

# the birth of new ideas

*UVM obstetricians and gynecologists help deliver new babies, new treatments, and the next generation of care.*

**T**he genesis of this science is the genesis of us all: a human egg and sperm meet, bond, and attach to a mother's uterus. If all goes well, nine months later a new egg or sperm donor will be born.

Or not. Sometimes the usual nine months' stay in the uterus is significantly shortened. Other times the mother's blood pressure rises to dangerous levels and the baby must be taken out of the womb early. Later on in life, cancer can invade the ovary that created the egg, and the mother may have no idea until it's too late. Or, after the mother has stopped the monthly production of those eggs, she goes on hormone replacement therapy and experiences devastating side effects.

The physician-scientists at the College of Medicine's Department of Obstetrics and Gynecology search for solutions to problems such as these, using every means available — from basic research techniques to multi-center clinical trials. Every year, they educate medical students and residents, treat thousands of patients, deliver hundreds of new babies — all while giving birth themselves to new knowledge and potential therapies.

by RACHAEL MOELLER GORMAN

photography by ROSE MCNULTY



Professor and Chair of Obstetrics and Gynecology Mark Phillippe, M.D.

When John Van Sicklen Maeck Professor and Department of Obstetrics and Gynecology Chair Mark Phillippe, M.D., came to the College of Medicine in 2001, his purpose was clear.

“My main goal when I came was to enhance basic research,” he says. “The department certainly had ongoing research, but the idea was to strengthen it, particularly by bringing in additional physician-scientists to complement the people who were



already here.” Phillippe set out to recruit four new physician-scientists, and has already hired two: Associate Professors Edward Chien, M.D., and Elizabeth Bonney, M.D. “We’ve got a good group of investigators who can collaborate and cross over in regard to research interests,” he says.

The department maintains cutting-edge clinical programs such as the Women’s Center for Pelvic Health, Fetal Diagnostic Center, and the In Vitro Fertilization Program, and funded research spanning the areas of General Obstetrics and Gynecology, Gynecologic Oncology, Maternal-Fetal Medicine, Reproductive Endocrinology and Infertility, and Urogynecology. Twenty board-certified academic physicians and four Ph.D. researchers are engaged in research, with support from medical students, graduate students, nurses, and technicians.

Each faculty physician in the department spends

an important portion of his or her time in the clinic, performing surgery on cancer patients, treating women with vulval-vaginal disease, or helping women deliver babies.

In Phillippe’s case, though, sometimes preventing a patient from having her baby is as important as helping her deliver it.

“This morning I was in labor-delivery and did a C-section on a woman at 30 weeks — two-and-a-half months premature,” he says one June afternoon. “She had been in the hospital for two weeks bleeding and contracting. We delayed delivery — she got inhibitors of contractions and medication to try to accelerate the baby’s lung maturity. But she began to have some subtle evidence of infection and other complications, so finally we decided it was just time. The risk of keeping her pregnant was greater than the risk of delivering the baby prematurely.”

This woman isn’t alone: about 12 percent of all pregnancies in the United States end in pre-term labor. Phillippe is trying to find out why this is so. He’s starting by looking at blood.

When doctors induce delivery, they sometimes use a natural hormone called oxytocin that triggers the phosphatidylinositol signaling pathway, releases calcium, and causes the muscles of the uterus to contract and the woman to eventually deliver her baby. Since bleeding in the uterus — usually an indication that the placenta has separated

from the uterine wall — often leads to early labor, Phillippe wanted to see if there was some substance in blood that worked in the same way as oxytocin. He looked at thrombin, the enzyme that helps blood clot, in a rat model, and hit pay dirt. Thrombin did in fact bind to receptors on uterine muscles and, through the same pathway as oxytocin, cause them to contract. He went on to clone and sequence two of the receptors that thrombin binds to — G-protein-coupled protease-activated receptors (PARs) -3 and -4 — in rat uterine smooth muscle.

