



An acupuncturist taps needles into a patient's back.

fooled: "The first time someone gave me a dummy needle, I said, 'You made a mistake. You gave me the real needle.'"")

The pill-takers spent eight weeks in treatment, the acupuncture patients six, and all had two appointments a week. (The researchers determined the minimum effective time frame for each treatment and, as a recruitment incentive, offered to treat subjects from each placebo group with the actual therapies once the study ended.) The results, published in the *British Medical Journal*, found that the "improvement slope" of the line that plotted the decrease in pain was more than twice as steep for the subjects who received placebo acupuncture as it was for those who took placebo pills. The sham

acupuncture recipients also scored significantly better than the cornstarch pill takers on the Levine symptom severity scale, which factors in the severity, frequency, and duration of symptoms such as pain, numbness, and weakness. (Kaptchuk declined to say which treatment—real acupuncture or real analgesic—was more effective; that comparison will appear in a forthcoming study.)

For now, Kaptchuk isn't sure why sham

acupuncture seems effective at relieving patients' symptoms. It could be the time invested, or the human contact—the patients in the pill groups received only follow-up phone calls, rather than in-person appointments. But Kaptchuk believes there was something about the act of placing needles on the body, whether those needles pierced the skin or not: "All medicine is a ritual," he says.

Further evidence for the placebo effect appeared in the incidence of side effects among subjects who received such treatments (see "The Nocebo Effect," May-June 2005, page 13). Nearly a fifth of the patients who underwent sham acupuncture reported pain during treatment, while nearly a quarter of the placebo-pill takers reported dry mouth; even more reported feeling drowsy. "We had people on the placebo pill...saying they were so tired they couldn't function," Kaptchuk says. (The solution: cutting the dummy pill in half to provide a smaller "dose.") The side effects reported by the placebo-group subjects exactly mirrored the side effects described by the researchers at the study's onset. That finding "gives us very good evidence that how you tell patients to monitor possible feelings actually precipitates those feelings," Kaptchuk said. It also has direct clinical implications for how doctors and drug companies should describe treatments' side effects. Ironically, Kaptchuk adds, the placebo effect doesn't exist even as a *concept* in Chinese thought, where an effect is an effect, placebo or not.

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CONFLICT EVOLUTION

Prenatal Competition?

COMPLICATIONS from pregnancy and childbirth are the leading cause of death and disability among women between the ages of 15 and 49, according to recent World Bank figures. These grim statistics raise a puzzling evolutionary question: Given the importance of reproduction to species success, why does pregnancy so often go wrong in the ab-

sence of modern medical intervention?

The answer may lie in a once-hidden area of genetic conflict. Professor of organismic and evolutionary biology David Haig argues that the womb is the site of a maternal-fetal struggle over resources, which only in the best cases ends in the stalemate of a successful birth.

Evolutionary science has long recognized the role of natural selection in pro-

ducing instances of post-natal conflict between parent and offspring. In the early 1970s, the Harvard-trained sociobiologist Robert Trivers theorized that offspring may be genetically selected to extract more nourishment from a parent than the parent is genetically selected to give. (Trivers pointed to weaning conflicts and certain whining behaviors in mammals as expressions of these competing fitness interests.) But most biologists have viewed pregnancy as an inherently symbiotic process—one in which the interests of mother and fetus concur to optimize offspring viability and minimize the cost to maternal health.

Haig challenges this harmonious view of pregnancy, based on his research in botany. "Because plants don't have conventional behavioral interactions, parent-offspring conflict in the plant is observed at an anatomical and physiological level," he explains: the embryo in the seed acts chemically to gain nutrients from the maternal tissues, while maternal tissues work to resist excessive demand. The same holds true, he believes, for the cellular interaction between a fetus and its mother.

In both flowering plants and mammalian pregnancies, genetic conflict arises from the competing interests of maternal and paternal genes regarding the volume of nutrients transferred from mother to embryo. The more resources an embryo extracts from its mother, the larger it will be at birth and the better its chances for survival and reproduction. But the greater the nutritional demands of the pregnancy, the greater the cost to the mother's future reproductive potential. Paternal genes in the embryo seek to maximize the acquisition of resources (because the mother's future offspring may have a different father); maternal genes will benefit from a more moderated flow. This inherent competition, Haig contends, explains the evolution of what are known as imprinted genes—

A Thai woman measures the size of her growing belly.

that is, genes that behave differently in an organism depending on whether they were in-


herited from the mother or from the father.

Haig suspects that parent-offspring conflict and genetic imprinting might account for some of the health risks of pregnancy. Experiments on mice have shown that paternal genes control the growth of the placenta, while maternal genes govern much of embryo formation. (When scientists created an embryo with two fathers, for instance, a large and healthy placenta formed, but the embryo itself remained a disorganized cluster of cells.) The placenta—as an agent of paternal genes—invades the maternal tissues in order to parasitize maternal blood supply and support fetal growth. Haig posits that if for some reason the placentation process goes awry, and insufficient nutrients are reaching the fetus, the placenta engages in compensatory tactics—by triggering the activation of genes that enhance blood flow to the fetus at a cost to the mother.

This appears to be the case in preeclampsia—a condition that affects 5 to 10 percent of pregnancies and causes substantial maternal and neonatal morbidity and mortality. It usually occurs near the end of the second trimester and is characterized by a sharp rise in maternal blood pressure, heightened protein levels in the urine, swelling of the feet (edema), and, in advanced cases, obstruction of the blood supply to the mother's vital organs. Because symptoms abate once the placenta is removed, it is



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often necessary to induce a premature delivery to save the mother's life.

Haig believes preeclampsia results from a fetal attempt to amass more resources in conditions of nutritional stress. When problems in placentation, or the presence of more than one fetus, interfere with adequate nutrition, the placenta produces excess amounts of a protein, sFlt₁, that damages the mother's endothelium (the lining of the blood vessels), causing the vessels to constrict. Because "things take the path of least resistance," Haig explains, more blood then begins to flow toward the placenta and away from the maternal tissues. In the

The placenta can trigger the activation of genes that enhance blood flow to the fetus at a cost to the mother.

worst cases, maternal tissues are literally starved of oxygen, causing kidney failure, liver failure, or cerebral hemorrhage.

Preliminary research on levels of sFlt₁ in women with preeclampsia supports Haig's theory. Assistant professor of obstetrics, gynecology, and reproductive biology S. Ananth Karumanchi found that sFlt₁ is highly elevated not only in women who have the condition, but also elevated *before* these women start to show overt symptoms—suggesting that it is a cause rather than a symptom of the disease. The frequency of preeclampsia in twin pregnancies bolsters the argument that the disease may arise when fetal demand outstrips maternal supplies. "If not for maternal-fetal conflict," Haig asks, "why should the placenta be releasing large amounts of sFlt₁ into the maternal circulation? What possible function could that be serving?" At the very moment when logic suggests that natural selection would have most efficiently optimized successful births, Haig's model helps explain the continuing precariousness of reproduction. ~ASHLEY PETTUS

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