HIGH HOPES FOR TECHNEGAS

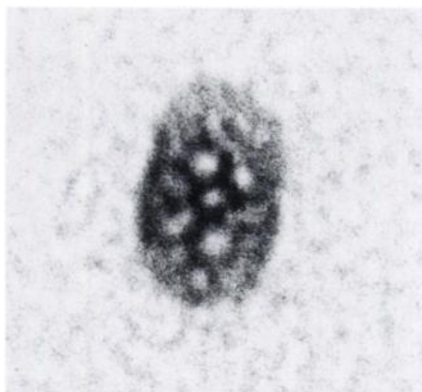
The lung scanning aerosol invented in Australia moves closer to approval in the U.S., but does it consist of buckminsterfullerenes?

TWO BURNING QUESTIONS nag the makers of the Australian lung scanning aerosol called Technegas. When, if ever, will the device that has won near ubiquitous use in Australia gain approval for lung ventilation studies in the U.S.? And when, skeptics ask, will somebody offer proof that Technegas particles are really buckyballs—the soccerball-shaped molecules of 60 carbon atoms with a surprising range of chemical properties that laboratories around the world are scrambling to exploit.

The reply to the first question will partly depend on the Food and Drug Administration now that an American distributor, Cheyenne Medical Equipment, Inc., is arranging to sell Technegas units in the U.S. with assistance from Syncor International. Facing dual FDA hurdles—device and drug approvals—several pharmaceutical companies have balked at distributing the technology in the U.S. Hoping to hasten approval of the device, the manufacturer is sponsoring fast-track clinical trials at two U.S. medical centers using a form of Technegas to diagnose opportunistic lung infections in AIDS patients.

If eventually approved for ventilation imaging, "Technegas would instantly become the gold standard," says John McAffee, MD, a George Washington University professor of radiology and one of a handful of American physicians with experience using the system. "It would do away with the use of xenon or aerosol DTPA, it's so vastly superior," says William L. Ashburn, MD, professor of radiology and chief of the division of nuclear medicine at the University of California Medical Center in San Diego. He is one of two researchers ready to conduct clinical trials using a form of Technegas to detect opportunistic lung infections in HIV positive patients.

To answer the buckyball question, a



An electron microscope view of condensed Technegas particles. The oblong object, 10 nm across the short axis, displays a hexagonal pattern suggesting fullerenes, says Technegas inventor Dr. William Burch of the Australian National University in Canberra.

team of scientists at Sydney University hope to determine soon the structure of Technegas. They are testing samples of the aerosol particles using a technique called electron energy loss spectroscopy to compare its molecular "fingerprint" to that of buckyballs.

Discovered by chance in 1985, buckyballs are spherical molecules of 60 carbon atoms bound together in a hexagonal array like a geodesic dome, the structure invented by R. Buckminster Fuller. The molecule, named buckminsterfullerene after the design guru who died in 1983, is just one of a whole new class of molecules called fullerenes. At this writing, the Sydney researchers expected definitive results to show whether Technegas consists of fullerenes, as its inventor has suspected almost as long as buckyballs have been known to exist.

At stake are possible rights to the process for making buckyballs, not to mention a Technegas company logo featuring a fullerene-like cage wrapped partway around a schematic technetium atom. The inventor of the Technegas generator, physicist William Burch, PhD, research director at the John Curtin School of Medical Research of the Australian National University in Canberra, and the company that makes the devices, Tetley Manufacturing, Ltd., are pressing worldwide patent claims covering their process, which they contend is essentially the same as the most common procedure for making buckminsterfullerenes—the Huffman-Kratschmer method named after Donald Huffman of the University of Arizona and Wolfgang Kratschmer of the Max Planck Institute for Nuclear Physics in Germany.

Enthusiastic researchers predict that the spherical cages of carbon will find their way into a host of lucrative industrial and research uses. If Dr. Burch is correct, then Technegas would be the first application of a buckminsterfullerene. Since September 1990, when a way to make buckyballs in bulk was announced by Huffman and Kratchmer, researchers have been busy swapping carbon atoms in buckyballs with other atoms and reporting enthusiastically on the potential of fluorinated buckyballs in the design of advanced teflon-like lubricants, light polarizing buckyballs in optical computers, and buckyballs doped with various elements to make high-temperature superconducting materials.

Others are busy devising ways to insert atoms inside the spherical carbon shell. "As soon as the idea of this hollow molecule became known," says solid-state physicist and buckyball researcher Peter W. Stephens, PhD, of the State University of New York at Stony Brook, "people were trying to figure out how to get something inside of it—I think it may have some psychological basis."

