DEVELOPMENTAL BIOLOGY

Organs Await Blood Vessels' Go Signal

Blood vessels are the body's plumbing, supplying food and oxygen and removing waste. Now two papers published online this week by *Science* (www.sciencexpress.org) show that blood vessels play a more active role than previously believed: They help direct the construction of the body they serve. The teams, led by Douglas Melton of Harvard University and Kenneth Zaret of the Fox Chase Cancer Center in Philadelphia, report that blood vessels induce development of the pancreas and liver—even before the blood vessels are functioning.

Time to grow up. Blood vessels (red) direct islets (green) to differentiate.

CREDIT: E. LAMMERT *ET AL.*

Cancer researchers stumbled upon the first evidence that blood vessels do more than ferry food and waste around the body. In 1995, a team reported that endothelial cells, which make up blood vessel walls, produce growth factors.

The new studies build on that work, showing that by sending another, as-yet-unidentified molecular signal, the embryonic blood vessels direct embryonic tissue not just to grow but to differentiate into complex structures. "The endothelial cells aren't just a bunch of pipes and tubing; they contribute to the formation of the organ," says liver regeneration researcher Robert Costa of the University of Illinois, Chicago. "That's really the most important part of the discovery."

Melton's team began scrutinizing blood vessels after noticing something odd about how cells in the mouse pancreas differentiate into islets, clusters of cells that produce insulin. The researchers observed that the endoderm—embryonic tissue fated to become middle organs such as the lungs, liver, pancreas, and stomach—directly touches a major blood vessel, the dorsal aorta. "It begs the question, is there a signal there?" says postdoc Ondine Cleaver, a co-author of the paper. The developed pancreas monitors blood vessels to assess blood glucose levels and tweak insulin production accordingly. The team suspected that the pancreas and blood vessels talk to one another chemically during development as well.

To test their hypothesis, the researchers first surgically removed cells fated to become the dorsal aorta from frog embryos. This dramatically reduced levels of insulin and two other pancreatic secretions in the developing embryos. To make sure the pancreas wasn't hobbled due to a lack of blood flow, Cleaver and fellow postdoc Eckhard Lammert grew undifferentiated mouse embryo tissue in culture with and without embryonic dorsal aortae. Only in the presence of the blood vessel did the tissue produce pancreas-specific markers, including insulin. Finally, the researchers overexpressed a blood vessel growth factor, VEGF, in mouse embryos. This increased blood vessel production as well as islet formation and insulin production.

The Philadelphia group, meanwhile, approached the blood vessel question from another angle. Zaret and colleagues examined liver development in mice with a mutation in a gene called *flk-1*, which encodes a receptor for VEGF. When such mice are developing, the team found, no blood vessels form in the part of the endoderm destined to turn into the liver. What's more, "in the absence of such endothelial cells, the liver bud stops dead in its tracks and doesn't develop further," Zaret says.

To verify that an absence of blood vessels prevented the liver from developing, visiting scientist Kunio Matsumoto of Osaka University in Japan invented a new cell culture system that permitted blood vessels to grow among cultured liver tissue. Once the system was in place, the researchers compared mutant cells with normal cells. The *flk-1* culture grew to the same size as the normal one. But whereas about 20% of the normal culture consisted of liver tissue, only 5% of the mutant culture became liver; the rest was connective tissue. Surprisingly, the endothelial cells' influence arose well before the cells turned into functional blood vessels, suggesting that the cells themselves—and not some component of the blood—were sending the growth signal.

Understanding how cells differentiate will be critical to any future stem cell–based treatments for disease, such as growing islets in the lab for transplantation into diabetics. "If we're going to induce organs to form, we have to have a thorough understanding of how the embryo develops them," says organ replacement biologist Michael Longaker of Stanford University School of Medicine in Palo Alto, California. "We will never do it in a more elegant way than the embryo."

