

*The New Yorker*  
July 24, 2006

## MEDICAL DISPATCH

### THE PREECLAMPSIA PUZZLE *Making sense of a mysterious pregnancy disorder*

BY JEROME GROOPMAN

In June, 2000, Ananth Karumanchi, a thirty-one-year-old kidney specialist at Beth Israel Deaconess Medical Center, in Boston, read an article in *Nature* about preeclampsia, a poorly understood disorder that affects about five per cent of pregnant women. In the developing world, preeclampsia is one of the leading causes of maternal death; it is thought to kill more than seventy-five thousand women each year. In the United States, where treatment is more readily available, few women die of the disease, but complications – including rupture of the liver, kidney failure, hemorrhage, and stroke – can cause lasting health problems. (In rare cases, patients with preeclampsia develop seizures or lapse into a coma; this is called eclampsia.) The only cure is delivery. “If a woman develops preeclampsia near term, then she is induced to have a delivery or undergoes a Cesarean section,” Benjamin Sachs, the chief of obstetrics and gynecology at Beth Israel Deaconess, told me. “In most cases, as soon as she is delivered we know she will get better. But, if preeclampsia develops early in the pregnancy, then we have a huge challenge, because we have two patients: the mother and the baby. If you deliver the baby early to spare the mother, then you put the baby at risk for the complications of prematurity; if you wait, then the mother can have severe complications and go on to eclampsia.”

Karumanchi had treated several pregnant women with the disorder for hypertension and kidney failure, and he was curious about the disease. The article in *Nature* described a study by researchers at the University of Reading, in England, who claimed that they had found elevated amounts of a protein called neurokinin-B in the blood of eight women with preeclampsia. The researchers reported that when they injected rats with high doses of neurokinin-B the animals’ blood pressure increased. (High blood pressure is a hallmark of the disease.) But the increase was fleeting, and the researchers did not say whether the rats developed other symptoms of preeclampsia, such as protein in the urine and edema (swelling, typically of the face or the limbs). Karumanchi was taken aback. “There was no rationale as to why this protein would be increased in preeclampsia,” he told me. “I said to myself, ‘Wow! If this paper can make it into *Nature*’” – arguably the world’s premier scientific journal – “I am sure we can do better work than that.”

Karumanchi has a full face and a mop of black hair that is graying at the temples, and he wears aviator glasses. He was born in Mayurnathapuram, a village in southern India, and as soon as he completed his medical degree, at the University of Madras, he sought a residency in the United States, only to discover that positions at prestigious programs are rarely given to foreign-

trained doctors. In 1996, after spending three years at Henry Ford Hospital, in inner-city Detroit, he obtained a fellowship to study kidney disease at Beth Israel Deaconess. (I'm on the staff of the hospital, but before writing this article I had never met Karumanchi.) For four years, he worked under Vikas Sukhatme, the chief of nephrology at the hospital, as part of a group of researchers studying the role of angiogenesis-blood-vessel formation-in cancer. But, after reading the article in *Nature*, he decided that he was more interested in figuring out what caused preeclampsia. He didn't know precisely what he would be looking for, but he was confident that he could obtain tissue from women with preeclampsia, since the disease is so common. "There are placentas being thrown in the waste can every day in the hospital," he told Sukhatme. "So why don't I apply some advanced molecular techniques and try to find what's coming from the placenta that might cause preeclampsia?"

Among medical researchers, obstetrics is often regarded as a dead end. "An enterprising young physician-researcher who seeks to make his name in a field faces huge hurdles if he wants to work with pregnant women," Sachs told me. When a pregnant woman takes a drug or undergoes a medical procedure, her fetus may be affected in ways that are difficult to measure or to predict, and, as Sachs pointed out, a fetus cannot consent to participate in a study. "Our ability to truly understand what goes on in the fetus is poor," he said. "You can't predict physiologically how a fetus is going to respond to some treatment given to the mother. So people are very hesitant to do this kind of research, and the committees that protect human subjects are, by and large, gun-shy." The memory of thalidomide, the sedative that was given to thousands of pregnant women in the nineteen-fifties and sixties and caused severe birth defects – including stunted limbs – still shadows the field, and pregnant women are understandably reluctant to volunteer to test new drugs and therapies. "The only large clinical trials that have been going on involve innocuous treatments, like antioxidants, low-dose aspirin, or supplements like calcium," Sachs said.