Besides tackling the challenge, however, the technical feat of loading fullerenes with single atoms or compounds might one day be used to make minuscule reaction tanks for chemical syntheses, or delivery vehicles for drugs or radionuclides. Dr. Burch, in fact, thinks that the Technegas particle he patented might be some form of buckminsterfullerene encapsulating a single technetium-99m (^{99m}Tc) atom.

Other patent contenders dismiss the Tetley-Burch patent claims. The Technegas claim predates the Huffman-Kratchmer patent application (the patent has not been issued yet), but the Technegas patent may prove to be worded too vaguely to cover fullerene production. Jeffrey Jacob of Research Corporation Technologies Inc., a non-profit company handling the University of Arizona claim, told *The New York Times:* "I'm sure there's hundreds of patents being filed, but Huffman-Kratchmer will be the grandfather." Says Dr. Burch: "Maybe our patent covers the field of making buckminsterfullerenes—I think it may be too much to hope for because we'd be sitting on an absolute gold mine."

Both the Huffman-Kratchmer and the Technegas processes for making buckyballs, which use an electric arc to vaporize graphite, may be rendered obsolete by improved methods that yield larger quantities of fullerenes. Dr. Burch says he's not much troubled by the thought. His goal all along was to invent a better way to do lung ventilation scans and despite a distinct lack of controlled clinical comparisons between Technegas, other aerosols, and true tracer gases, by most accounts Dr. Burch has succeeded, particularly in Australia.

In its homeland, Technegas for pulmonary ventilation studies "has actually become so much part of daily routine that it is taken for granted and, in general, many have forgotten just how superior are the images to those previously obtained with alternative methods," according to I.P.C. Murray, MD, of the Prince of Wales Hospital in Sydney (1). His survey of 22 nuclear medicine centers in Australia yielded the unanimous conclusion that the agent offers "an overall improved approach in the diagnosis of embolic disease." Some 70% of the hospitals in Australia use Technegas, according to a manager at Medgenix Diagnostics, the Belgian company recently signed to distribute the units in Europe. Tetley Manufacturing has sold 170 of the machines to centers in 18 countries.

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Unlike the rapid clearance of true gases such as xenon-133 (^{133}Xe) and krypton-81m (^{81m}Kr), Technegas particles deposit in the lung tissue and clear at a rate roughly equal to the half-life of the tracer, ^{99m}Tc. This slow decline of count rate allows imaging of the lungs in multiple projections, or tomographic imaging, which in some cases may allow better identification of mismatches with perfusion scans for diagnosing pulmonary emboli (2). Compared to ^{99m}Tc DTPA aerosols, some physicians say, technegas penetrates deeper into the periphery of the lungs and less of it clumps in the bronchial tree. The notable disadvantage cited by various physicians is the cost of purchasing a Technegas generator — about $24,000 in Australian currency.

The positive accounts of the aerosol are tempered by a number of studies that have found Technegas lacking. An 11-patient study from the Netherlands, for example, concluded that "despite the promising name, ^{99m}Tc-Technegas has the properties of an aerosol rather than a gas like ^{81m}Kr. The results obtained do not justify its greater technical and economical expense compared to that of aerosols" (3). The authors of a Belgian study stated that Technegas may prove valuable, but in 9 out of 24 elderly patients the method failed because the patients couldn't inhale the aerosol deeply enough, or because the tracer deposited too heavily in the bronchial tree (4). A British study concluded that Technegas "represents a major advance in lung ventilation imaging," but the authors qualified that by adding the phrase "where ^{81m}Kr is not available" (5).

Dr. Burch began developing ideas for lung ventilation scanning in 1976, inspired by a lecture visit that year from George Taplin, MD, who talked about the principles of detecting pulmonary embolism by comparing images of lung airway ventilation with views of blood vessel perfusion. The logic of the method—a defect in blood flow unmatched by a blocked airway to account for it indicates pulmonary embolism—appealed to Dr. Burch. "From my point of view as a radiation physicist, I was very interested in the instrumentation and how simple it could be," he says.

After some lung scanning experience working with clinicians at the John Curtin School of Medical Research, Dr. Burch saw a problem: obstructive pulmonary disease often rendered ventilation scans equivocal, he says, in the very patients in whom diagnosis of pulmonary embolism was crucial.

What was needed, he figured, was a labeled aerosol with particles much smaller than anything on the market. Automobile exhaust came to mind. "You're suspending tens of thousands of tons of organic lead over cities and it can hang around there for days," he says.

From this idea came the now forgotten precursor to Technegas, which involved burning an alcoholic solution of ^{99m}Tc and having the patient inhale the fumes of carbon dioxide, water vapor, and ^{99m}Tc atoms. In retrospect, Dr. Burch says, "when you think about it—letting off an explosion with radioactive rocket fuel in a chamber in a clinical department—it's a little crazy to think that you'd ever get that passed by any regulatory authority."

