



On the forefront. Another pain pioneer, Clifford Woolf, is now analyzing pain responses using DNA microchips.

Changes in gene expression could underlie this persistent neuronal hypersensitivity.

These changes could include, for example, upregulation of the genes for the various receptors or ion channels. Genes for the neurotransmitters themselves may also get turned up. Two years ago, Salter's team, working with Josef Penninger and his colleagues at the Amgen Institute in Toronto, identified a protein called DREAM as a modulator of pain responses. DREAM represses the transcription of certain genes, including the one encoding an endogenous opiate called dynorphin. Animals lacking DREAM displayed reduced pain responses in experiments that mimic both inflammatory and neuropathic pain, presumably because dynorphin concentrations go up in their spinal cords in its absence.

And those changes in gene expression could be just the tip of the iceberg. Woolf and his colleagues have recently applied the new technology of DNA microchips to identify changes in gene-expression pattern in sensory nerves during pain responses. So far, the team has come up with some 240 genes and is now working to see how they might be involved. "We are getting suggestions of genes no one even thought were involved in pain," Woolf says. "It's opening up new avenues of research."

But there's something even more permanent than changes in gene expression: cell death. Woolf and his colleagues have found that spinal cord neurons that produce the inhibitory neurotransmitter called gamma aminobutyric acid die after various types of nerve injury. Loss of this inhibitory influence could thus result in increased activity of their target neurons. "We think this is exciting," Woolf says. "It means we need to look at neuropathic pain as a progressive neurodegenerative disease." He suggests that it may be possible to prevent neuropathic pain if a way can be found to inhibit this cell death.

The brain gets involved

Persistent pain may operate through neurons other than just peripheral nerves and the spinal cord; it may also involve neurons originating in the brain. Dubner and Porreca, among others, have found that neurons in an area at the base of the brain called the rostroventromedial medulla (RVM) play opposing roles: Some facilitate the transmission of pain signals up the spinal cord into the brain, whereas others inhibit that transmission.

Dubner suggests that this may have evolutionary value. He and his colleagues find that facilitation takes precedence early on, perhaps enhancing an injured animal's efforts to get out of harm's way. Later, when the inhibitory neurons dominate, the decreased pain may help the animal rest. "Once one gets into a safe environment, one needs to recuperate and recover," Dubner hypothesizes.

Porreca's team has evidence that when the pain continues long after it should stop, activation of the facilitatory RVM neurons may be to blame. For example, they found that a treatment that destroys the suspected neurons in rats can prevent, and even reverse, the development of neuropathic pain.

"Initially the pain state is produced by damage to peripheral nerves, which become

hyperactive. Over time that influence produces adaptive changes in the nervous system that will maintain the pain," Porreca says. Exactly what those adaptive changes are is unclear, but many pain researchers think that they include the same type of synapse strengthening involved in learning and memory.

Ultimately, of course, pain signals reach the brain, where they can be interpreted and appropriate action initiated. Researchers, including M. Catherine Bushnell of McGill and Kenneth Casey of the University of Michigan, Ann Arbor, have been using various imaging techniques to see how the brain responds when people experience pain. They have identified several areas where neuronal activity increases. Casey, Jürgen Lorenz of the University of Hamburg, Germany, and colleagues have found, for example, that the brain responds differently to inflammatory pain than it does to a simple noxious heat stimulus.

Researchers now plan to put together information from imaging with findings on underlying pain mechanisms. Dubner hopes that will lead to "a case definition of a particular chronic pain condition that allows us to give it a signature"—and, ultimately, better therapies designed to match those pain signatures.

—JEAN MARX

Japan

Conservation Takes a Front Seat As University Builds New Campus

Kyushu University needed to expand. Biologist Tetsukazu Yahara is making sure that the move is ecologically friendly—and good science

FUKUOKA, JAPAN—Wander through a back gate to Kyushu University's new campus here in southwestern Japan, and you won't believe that construction crews have come and gone. There's not a single new building in sight, nor are there freshly paved roads or parking lots, playing fields, or the beginnings of a quadrangle. Instead, the small valley is dotted with ponds and marshes thick with reeds and water lilies. Pines and oaks cover the slopes. The sounds of croaking frogs and chirping insects fill the air.

The trees and shrubs, turtles and salamanders, even some of the insects were plucked out of the path of bulldozers over the ridge and replanted here. It's a unique effort to convert more than 40% of Kyushu's 275-hectare campus into a conservation experiment. The \$2.75 million transplantation project has already provided graduate students with dissertation topics, spawned a new undergraduate course, and given the

university a growing reputation in conservation biology. And what's happening at the new campus, which will partially open this fall, has attracted broader notice, too.

The Japan Society of Civil Engineers has praised the university for "setting an example that the civil engineering profession should follow." Lessons from the new campus are being applied to a dam project and a riverbank improvement scheme elsewhere in Japan. "It's utterly different from any campus construction project I have ever experienced in the U.S.," says Robert Colwell, an ecologist at the University of Connecticut, Storrs, who is familiar with the project and would like to see U.S. universities pay similar attention to environmental concerns during construction projects.