—CAROLINE SEYDEL

Caroline Seydel is a science writer in Los Angeles.

PLANETARY SCIENCE

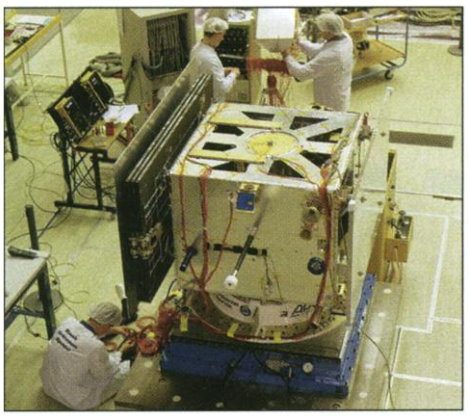
New Visitors Set For Lunar Voyage

NAPLES, ITALY—Like flared jeans and disco, exploration of the moon is back in fashion. Next week, at a meeting of the International Astronautical Federation in Toulouse, France, Japanese and European scientists will present new missions that will probe the satellite's surface and interior.

Apart from two U.S. missions—Clementine in 1994 and Lunar Prospector in 1998—the moon has been largely ignored since Apollo 17 departed with a load of moon rocks in 1972. But plenty of good science remains to be done. "The moon still has many, many mysteries, such as its origin and evolution," says Hitoshi Mizutani, head of planetary research at Japan's Institute of Space and Astronautical Science (ISAS).

By far the most ambitious project is Japan's Selene—"we call it the Rolls-Royce for the exploration of the moon," says Bernard Foing of the European Space Agency (ESA). Costing $350 million and carrying 200 kilograms of instruments, Selene will be launched jointly by ISAS and NASDA, Japan's space agency, in 2005. The craft's 14 sensors include x-ray and gamma ray spectrometers to chart elements on the surface and an alpha-particle spectrometer to analyze radiation emitted by radon gas and polonium. A stereoscopic camera will also map the lunar topology.

Scientists expect that Selene will improve our understanding of the origin and evolution of the moon. Some observers,



Fine-tuning. Europe's Smart-1 undergoes tests in the Netherlands.

CREDITS: (TOP TO BOTTOM) ESA; DAVID JENNINGS/AP

however, disagree. Although the mission "will create a massive data set on the moon, much of it unfortunately would not add materially to the things we already know," says lunar researcher Wendell Mendell at NASA's Johnson Space Center in Houston. Mizutani counters that "the quality and precision of the Selene instruments will provide much better data than those obtained by previous or existing observations."

A second Japanese probe, the $100 million Lunar-A, will swoop to within 40 kilometers of the surface in 2005 and launch two "penetrators"—80-centimeter-long projectiles that will pierce the surface to a depth of up to a few meters. Positioned on opposite sides of the moon, the sensors will monitor seismic waves traveling through its core. Analysis of the waves should reveal the size of the moon's core and determine whether or not it is liquid. Sensors on the penetrators will also measure heat flow through the crust, essentially taking the moon's internal temperature. "These geophysical data would be tremendously important toward understanding the moon as a planet," says Mendell.

The aim of ESA's more modest Smart-1 is to test new technologies, such as solar-powered ion propulsion, for later missions including ESA's Bepi-Colombo probe to Mercury. After the $80 million spacecraft is launched at the end of 2002, it will take 16 months to reach the moon, using only sunlight to drive it. Solar panels will provide the power to ionize xenon atoms and fling them out the back of the craft. "It is the first time that it will be used as a primary means for transportation," says Foing, ESA's project scientist for Smart-1.

Smart-1's tiny suite of six sensors, weighing only 15 kilograms in all, may help explain the moon's origin. In the most widely accepted theory, the moon is a bit of Earth broken off by a collision with a Mars-sized object. If so, the relative abundances of the moon's common constituents—iron, magnesium, and aluminum—should match those on Earth. Smart-1 will create a global map of abundances. The most important ratio is magnesium to iron, says Manuel Grande, a space physicist at the Rutherford Appleton Laboratory near Oxford: "That number really constrains whether the Earth and moon come from the same place."