He abandoned the combustion aerosol and began tinkering with a device to vaporize technetium directly with graphite in an inert atmosphere. "My thought," Dr. Burch says, "was to find a compound of technetium that vaporized at a lower temperature than 2900°C or 4000°C" (the approximate melting and boiling points of elemental technetium). He found a way to make such a compound and named the resulting aerosol "Technegas."

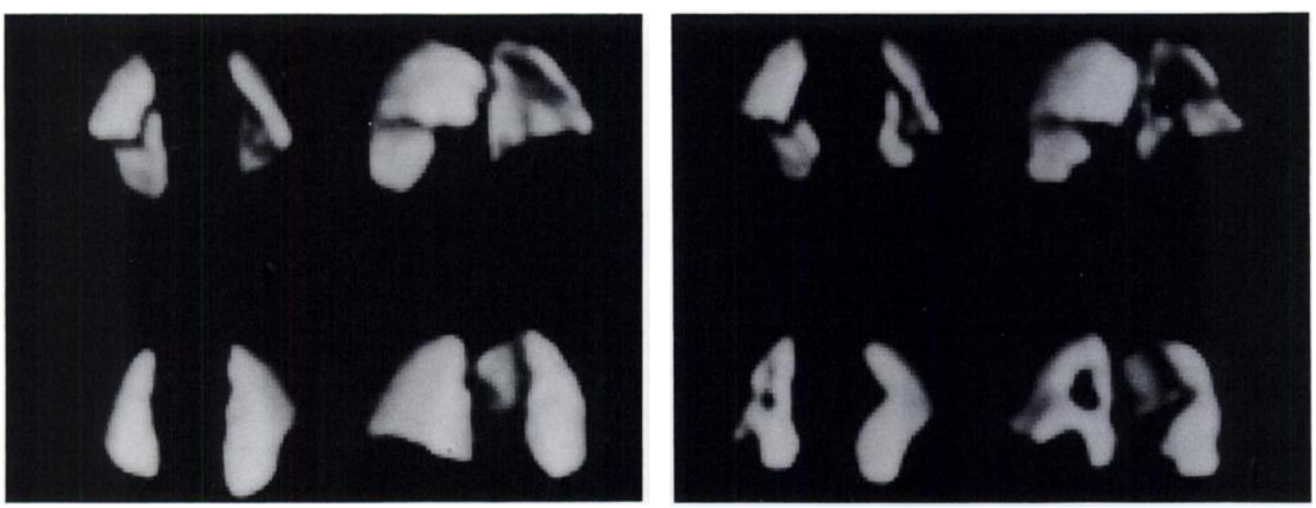
The workings of the Technegas generator are straightforward: a tenth of a cc of ^{99m}Tc chloride solution is poured into the hollow of a graphite crucible about the size of a pencil eraser, which is placed between the poles of a power supply in an enclosed chamber. The salt solution is boiled off and the air purged from the chamber with the inert gas argon. Cranking the electric current to an arc temperature of 2500°C vaporizes the graphite into an invisible cloud of technetium-laden carbon particles each less than 5 nanometers in diameter and almost uniform in size (a buckyball spans a bit more than one nanometer). "We get a spectacular lift off, a sudden puff of radioactivity that's really very pretty to watch on a gamma camera," says the inventor, who at the age of fourteen once built a working cloud chamber in his parents' garage.

In theory, what the vaporized carbon atoms could be doing in this puff of vapor is recombining and annealing in energetically comfortable curves around a technetium atom, eventually forming a complete sphere of 60 or more carbon atoms, or a buckyball. Then again, technetium might be sticking to carbon particles nothing like buckyballs. Some physicists are quite skeptical of a fullerene hypothesis to explain Technegas.

"Our guess is that they have technetium trapped in small particles, but that the particles aren't buckyballs," says physicist Richard Smalley, PhD, of Rice University, whose research group identified the existence of buckminsterfullerene in 1985. "I wouldn't think 2500° would be hot enough to vaporize carbon into radicals." Dr. Smalley's group is the first to document the production of macroscopic quantities of fullerenes with single atoms trapped inside—an 82-carbon molecule with a lanthanum inside. He says temperatures around 3000-4500°C are necessary to generate reactive carbon radicals in sufficient numbers. Upon cooling to the 1000-2000° range, carbon radicals are eager to bond to other atoms and begin to coalesce into the curling sheets of carbon postulated to form buckyballs.

A co-discoverer of buckyballs, Harold W. Kroto, PhD, professor of chemistry at the Universitiy of Sussex, England, thinks that Dr. Burch's device may well be producing some buckyball molecules, or C_{60}, but says, "the real question is whether C_{60} is the major carrier of technetium atoms." Molecules of C_{60} usually make up about 10% of the material produced under the best of fullerene-producing conditions, although slightly larger yields have been reported. "My guess," the British chemist says, "is that 90% of the technetium carriers are carbon dust."