Evolutionary biologist Tetsukazu Yahara, the driving force behind the project, admits that he would have preferred to see the entire site preserved and still has mixed feel-

ings about developing some of it. But he says the transplantation project shows that construction and conservation can be mixed “better than most people expected.” And he welcomes the new direction it has given his own research.

Time for preservation

The transformation of Kyushu’s new campus into a biological experiment almost didn’t happen. In the late 1990s, the 4800-student university had outgrown two downtown campuses and was looking for more land. Fukuoka City offered a location on the western edge of town, a patchwork of old rice paddies, orchards, and commercial forests spread over a cluster of small hills. The first report by a university planning committee recommended bulldozing the hilltops into the valleys, essentially leveling the entire site.

The plan didn’t go over well with environmentally conscious faculty members. As president of the university’s labor union, Yahara took those concerns to the administration, where he found a sympathetic ear in Toshifumi Yada, an economic geographer and then a university vice president. Yada agreed to take a second look. “We destroyed enough mountains in the past [in Japan],” Yada says. “Now it’s time to preserve them.”

Yahara helped revise the master plan to largely maintain existing contours, concentrate the buildings along a curving central spine, and leave the flanks of the campus for preservation. He also saw an opportunity to do more, particularly in a 10-hectare valley that nearly bisects the site. Rather than letting nature take its course with the valley’s abandoned rice paddies, Yahara proposed turning it into a refuge for plant species displaced by construction.

Yahara feared that his idea for “no species loss” would be a hard sell. cursory investigations hadn’t turned up any endangered plants. “Ecologically, the site is very ordinary,” he says. He also worried about neglecting his own research on the evolution of sexual reproduction in plants. “I was afraid of being criticized for working on conservation instead of research,” he says. But after winning support from the administration, Yahara accepted the challenge—adding it to his normal course load and work in the lab.

The first step was an exhaustive survey of the site’s terrestrial and aquatic plant species. He modified the usual square-grid approach by running transect lines along and perpendicular to hill contours to get a more accurate picture of the flora at different elevations. Unexpectedly, the students and consultants working with him turned up several endangered species and many more that occurred in very limited numbers. About half of the 270 species were found in fewer than five survey blocks.



Transformation. Biologist Tetsukazu Yahara has overseen the effort to turn a valley on campus into a refuge for plant species displaced by construction.



High road. The new campus of Kyushu University hugs a ridge that winds down to the coast in southwestern Japan.

Maximizing biodiversity meant not just saving individual plants but also the seeds embedded in the soil and subsurface microbes and nutrients. Yahara found a local contractor who, by using modified earth-moving equipment, could dig up 50-centimeter-thick blocks of soil, 1.5 meters on a side, complete with the covering vegetation. More than 3600 of these blocks were dug up and replanted.

Some objectives required a more active hand. Deciduous forests that once covered the site had long ago been logged and succeeded by firs. So isolated mature oaks standing in the way of buildings were trimmed, dug up, and gathered into clusters within the conservation zones. The rice paddies that stepped up the central valley were carefully sculpted into wetlands, with differ-

ing water depths and bank slopes tailored to the needs of different vegetation. In one case, an entire pond was moved. The aquatic vegetation and its supporting soil were also moved in blocks, along with another meter or so of underlying fine silts needed to ensure that the new pond would hold water.

Yahara made a point of enlisting the public, too. Adult volunteers and schoolchildren captured frogs, salamanders, turtles, and dragonflies from around the site and released them in the new marsh. Although the bulk of the preservation work is complete, it may take decades to know the fate of some of the transplanted ecosystems. And there will be some tinkering with nature, Yahara admits. A nonnative bamboo species once cultivated here for its shoots would strangle native trees if not kept in check, and species that thrive on the edges of logged forests and roadsides, such as a wild relative of the snapdragon family, have been introduced while awaiting the arrival of harder vegetation. “To preserve such species, ecosystem management is inevitable,” Yahara says.

Once skeptical that his efforts would bear fruit, Yahara says he is “very happy with the way things worked out.” Setsuo Arikawa, another university vice president, says that Yahara’s project has helped give the university “a 21st century campus where students are involved in studying and appreciating their surroundings.” The University of Connecticut’s Colwell says that what Yahara and Kyushu have done “should make it easier for the next [conservation] case, at least in Japan and, if we are lucky, elsewhere as well.”

By staying in his office until 11 p.m., Yahara also has managed to maintain his research on plant sexual reproduction. And he’s expecting to generate several papers based on the new campus project. “It’s a good opportunity to learn about ecological systems,” he says.

In addition to its investment in the transplantation project, the university has recently given Yahara a \$40,000, 3-year grant to explore creating a Biodiversity Research Center. In a pilot project, Yahara is collaborating with civil engineers to study mud flats near the campus that host hundreds of wild birds and are threatened by agricultural runoff and a planned dam. It’s the latest application of what Yahara has learned: Minimizing environmental impacts can sometimes maximize the academic payoff.

—DENNIS NORMILE