Disorders of pregnancy receive relatively little research funding from the federal government, even though they exact a considerable medical and financial toll. Preeclampsia is among the most common causes of premature birth in the United States, at an average cost of more than fifty thousand dollars per infant, and doctors now believe that women who suffer complications during pregnancy are at risk for medical problems in the future. According to several recent studies, women who have had preeclampsia are twice as likely as other women to experience hypertension, stroke, and other cardiac conditions. As Christopher Redman, an internist at the John Radcliffe Hospital, in Oxford, England, and a leading expert on preeclampsia, put it, pregnancy is "a stress test for life."

Redman began studying preeclampsia in the early seventies, after some of his patients developed it. He was motivated in part, he said, by the fact that "the state of the art was beggarly." By this time, the disease had been observed for more than two thousand years. As one ancient Greek text put it, "In pregnancy, the onset of drowsy headaches with heaviness is bad; such cases are perhaps liable to some sort of fits at the same time" – apparently an allusion to the seizures that occur when preeclampsia becomes eclampsia. ("Eclampsia" is derived from the Greek word for "a shining forth," and is thought to refer to the bright flashes that women sometimes see during their seizures.) Preeclampsia was defined as a distinct syndrome in the nineteen-twenties – after blood-pressure measurements and tests to detect protein in the urine

became more common – but its cause remained a mystery. Among obstetricians, Sachs said, preeclampsia is known as “the disease of theories.”

One theory, popular in the nineteen-nineties, held that women with preeclampsia were allergic to antigens passed to the fetus through their husbands’ sperm. (Some doctors prescribed oral sex as a means of desensitization.) The notion was largely inspired by epidemiological studies showing that women were more likely to develop preeclampsia during a first pregnancy (requiring minimal prior exposure to a partner’s semen). Moreover, the studies suggested, women who developed the disorder during a second pregnancy were also likely to have changed partners. Other epidemiologists, however, were able to account for this effect by noting that women who had children by two different men tended to experience a longer interval between pregnancies than women who stayed with the same partner. When women who had changed partners were compared with women whose pregnancies were similarly spaced but who had remained with their original partner, the incidence of preeclampsia was the same. (Doctors now believe that the more time that elapses between pregnancies the greater a woman’s risk of developing the disorder.)

Other theories have focussed on the potential of calcium supplements and antioxidants, such as Vitamin C, to prevent the disease. Between 1992 and 1995, the National Institutes of Health conducted a study of forty-five hundred and eighty-nine women to test the calcium hypothesis, but the results were negative. More recently, studies in Britain and Australia have shown that giving pregnant women extra doses of Vitamins C and E does not reduce the risk of preeclampsia, and, according to the British study, might cause some women to have babies with low birth weights.

Sachs recalls attending a scientific meeting in the nineteen-eighties at which a researcher announced that she had discovered a parasite in the placentas of women with preeclampsia. The researcher published her findings in the *American Journal of Obstetrics and Gynecology*, to much astonishment. But the discovery proved to be an illusion: pieces of cotton swabs had become mixed in with the placentas; under the microscope, they looked like parasites. When, in July of 2001, Sukhatme called Sachs on Karumanchi’s behalf to ask for some placentas, Sachs was skeptical. “I moved the phone away from my ear and rolled my eyes, thinking, What is it going to take to make these guys happy? How many specimens?” he said. Ultimately, however, he agreed to provide twenty-one placentas from women with preeclampsia, and seventeen placentas from women who did not have the disease. “Every academic obstetrician would love to find the cause of preeclampsia,” Sachs told me.

**I**n the past fifteen years, there has been a growing consensus that the disorder damages the mother’s endothelial cells, which line blood vessels, including those in the kidney, the liver, and the brain. During the first weeks of pregnancy, fetal cells called trophoblasts invade the inner lining of the mother’s uterus, where they behave much like “an alien parasite,” according to Redman. In normal pregnancies, trophoblasts burrow deep into the uterus, and, through a process that is not well understood, remodel the mother’s arteries. Initially narrow, with thick walls, the vessels around the placenta become wide, with thin walls-and capable of carrying a hundred times more blood. By the twentieth week of pregnancy, the process is largely complete: the fetus

has commandeered enough blood to supply the expanding placenta, on which it depends for nutrients. “There is nothing like it in human biology,” Redman said of the fetus’s ability to transform the mother’s vessels. “Even when the adult heart is pumping at a maximum rate, blood flow to the body may increase at most by fivefold.”

In some women, however, the remodelling process is unsuccessful; the trophoblasts fail to penetrate the mother’s vessels completely, resulting in scant blood flow to the placenta, thus depriving the fetus of oxygen and nutrients. Karumanchi believed, as did other doctors, that in such cases the fetus releases substances from the placenta that attack the mother’s endothelial cells, causing hypertension and protein in her urine. Using a technique called microarray – which involves a “gene chip,” the size of a saltine, that has embedded on it parts of the DNA sequences for thousands of genes – Karumanchi began to evaluate genes that are active in the placenta. He extracted genetic material from the donated placentas and placed it on the chip; genes that were more active in the placenta would stick to the chip in greater numbers.

