surface area. Particles larger than about 10 microns are too big to penetrate far into the lungs, and so probably pose little health risk.

Paustenbach contends, however, that the hundreds of thousands of air samples collected in studying beryllium over the last 40 years have limited research value. "This total dust data just is not going to give us the answer of how to set an occupational exposure limit, what a safe level will be," he says.

To provide the needed detail, NIOSH scientists have in the last two years begun collecting exposure data that include careful records of particle size and chemical form. These data, collected at Brush Wellman facilities nationwide, will be compared to historic air samples to extrapolate likely dose, particle size, and chemical characteristics, says NIOSH environmental health and safety specialist Mike McCawley. NIOSH epidemiologists are analyzing these new data, existing sample data, historic health records, and ongoing health studies to uncover relationships between beryllium-induced diseases—primarily CBD and lung cancer—and these potential exposure characteristics. The new OSHA standards now being developed, says Infante, will consider all new information related to the toxicity of beryllium in the workplace.

Scott Fields