Additionally, doctors know that inflammation and infection can force a mother to prematurely

deliver her baby; Phillippe discovered that thrombin again plays an integral role in this. He found that a gene in rats called fibrinogen-like protein 2 (fgl-2) is activated by inflammatory cytokines and converts prothrombin to thrombin, resulting in uterine contractions.

“For a woman to survive her pregnancies, she needs to be able to have a mechanism to empty the uterus if major complications, including significant bleeding and/or infection within the uterus, occur,” he says. “Once we understand all of the mechanisms, we can design better interventions.”



In the early morning hours of December 23, 1997, on-call doctor Ira Bernstein, M.D.’82, professor of OB/GYN, was trying to sleep after a particularly stressful day in the lab. “I’d had too much caffeine and holiday chocolate, I was tossing and turning, running through data in my head,” he said. But the data eventually solidified into an idea, and the idea became a hypothesis — a brand new one tackling why preeclampsia — one of the leading causes of maternal mortality in the world — occurs. “I got up and wrote it down at about 2 o’clock in the morning,” he said.

Preeclampsia, which affects about 5 percent of all pregnancies, has been documented for thousands of years, but no one knows why it happens, or which pregnant women will develop it. The condition is characterized by high blood pressure and protein in the urine of expectant mothers and is found only after the twentieth week of pregnancy. It can progress into seizures, hemorrhage, and strokes in the mother and early delivery for the baby — the only cure for the disease. Often the baby is too young to survive.

But on that night in 1997, Bernstein was thinking about the fact that many women with preeclampsia also have low plasma volumes — blood minus the blood cells — circulating in their bodies. Researchers had previously shown that women with a certain type of angiotensinogen gene, which plays a role in fluid balance in the body, are more likely to develop preeclampsia, and Bernstein had just found that those women also had lower plasma volumes before they ever became pregnant.

“My hypothesis was that many of the women who develop preeclampsia develop it not because of an abnormality of pregnancy, but because they entered pregnancy with some different physiology, or phenotype, that led to a poor adaptation to the normal changes of pregnancy,” he said.

Studying women who had never been pregnant, Bernstein set about defining that phenotype. “The primary risk was, we thought, an intolerance to



**Elizabeth Bonney, M.D., studies maternal immune systems.**

plasma volume expansion,” he said.

Plasma volume expansion occurs when, during pregnancy, a woman’s blood supply increases by about 50 percent to nourish her growing

fetus. Bernstein theorizes that in women with low plasma volume, whose blood vessels constrict to maintain a normal blood pressure, this increase in blood supply during pregnancy leads to high blood pressure and preeclampsia, because their vessels cannot adjust to the higher plasma volume.

He has already linked low plasma volume to a higher likelihood of blood vessel constriction, or high sympathetic tone, as well as blood that is more likely to form clots, and blood with higher numbers of inflammatory substances. In addition to his other work on fetal growth and associated abnormalities, Bernstein now has a new five-year longitudinal study

he hopes will solidify his preeclampsia findings — and eventually allow doctors to predict which women will develop the disorder before it occurs.



Associate Professor Elizabeth Bonney, M.D., remembers when the question of why a mother's immune system does not reject its half-foreign fetus first intrigued her.



“I was standing in the middle of labor-delivery at Brigham and Women's Hospital, and there were a huge number of women in labor,” she said. “I said, ‘There's gotta be a way to reject these tumors right now.’ And as soon as it came out of my mouth I said, ‘huh!’”

For years researchers have been struggling to understand why a mother's immune system, which easily recognizes and eliminates dangerous viruses and bacteria, seems to turn a blind eye to the 50 percent foreign tissue developing within its own uterus.

“My question is whether the need to tolerate the fetus has produced an immune system that is different during pregnancy,” says Bonney.

To answer this question, she has been studying T cells and their response to foreign agents. Researchers have hypothesized that pregnancy restricts the mother to only certain classes of

immune response, such as the T helper type 2 response, which is not as toxic to cells as T helper type 1. Because Th2 responses are highly dependent on a substance called IL-4, Bonney tested whether mother mice that lacked IL-4 mounted an immune response to an antigen called H-Y, found on male fetuses, and subsequently delivered fewer male pups. She found that, when injected with H-Y, the mothers did mount an immune response, but they also delivered the same number of male offspring as the controls. She did a similar experiment with IL-10, another Th2 cytokine, and found the same results.

