Dartmouth neurologist James Bernat, M.D., gave the keynote lecture at the 2008 annual meeting of the Vlaamse Vereniging voor Neurologie, the Flemish Neurological Society, in Antwerp, Belgium.

A push for new knowledge about labor

No one fully understands the intricate dance of the hormones that trigger labor. Two DMS researchers thought they'd come close recently and submitted a paper detailing their findings to the *Journal of Clinical Investigation*. But the discovery—that a muscle *relaxant* triggers labor's forceful uterine contractions—was so surprising that the journal's reviewers asked the investigators to perform additional experiments to confirm the finding. They did so, and the paper was published a few months ago.

"I simply thought they were wrong," laughs ob-gyn Roger Young.

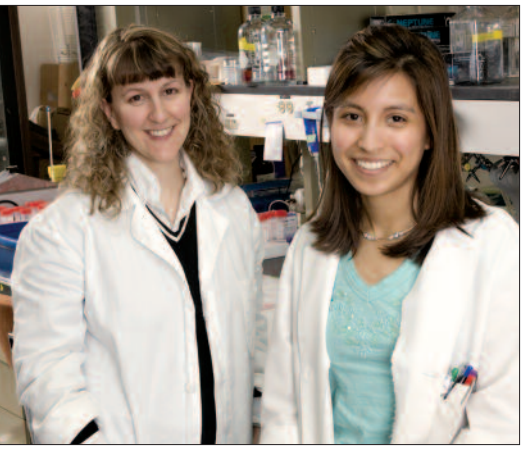
Trigger: The researchers—graduate student Kristina Fetalvero and vascular surgery researcher Kathleen Martin, Ph.D.—weren't surprised their discovery was controversial. It's long been known that prostacyclin, a fatty acid, is present in low levels in the uterus during pregnancy and spikes before labor starts. But until now no one suspected it might actually trigger labor.

Dartmouth ob-gyn Roger Young, M.D., Ph.D., recalls attending a meeting where Fetalvero and Martin presented their data—showing that prostacyclin both relaxes and enhances the contraction of smooth muscle cells in blood vessels and in the uterus. "I simply thought they were wrong," laughs Young. "I thought they were right in vascular, but that it would be a different result in uterine cells."

Soon the researchers made a believer out of him. Young, who is now at the University of Vermont, became a partner in the study. He provided tiny strips of uterine tissue, which he obtained from 21 volunteers about to undergo elective c-sections. The slices—two per patient—were attached to 400-milligram weights and suspended in test tubes. The weights helped the tissue maintain the ability to contract, which it would rapidly lose in a normal culture dish. One strip of each pair was treated with prostacyclin for 48 hours; the other was untreated. Then all the strips were stimulated with oxytocin, a muscle contractant present in labor. The treated samples underwent much stronger contractions than the untreated ones. The researchers determined that the prostacyclin had upregulated proteins that stimulate the contraction of smooth muscle cells.

Signals: The study has limitations, however, says Fetalvero, who's now a postdoctoral fellow at Novartis in Cambridge, Mass. Uterine tissue outside the body can't be stimulated by the signals that normally come from the fetus and hormones in the body. "All of these work together to trigger the labor phase," she says. But studying uterine tissue in the lab "is the next best thing to understanding human labor right now."

The study, which was funded by the National Institutes of Health, has implications for preventing preterm delivery, which has been increasing and now occurs in about 12% of pregnancies, says Young. "It makes it more incumbent on us to find at least one therapy that seems to work," he points out. "Right now we have none." Laura Stephenson Carter



CHRIS MILLIMAN

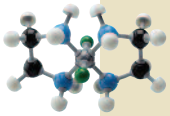
Martin, left, and Fetalvero studied labor's onset.

Back talk

Surgery trumps physical therapy, education, exercise, and medicine when it comes to relieving pain and improving physical function in people with a herniated lumbar disc. So reported James Weinstein, D.O., and his colleagues in the December 2008 issue of *Spine*. "The treatment effect for surgery was seen as early as six weeks, appeared to reach a maximum by six months, and persisted over four years," they wrote. The group of patients who didn't have surgery improved, too, the authors noted, just not as much as the group who had surgery.