The microarray experiments revealed more than two hundred genes that were unusually active in the placentas of the women suffering from preeclampsia. Karumanchi discounted all but twenty of these genes, since they involved proteins that could not be released by the placenta into the mother’s bloodstream. Of the remaining genes, he focussed on those which could affect endothelial cells. “It wasn’t really that intelligent,” Karumanchi told me, describing how he narrowed his search. “The microarray just repeatedly came back showing me soluble FLT.”

Soluble FLT is a protein that acts like glue, binding to other proteins in the blood and preventing them from nourishing the endothelial cells; after just two months of work, Karumanchi had a promising result. “I was sifting through all of these data, and I said to myself, ‘It can’t be this obvious,’” he recalled. “‘It can’t be the predominant factor in preeclampsia, because people would have discovered it by now.’ This couldn’t be just waiting for me.”

The next step was to determine whether women with preeclampsia had elevated levels of soluble FLT in their bloodstreams. First, Karumanchi established baseline levels of the protein in eleven healthy pregnant women and in six women who were delivered before term but did not have preeclampsia. Then he measured the amount of soluble FLT in eleven women suffering from mild preeclampsia and in ten women with a severe form of the disease. The women with mild disease had twice as much soluble FLT in their blood as the healthy pregnant women did, and the women with severe disease had five times as much. Karumanchi also tested the women for two proteins that supply their blood vessels with much of their nourishment: VEGF and PlGF. He found that those with preeclampsia had between sixty and eighty-five per cent less of the proteins floating freely in their blood than those without the disease.

**K**arumanchi knew that other researchers were likely to be skeptical of a new theory of preeclampsia; he wanted to show not only that elevated levels of soluble FLT corresponded with decreases in VEGF and PlGF in pregnant women suffering from the disease but also that soluble FLT damaged blood vessels. He decided to grow endothelial cells in laboratory dishes. He filled some dishes with blood serum from women with preeclampsia; the rest he filled with blood serum from healthy pregnant women. The cells in the healthy women’s serum grew into a lattice

of delicate vessels. Those in the preeclamptic women's serum were frayed and disconnected; they looked like spiderwebs that had been torn apart. When Karumanchi added soluble FLT to the healthy women's serum, the fine lattices also became frayed. He wondered whether he could repair vessels by adding abundant amounts of VEGF and PlGF to the dishes. When he did so, the vessels recovered. Karumanchi was delighted. "This meant that we might find a way to treat these women and protect their blood vessels," he said.

He discussed his findings with Vikas Sukhatme, the Beth Israel Deaconess nephrology chief, who told him about a group of kidney-cancer patients who were being treated with an experimental drug called Avastin and had preeclampsia-like symptoms, including hypertension and protein in their urine. Like fetuses, malignant tumors depend on a constant flow of blood for nourishment, and recently researchers have developed medications aimed at reducing the blood supply to tumors by inhibiting the formation of new vessels. Avastin is one such drug, and it works as soluble FLT does, by trapping VEGF and starving endothelial cells. "This is the closest you are going to get to pregnant women, because you are giving a soluble-FLT-like drug to cancer patients," Sukhatme told Karumanchi. (Avastin has since proved to be remarkably effective at killing tumors, although patients must be carefully monitored while they take it. A drug modelled on soluble FLT is now being developed by Regeneron, a biotech company, for use in treating cancer.)

The Avastin trials suggested to Karumanchi that soluble FLT's role in triggering preeclampsia was even more important than he had originally suspected. "I wasn't thinking this would be the causative molecule until I talked to Vikas," he said. Still, as a novice researcher, without a reputation in obstetrics, Karumanchi felt that he needed more data. He decided to test his theory on pregnant rats. Pregnancy in rats lasts about twenty-one days; to mimic the typical course of preeclampsia, he injected five rats after the first week of their pregnancies with a genetically engineered virus that would not make them sick but that contained the soluble-FLT gene and released the protein continually into their bloodstreams. At the beginning of the rats' third trimester – when preeclampsia usually develops in women – a cardiologist working with Karumanchi threaded a device into the rats' carotid arteries to measure their blood pressure. In the control rats, which had received a version of the virus without soluble FLT, the average blood pressure was seventy-five. In the rats that had received soluble FLT, the average blood pressure was between a hundred and nine and a hundred and eighteen – hypertension. Moreover, the rats exposed to soluble FLT had between ten and a hundred times as much protein in their urine as the control rats did.

