MATERIALS SCIENCE

From New Phosphor, a Double Crop of Photons

Cheap, efficient, and cool, fluorescent tubes are so common that it is hard to imagine a public or office building without them. But they are not ideal. They contain mercury, which is poisonous and has to vaporize each time the power goes on, resulting in a lag that keeps them from being used as brake lights for cars and in fax and photocopy machines. In this issue, a team of Dutch researchers reports a step toward a better fluorescent tube, which could end up making these lights even more ubiquitous.

Replacing the mercury inside the tubes with a noble gas like xenon would eliminate the hazard and speed start-up. The stumbling block is the phosphor: the coating that absorbs ultraviolet (UV) light given off by the vapor inside the tube and reemits white light. Although current phosphors absorb UV photons from the mercury and reemit them as visible photons with about 90% efficiency, that's not good enough for xenon. Xenon generates UV photons at much higher energies than mercury, so one-to-one conversion to low-energy visible photons means that much of the energy going into the xenon is wasted as heat. For practical xenon tubes, "it became necessary to develop phosphors that give more than one [visible] photon for every absorbed UV photon," says Alok Srivastava, a chemist at General Electric in New York. On page 663, chemist Andries Meijerink and his colleagues at Utrecht University in the Netherlands report an experimental phosphor that does just that.

The quest for a photon-doubling phosphor started almost 30 years ago. Researchers began looking for the effect in materials containing lanthanides—the heavy elements that are a standard ingredient in ordinary phosphors. Some early formulations did manage the two-for-one conversion, but they emitted lots of ultraviolet or infrared photons, and not enough visible light. "By the 1990s, people gave up," says Meijerink.

Meijerink, however, was one of the few who persisted, studying how lanthanide ions lose energy after UV light has excited their electrons to high energy levels. He hoped to find that a lanthanide boosted to a high energy level could, say, lose energy in two steps, emitting a visible photon each time. But it turned out, he says, "that using only one ion would never work." Then Meijerink's colleague Harry Donker thought of distributing the energy from each absorbed UV photon between two different types of lanthanide ions.

Meijerink and his colleagues tested a pair of lanthanides, gadolinium and europium, in the form of crystals of lithium gadolinium fluoride, doped with europium. They bombarded the crystals with high-energy UV photons, which bumped the gadolinium into an excited state. The gadolinium got rid of its excess energy by transferring it to two nearby europium ions through a complex interaction of electric fields. The europium ions in turn shed the energy by each emitting a single red photon, giving a total of two red photons emitted for each UV photon.

To make sure that each UV photon really was generating two red photons, the researchers bombarded the crystals with two different levels of UV radiation, one energetic enough to drive the two-step process, the other able only to drive a one-step process that produced just one red photon. The red fluorescence sparked by the higher energy UV was twice as intense, indicating that double the number of photons was being emitted.

Because plain red light isn't useful in most settings, Meijerink now wants to hunt for other phosphors that will use the same principle to emit green and blue photons, which in combination with red photons would yield white light. He also needs to find a way to make his phosphor absorb more UV photons, so that it can emit brighter light. "There are engineering issues, like sample purity and stability, that have to be addressed," says Kevin Bray, a chemist at Washington State University in Pullman, "but they have shown that it is possible to take a high-energy UV photon and extract from it two visible photons. That is very promising." Srivastava agrees: "This is the first experiment to demonstrate that you can get a practical system out of these ideas." —MEHER ANTIA

Meher Antia is a writer in Vancouver.

CREDITS: (BOTTOM, LEFT TO RIGHT) MICHAEL BAKER; KYUNGHEE UNIVERSITY

CLONING

Report Casts Doubt on Korean Experiment

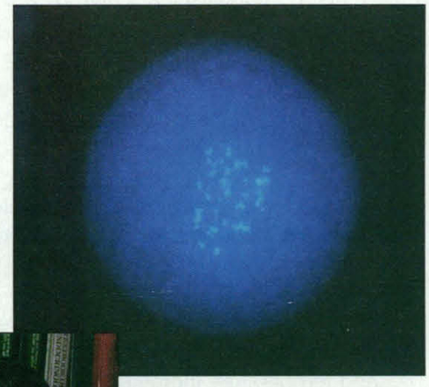
SEOUL, KOREA—One month after Korean fertility specialists declared that they had cloned a human embryo, the Korea Medical Association (KMA) has issued a report casting serious doubt on the claim. Even without evidence of success, however, the experiment has prompted calls for stricter government regulation of such research and closer university oversight of its faculty.

The 10-page report, presented this week, was written by a four-member panel convened by the medical association to investigate press reports of work done in early December by researchers at Kyunghee University Hospital here (*Science*, 1 January, p. 16). The team said it transferred the nucleus of a somatic cell into an egg cell whose nuclear material had been removed. Both cells were donated by the same patient. The reconstituted egg cell then divided twice before the researchers discarded it and ended the experiment.

The KMA report questions whether the nuclear transfer was done properly, if at all, and whether the DNA from the transplanted cell or the egg cell was driving the division of the new cell. It noted that the decision to take both cells from the same woman, a patient in the hospital's fertility clinic, makes the results extremely hard to interpret. "They insist they did this. But I don't know," says biochemist Seo Chung Sun of Seoul National University, who headed the investigation.

The KMA report notes that, instead of fixing the four cells on a microscope slide for future reference, the researchers simply threw them away. They also did not culture and save the somatic (cumulus) cells, a kind of cell that surrounds the oocyte, from which the DNA was transplanted. "We don't have any material to judge. That's a big problem," says Seo.

The Kyunghee team says they did not retain material from the experiment because they never intended to prove anything. Referring to a cloning technique used on mice (*Nature*, 23 July 1998, p. 369), team member Lee Bo Yeon says the work was done "to confirm if the Hawaii technique was possible in this lab." A press release that generated international news coverage was intended only to inform other scientists interested in the technique, Lee explains.