Smoke alarm

DMS researchers found a possible link between maternal cigarette use and Sudden Infant Death Syndrome (SIDS). SIDS is a major cause of infant mortality in the U.S., but its mechanisms are still unknown. One possibility is laryngeal chemoreflex apnea, a condition in which liquid in the larynx may cause infants to stop breathing. The DMS study showed that apnea lasted longer in rat pups whose mothers had been exposed to tobacco smoke than in rat pups from unexposed mothers. "This finding may be significant for the pathogenesis of SIDS in human infants," wrote Luxi Xia, M.D., and her coauthors in *Respiratory Physiology and Neurobiology*.



In certain subsets of individuals, including women and moderate smokers, the trace mineral selenium may help prevent bladder cancer, determined a recent Dartmouth study.

Addition to knowledge about egg division

Every pregnant woman dreams of holding a healthy newborn in her arms. But a woman's age has a "very scary" effect on her chance of having a healthy baby, says Dartmouth biologist Sharon Bickel, Ph.D. A woman's risk of conceiving a baby with the wrong number of chromosomes increases from about 2% at age 25 to 35% at age 42. Aneuploidy—having an abnormal number of chromosomes—is the leading cause of miscarriage, as well as of mental retardation in babies who live. Bickel and former graduate student Vijayalakshmi Subramanian, Ph.D., found evidence that supports a long-standing hypothesis about the link between maternal age and fetal aneuploidy.

They demonstrated that the "glue" does deteriorate over time.

Cell: Eggs develop through meiosis, a special kind of cell division in which the number of chromosomes is halved; a human cell with 46 chromosomes divides into daughter cells with 23 each. Prior to cell division, the maternal and paternal versions of each chromosome, known as homologues, "are held together by a molecular glue," says Subramanian. One hypothesis suggests that as egg-precursor cells age, loss of this glue may cause chromosomes to mis-segregate more often.

During meiosis, microtubules from either end of the cell attach to paired homologues and pull them toward opposite poles of the dividing cell. "Think about a situation where they aren't held together," says Bickel. Microtubules would then tug the chromosomes randomly toward either pole. Occasionally, both homologues of one chromosome end up in the same daughter cell, giving it more than 23 chromosomes. Such an aneuploid egg can lead to an aneuploid pregnancy. Bickel and Subramanian demonstrated in fruit flies that the cohesion proteins (the "glue") that hold homologues together do deteriorate over time.

In humans, the first steps of meiosis occur in the eggs of a female's ovaries before she is born. Homologues recombine and attach to each other with cohesion proteins. Then, says Bickel, cells "are hanging out" until ovulation. An egg cell doesn't divide until it's released from the ovary, usually decades later. During this period of meiotic arrest, homologues rely on cohesion to keep them together.

Eggs: Since studying human eggs over such a time span is impractical, Bickel and Subramanian used flies. They aged some fly eggs by suppressing egg-laying for four days, then determined that chromosomes mis-segregated more often in aged than non-aged eggs. And the segregation errors occurred more often in eggs aged during a stage of development corresponding to the one that human eggs "hang out" in before dividing during ovulation.

The study, published in *PLoS Genetics*, is "the first time that someone's looked at the normal proteins that are operating during meiosis and been able to show [increased segregation errors] over time," notes Bickel. The reason this occurs more often in older eggs won't "boil down to one thing," she suspects, but she believes the loss of cohesion is "a major determinant." Now she wants to explore why that happens. KATHERINE VONDERHAAR

Biologist Bickel studies chromosome segregation.

When more is less

For chronically ill patients, spending more time in the hospital is associated with lower quality-of-care and patient satisfaction scores, reported DMS researchers. The group compared quality and satisfaction in regions with a high intensity of hospital care to regions with a low intensity of hospital care. "The common thread linking greater care intensity with lower quality and less favorable patient experiences may be poorly coordinated care," wrote John Wennberg, M.D., et al. in *Health Affairs*. Patients from high-intensity regions cited "dirty rooms, noisy nighttime, poor pain control, and shortfalls in communication with doctors and nurses" as reasons for low ratings.