The more common dust, or soot, produced by vaporizing graphite would be a "superb" carrier for metal atoms,



SPECT ventilation imaging with technetium-99m Technegas (0.5 mCi) on the left, compared with SPECT perfusion imaging with technetium-99m MAA (3 mCi) on the right. Shown are 4 out of a total of 30 frames of "surface rendered" three-dimensional images of ventilation and perfusion in a patient with pulmonary emboli. The perfusion images reveal defects unmatched by defects in ventilation. The patient inhaled four normal tidal breaths of Technegas and ventilation imaging was performed immediately before MAA was given intravenously. The patient was not moved from the SPECT gurney between studies.

Courtesy of William L. Ashburn, MD, UCSD Medical Center according to Dr. Kroto. After graphite is vaporized, some sheets of reactive carbon atoms curl and knit together to form buckyballs. More often, however, he says, the growing edge of the graphitic sheets advances beyond the starting edge. The result is a three-dimensional spiral of concentric layers around a nucleus—analogous to a nautilus shell. Says Dr. Kroto: "Soot type particles are like a maze that the metal atom is never going to escape." (Dr. Kroto has even proposed that such particles, abundantly produced by fire, are the dominant carriers of radioisotopes in nuclear fallout.)

A year after Dr. Burch developed Technegas scanning in 1984, he began to wonder if he was making buckyballs when a colleague told him about the process Dr. Smalley and Dr. Kroto had proposed to generate the strange new molecules. Dr. Burch noted the strong similarity to his process of vaporizing graphite in an inert atmosphere. With difficulty he managed to get some of the aerosol to stick to electron microscope grids and obtained a few blurry images suggesting hexagonal arrangements of atoms—"which just blew us away," says Dr. Burch, who originally thought the aerosol was a simple technetium carbide. Oddly, the particles measured 10 nanometers across, about ten times larger than classic buckyballs, which left unanswered some intriguing questions with no further investigation until the Huffman-Kratchmer announcement sparked renewed interest last year. The inventor says, "My charter really was to get on with doing clinical work—I put all that information to one side and just got on with perfecting our Technegas for clinical studies."

The clinicians in Dr. Burch's department were impressed with how many millicuries of technetium-99m activity could be squeezed into a liter of gas containing the aerosol. "It meant that even with patients who had poor breathing capacity we could get a lot of activity into the lungs," says Dr. Burch. "Most patients can breath Technegas in about two to three breaths, and very poor breathers might take six or seven breaths, compared to two to three minutes of heavy breathing with aerosols."

Australian doctors have since used Dr. Burch's invention to detect opportunistic infections of the lungs as well as pulmonary embolism. Researchers found that adding about 3% oxygen to argon in the vaporization chamber created a labeled aerosol that, unlike Technegas, readily crossed the alveolar membrane out of the lungs and into the capillaries.

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Philip Monaghan, MD and others at Prince of Wales Hospital in Sydney used the altered form of the aerosol to detect opportunistic infections in immunocompromised patients. In normal controls, about six to ten minutes are required for half of the activity in the lungs to disappear. In patients with opportunistic lung infections such as Pneumocystis carinii pneumonia, half of the activity clears the lungs in as few as two minutes (6).

The agent might allow early diagnosis and hasten treatment of opportunistic lung infections that can be lethal to immunocompromised patients, according to F. Deaver Thomas, MD, professor and director of the division of nuclear medicine, State University of New York, Syracuse. Dr. Thomas and Dr. Ashburn of UCSD, whose institutions are the only two in the U.S. with Technegas units, will soon commence clinical trials of the Technegas derivative, called "Pertechnegas" because it behaves like pertechnetate in the lungs.

Typical of nuclear medicine technology, the makers of Technegas don't know if the FDA will require approval of both the device and the "drugs" created by it. Because the FDA has approved the radiopharmaceutical ^{99m}Tc pertechnetate, Tetley Manufacturing filed a 510K application to the FDA for the device as it is used to make the clearance agent. Approval of the device for this purpose may open the door to use in ventilation scanning once Technegas gains approval as a radiopharmaceutical.

Content with the progress of clinical applications for Technegas, inventor Dr. Burch downplays the buckyball question as "academic," but sizing up the growing commercial interest in fullerenes he says, "It's got to be worth a few bobs for our patent attorney to have a look." Apparently others are taking his claim seriously as well. According to Dr. Burch, Tetley has already sold five Technegas units to non-medical research institutions, presumably interested in making buckyballs.

J. Rojas-Burke

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