“This suggests that IL-4 and IL-10 in and of themselves may not be critical for maternal tolerance,” she said. “Passing genes onto the next generation is such an important mechanism that it makes sense for there to be overlapping mechanisms to protect the baby from the maternal immune system. My work now asks: Are the T cells activated? Where do they get activated? How do they respond? Do they go to certain places or not?”



The recent groundbreaking Women's Health Initiative (WHI) study found several severe long-term side effects of hormone replacement therapy (HRT) in postmenopausal women, including increased risk of cardiovascular disease and stroke. Associate Professor

Cynthia Sites, M.D., now adds diabetes to that list.

In a randomized, placebo-controlled, double-blind trial of 76 non-obese women, Sites found that women taking HRT had a 17 percent decrease in insulin sensitivity — a precursor to diabetes — after only six months on the drug. The women, however, never actually developed diabetes and, “Fortunately these bad changes completely reversed after that time,” she says.

“After the WHI, it was the patients who helped point the direction of my research,” she said. “They sometimes ask the questions themselves. Other times you try to figure out ways to treat patients and

you realize there isn't a lot of good data out there to explain why you want to treat them in a certain way.”

She saw that many patients were trying soy — which contains a phytoestrogen — to help alleviate their menopausal symptoms. She recently began a three-month study looking at the glucose metabolism and insulin secretion of women drinking a soy shake twice a day that contains both soy protein and isoflavones.

There are no results yet — the study is still “blinded” — but she has high hopes.

“I'd always been very suspicious of complementary or alternative medicine, but I now believe that there's really something there,” she says. “I think there's a desire by doctors to find out what's out there, but it just hasn't been studied enough.”



“A lot of my patients end up being like my adopted family because I treat them for so long,” says Assistant Professor Cheung Wong, M.D. “I see some of these people more than I see my own family.”

Wong heads up Fletcher Allen's gynecologic oncology division, and over 80 percent of the patients he sees are being treated as part of fourteen open studies UVM/FAHC runs through the Gynecologic Oncology Group, a nationwide network of clinical studies funded by the National Cancer Institute. Patients can choose to be treated under the research protocol that best fits their condition, or receive the traditional standard of care. Most choose the experiment, despite the lack of guarantees.

Wong, however, hopes his research can generate more guarantees.

“I think one of the failures we've had is that we've been trying to always treat the cancer but not really trying to understand what causes it to grow,” he said. He studies ovarian cancer, the most common cause of death among all types of gynecologic cancers. Previously known as a “silent disease,” most women do not find out they have it until they reach the later stages, and at that point the five-year survival rate is only 20 to 40 percent. Symptoms range from weight gain, feeling bloated, and

decreased appetite, but many times the complaints are at first dismissed as hormonal changes.

Wong and colleague Karen Lounsbury, Ph.D., assistant professor of pharmacology, decided to test two proteins found in other cancers — VEGF, which promotes blood vessel growth, and HIF-1a — which is a transcription factor that turns on the VEGF gene — for new blood vessel formation in ovarian cancer. This process — called angiogenesis



**Cheung Wong, M.D. and his colleague Karen Lounsbury, Ph.D.**

— must occur in order for tumors to expand. Examining ovaries from women with and without the disease, Wong found that VEGF and HIF-1a were expressed more often in cancerous ovaries than in controls. Additionally, later stage tumors — stage III and IV — had more of the proteins than earlier stages.

In another study of human ovarian cancer cell lines, Wong found that a drug called Procrit could also decrease HIF-1a in hypoxic situations, which reduces VEGF, and thus reduces angiogenesis.

“My ultimate goal is to do translational research — to do experiments in the lab, and then to bring those experiments to the patient's bedside,” he said. “I think that if we can improve survival with what we're doing or give another medication that has very little side effects and can decrease tumor growth, I think that's really the big goal.” **VM**