Just as Cold War politics whipped up the moon frenzy in the 1960s, political forces may be behind the upcoming moon shots, some analysts contend. "The Selene mission ... is really the first step toward a resource-oriented commercial development," contends Mendell. Mizutani, however, insists it is far too early to talk about exploiting the moon. "We will need more basic study," he says. **–ALEXANDER HELLEMANS**

Alexander Hellemans is a writer in Naples, Italy.

STEM CELL RESEARCH

Reports Give Green Light in Australia, Israel

BERLIN AND MELBOURNE—Two countries at the forefront of work on human embryonic stem (ES) cells, Australia and Israel, have just recommended policies to ease the way for their researchers.

After 2 years of deliberation, an Australian government committee has endorsed legislation that would allow both ES cell research and the derivation of ES cells from unwanted embryos created during fertility treatments. The 10-member committee, made up of members of parliament, also called for a national licensing body to monitor and regulate all such research, whether publicly or privately funded. And although the parliamentarians unanimously condemned the use of ES cells for reproductive cloning, they left open the door to the creation of embryos as a source of genetically matched ES cells—so-called therapeutic cloning—by calling for a 3-year moratorium on the practice. The Australian government is expected to seek legislation to implement the recommendations.

This stands in stark contrast to restrictive conditions imposed on U.S. researchers. On 9 August, President George W. Bush announced that federally funded scientists could obtain ES cells only from existing cell lines; shortly before, the U.S. House of Representatives passed a bill that would ban cloning for research purposes.

In Australia, Catholic commentators condemned the report for failing to ban outright the creation of embryos for research. But medical ethicists such as Helga Kuhse of the University of Melbourne and Monash University believe the committee should have gone further. "I can't see why scientists should be limited to surplus embryos" from fertility treatment, she says. "Embryos are hard to come by, and, to me,

ScienceScope

Court Asked to Reconsider Several academic groups are asking the Maryland Court of Appeals to reconsider part of a recent decision that they say could halt "virtually all" research involving children.

The 16 August ruling, which concerned a study of home lead cleanup by the Johns Hopkins University (JHU)–affiliated Kennedy Krieger Institute, says no child or legally impaired adult should be allowed to participate in "nontherapeutic" studies involving "any risk" (*Science*, 31 August, p. 1567 and 14 September, p. 1997). This sweeping wording "would have a devastating impact" on research by barring standard procedures such as needle sticks and the use of placebos, says an amicus brief filed by JHU, the Association of American Medical Colleges, the Association of American Universities, and the University of Maryland Medical System. The groups ask the court to rescind this portion of the decision. An AAMC spokesperson says the court has indicated it may hear the appeal in October.

West Nile Watch The West Nile virus keeps popping up in more U.S. states. In the last month, health authorities in Maine, Illinois, Wisconsin, Iowa, Kentucky, Alabama, and Tennessee reported detecting the agent in birds or other animals for the first time.

West Nile, which had never been found in the Americas until it hit New York City in 1999, has now been reported in 24 states and the District of Columbia, and "we need to assume that it's going to spread throughout the country," says Duane Gubler, head of the Centers for Disease Control and Prevention's arthropod-borne virus lab in Fort Collins, Colorado. Gubler suspects that migratory birds transported the virus to southern states such as Florida and Louisiana in the fall of 1999 or 2000; from there, it probably hitched a ride to the northern Midwest this spring.

So far, the human toll has been relatively low: Early this week, there were 26 reported or suspected cases, including one fatality, compared to 62 cases in 1999 and 18 last year. And even if it conquers the rest of the country, good surveillance, prevention, and control measures should prevent the virus from becoming a major public health threat, says Gubler: "This is a virus we can deal with."