Wait lifted

Veterans in need of mental health care at the DMS-affiliated VA Medical Center in White River Junction, Vt., used to have to wait an average of 33 days to see a specialist. Now the average wait time is 19 minutes. So reported a team that implemented a new model of care, making mental health specialists immediately available in a primary-care clinic. "The primary mental health clinic dramatically enhanced access to mental health care . . . while doubling clinician productivity," Andrew Pomerantz, M.D., et al. wrote in *General Hospital Psychiatry*.

Dr. Joyce DeLeo, the chair of Pharmacology and Toxicology, was recently quoted in *Nature Biotechnology* about progress in studying glial cells; she's worked in the field since the 1980s.

Vioxx shows some long-term cardiac effects

In 2000, John Baron, M.D., had high hopes for Vioxx, and he wasn't alone. The drug was helping to ease the pain of millions of patients worldwide, without causing the gastrointestinal problems associated with aspirin. When Merck, Vioxx's manufacturer, asked Baron to help lead a clinical trial testing the drug's effectiveness for colon-cancer prevention, he was excited. "Here were drugs almost without side effects, so it seemed, and with potential cancer-protective properties," he recalls thinking. "But, well, that's not what happened."

In the study—the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial—the drug did, indeed, show signs of protecting patients from adenomas, benign growths that can progress to cancer. Unfortunately, it also doubled the risk of cardiovascular problems, such as heart attacks and strokes. When this became clear, in September 2004, the trial's safety and data monitoring committee let Baron know; he informed Merck, and within a week Vioxx was off the market.

Trial: Over the next few years, Baron and his collaborators analyzed the data from the trial and wrote two papers on the drug's apparent cardiovascular risks and chemopreventive effects. In a third paper, recently published in the *Lancet*, Baron discussed a follow-up effort intended to discover if the heightened risk of cardiovascular problems continued even after patients stopped taking Vioxx.

Risks: The APPROVe subjects were contacted and asked if they'd had a heart attack or stroke in the year after going off Vioxx. The results were broadly similar to those of the earlier studies, though the overall relative risks were somewhat smaller. Baron says that the number of people in the study and the number who suffered death or disease were too low to draw definitive conclusions. The risk in the year after going off Vioxx "was not statistically significant but was elevated," he says. "Probably . . . there is an increased risk but . . . the study was too small to see it conclusively."

Baron says that he is "marginally confident" about the conclusion.

Baron's analysis also revealed that preexisting cardiovascular risk factors—such as hypertension, smoking, or being overweight—seemed to raise the cardiovascular risk from taking Vioxx. Baron says that he is "marginally confident" about the conclusion but cautions that he can't be certain of this link.

Questions have been raised recently about when Merck first knew about the risks of Vioxx. According to the *New York Times*, lawsuits against the firm have stated that "scientists at Merck were worried about Vioxx's potential cardiovascular risks as early as 1997." Still, for a time, the drug appeared to have real benefits.

Baron, who has stayed out of the legal turmoil that followed the revelations of 2004, says it can be difficult to come to definitive conclusions about the risks and benefits of a treatment. "You have to weigh the merits of one kind of endpoint against the harms of another," he says. "And that's not easy." AMOS ESTY

JON GILBERT FOX

Baron has written several papers about Vioxx.

Pressure point

Albuterol, an asthma medication, may contribute to acid-reflux attacks, according to a DMS study. The study, published in *Digestive Diseases and Sciences*, found that repeated use of albuterol may reduce pressure in the lower esophageal sphincter (LES). The LES normally prevents stomach acids and enzymes from entering the esophagus, so decreased LES pressure may "raise the possibility that gastroesophageal reflux may occur after bronchodilator therapy," wrote Brian Lacy, M.D., et al., suggesting that changes in LES pressure could be the link between asthma and gastroesophageal reflux disease.

Infective idea

A common ingredient in cosmetics, foods, and drugs—an emulsifier called polysorbate 80 (PS80)—inhibits the colonization of bacteria on a variety of surfaces, a DMS team recently found. About 80% of health-care-associated infections are caused by bacteria in the form of biofilms—the very structure that PS80 breaks down. "Potential clinical applications of the antibiofilm effect of PS80 or derivatives include the treatment of medical prosthetic devices, such as artificial joints and intraocular lenses, prior to implantation," wrote Michael Zegans, M.D., and his coauthors in *Antimicrobial Agents and Chemotherapy*. ■