Visible proof? Lee Bo Yeon and colleagues at Kyunghee University say they produced the cell shown above by transplanting human DNA from an adult cell into an enucleated egg.

Lee says that further experiments could help his research on infertility, for example, in overcoming deficiencies in the eggs of patients trying to become pregnant. But he says he plans to wait for new regulations that define what procedures to follow.

Such regulations were the topic of two recent public forums. On 18 January, a citizens' group assembled a panel here to discuss what was billed as "a legal response to human cloning." The panel included a lawyer with expertise in litigating medical issues, a Catholic human rights activist, a private-sector biotech safety advocate, and Seo. The panel urged legislators to strike a balance in its regulation of this powerful technology.

The conference was one in a series organized to encourage public dialogue on important civic issues. And the comments reflected a range of views on the subject of cloning. One citizen complained about paying taxes to support work by unethical scientists, while another asked, hopefully, whether this technology might make it easier for lesbian couples to have babies.

On 20 January, national legislator Lee Sang Hee convened a cyber-conference to discuss his plans to amend existing laws governing bioengineering. Lee hopes to address ethical concerns without hindering the country's scientific competitiveness, says an aide.

Lee has proposed a national ethics review that would report to the science minister. Although such a body is essential, says Park Byung Sang of the private Biosafety Ethics Association, it needs to report directly to the prime minister to remain independent of special interests. Whether that is done, academic observers predict that the Kyunghee experiments will spur more universities to establish their own ethical review boards. Such boards now exist at only two universities, Yonsei and Seoul National.

—MICHAEL BAKER

Michael Baker writes from Seoul.

DRUG DELIVERY

Silicon Chips Find Role As in Vivo Pharmacist

Once upon a time, microchips were confined to the hearts of computers. Now they inhabit everything from children's toys to toasters. Before long, according to a team of researchers at the Massachusetts Institute of Technology (MIT) in Cambridge, they will turn up inside your body. In this week's issue of *Nature*, the team reports creating the first drug-delivery microchip, the progenitor of devices that may be capable of releasing variable doses of multiple drugs over an extended time once swallowed or implanted under the skin. The new chips have yet to be tested in animals or humans, but already some experts believe they have the potential to radically change the way many patients take medication.

"It's conceptually an extraordinarily exciting breakthrough," says Henry Brem, a neurosurgeon and oncologist at The Johns Hopkins University School of Medicine in Baltimore, Maryland. The centimeter-square silicon chips bear a series of tiny wells, sealed with membranes that dissolve and release the contents when triggered by an electrical signal. If loaded with potent medications, the chips could administer doses of one or more different drugs for months at a time. "The ability to modulate multiple drugs in a local environment would be an incredible step forward," says Brem. The researchers also hope to engineer the chips so that they can change the drug-release schedule or medication type in response to commands beamed through the skin. Such an ability would aid treatment of conditions such as Parkinson's disease and cancer, where doctors need to adjust medications and dosages.

Dime store. Implanted chips (shown front and back) could release controllable drug doses.

PHOTO: PAUL HORWITZ; SOURCE: SANTINI ET AL.

Controlling how drugs are released in the body is already a big business. Timed-release capsules, nicotine skin patches, and their ilk racked up $14 billion in sales in 1997. But these either provide a single pulse of a drug as the protective capsule dissolves, for example, or continuously release the drug for a set length of time as a degradable matrix dissolves. "What doesn't exist is a pulsatile delivery system that you can control," says MIT chemist Robert Langer, who led the new effort.

To create one, Langer enlisted the help of MIT doctoral student John Santini and Michael Cima, an MIT colleague and microelectronics fabrication expert. The trio started with a standard silicon wafer, normally used to make computer chips, and used conventional chip-processing techniques to carve a series of 34 tiny reservoirs in the chip, each capable of holding just 25 nanoliters of liquid, less than the volume of a grain of salt. Additional deposition, patterning, and etching steps created a circuit of gold wires on the top surface of the chip and tiny gold membranes capping each well. The bottom of each well was still open, allowing the researchers to flip the chip over and fill each compartment with fluorescent and radioactive compounds—easy to detect in initial tests. Finally, they sealed the back with a sheet of either glass or epoxy.

To test the chip, Langer, Cima, and Santini dunked it in a buffer solution mimicking the body's pH and chloride concentration. They then flipped a switch to send a current through one of the gold electrodes covering a single well. Robbed by the current of some of their electrons, positively charged gold ions in the electrode readily reacted with chloride ions in solution to create a metal salt. The gold membrane covering the well dissolved in just seconds, spilling its contents into the solution. Now that the team has demonstrated the principle, they have more ambitious plans. "You can put thousands of [wells] on a chip the size of a dime," says Langer. And because each reservoir-topping electrode can be wired separately, researchers can control exactly when each reservoir releases its contents.

But the new pharmacy chips still have a long way to go before reaching the market, says Langer. Researchers must first test them in animals and humans to ensure that all of the components are biocompatible. To operate autonomously inside the body, the chips will need additional circuitry and battery power. Also, the chips will not be suitable for all drug therapies: Insulin, for example, must be taken in doses of up to 1000 milligrams several times a day, more than the chips can handle. Instead, the pharmacy chips will more likely find use delivering precise amounts of extremely potent compounds, such as hormones and ultrastrong painkillers.

Other uses outside the body could come sooner. Chips designed to stagger the release of different compounds could help automate tasks ranging from laboratory tests to pharmaceutical drug discovery. The team says a chip could even be charged with different fragrances and put in a TV set to release, say, the aroma of pepperoni as accompaniment to a pizza advertisement.

—ROBERT F. SERVICE