Finally, Karumanchi asked Frank Epstein, a nephrologist, and Isaac Stillman, a renal pathologist, both at Beth Israel Deaconess, to examine tissue samples taken from the rats' kidneys. "That's preeclampsia," Stillman said when he saw the samples under a microscope. "The rats have the same lesions in the kidney that women with the disease have."

Paradoxically, Karumanchi's experiments showed that the placentas of women with preeclampsia had normal amounts of neurokinin-B, the protein touted by the University of Reading researchers as contributing to the disease. "You know, in science, it's not whether you publish a paper in *Nature* or not," Karumanchi told me. "It's whether the data can be reproduced by others consistently. The truth eventually comes out. And then I thought, If those guys can

send this paper to *Nature*, then we should publish the protein we found. Maybe I was a little bit arrogant and a little bit naïve.”

In July, 2002, Karumanchi submitted a paper on soluble FLT to *Nature*, and it was rejected. “You should have seen the comments from the reviewers,” he said. “The general tone was ‘This guy has never published in the field.’” One reviewer complained that there were insufficient data from humans and thus no way to be sure that soluble FLT caused preeclampsia. Epstein consoled Karumanchi by saying that he had fulfilled “Koch’s postulates” – a reference to the Nobel laureate Robert Koch, who argued that the cause of a disease could be established by injecting animals with bacteria from sick patients. “You’ve shown that this protein is high in women with preeclampsia,” Epstein told Karumanchi. “You’ve taken the protein out and injected it into animals, and you’ve shown that the animals developed the key features of preeclampsia.” Though two of the reviewers were dismissive, a third wrote that he thought Karumanchi’s paper was extremely promising. “He was thoughtful, and pushed me to think more deeply about how to prove my hypothesis,” Karumanchi said.

Karumanchi rewrote his paper, taking some of the reviewers’ objections into account, and the following March he published it in *The Journal of Clinical Investigation*. In the same issue was an article by Susan Quaggin, a nephrologist at the University of Toronto, describing her successful effort to genetically engineer a mouse so that only small amounts of VEGF were produced in its kidneys; the animal developed lesions similar to those in women with preeclampsia. “It was done totally independent of my work,” Karumanchi said. “Another young assistant professor starting out – I thought this was extraordinary.”

The articles attracted considerable notice. Critics argued that, although Karumanchi’s data were impressive, they failed to explain every aspect of the disorder. None of his rats had shown decreases in red blood cells and platelets, or damage to the liver, which are characteristic of severe forms of the disease. What’s more, a few of the women in his study with mild preeclampsia had levels of soluble FLT that were only modestly elevated and not clearly sufficient to explain their disease.

Karumanchi speculated that the placenta released proteins in addition to soluble FLT that were potentially toxic to the mother. Or perhaps, he thought, preeclampsia was actually a number of distinct disorders. Even before his paper appeared, he had begun to apply for grant money so that he could study more women with the disease. “The first grant that I sent to N.I.H. was turned down,” he recalled. He revised his proposal and resubmitted it, but it was again rejected. Finally, he submitted a new proposal, to the National Institute of Diabetes and Digestive and Kidney Diseases, which focussed on the effects of hypertension on the kidneys and made no mention of placentas or pregnant women. “That got funded immediately,” Karumanchi said. “You would think that with all of the crazy ideas that have been proposed around preeclampsia, even if mine turned out to be wrong it had a strong biological basis, and you would think that I would have been given a chance.”

The largest placebo-controlled clinical trial on preeclampsia conducted in the United States was the 1992-95 calcium-supplement study, which was supervised by Richard Levine, an epidemiologist at the National Institute for Child Health and Human Development, at the N.I.H. “The idea that calcium was important in preeclampsia was being promoted by someone who had a career interest in calcium,” Levine told me. “And the biological basis for it was remote, at best.” Although the results of the trial were negative, Levine preserved the blood and urine specimens that his research team had collected from the more than forty-five hundred pregnant women who participated. The team had also compiled a detailed medical history for each woman and gathered information about their ethnic backgrounds and their smoking and drinking habits. “It was the most anally conducted trial that was done in the preeclampsia area, so we got excellent data,” Levine said.

Other researchers had since approached him, hoping to borrow the specimens, but Levine found few of the proposals compelling. In one instance, he used the specimens to test a theory favored by Christopher Redman, the Oxford internist, and several other researchers, which claimed that preeclampsia occurred when debris released by the placenta triggered an inflammatory reaction in the mother. But analyses of the mothers’ blood revealed no evidence of inflammation or of excess fetal DNA. Then, in the summer of 2002, an obstetrician from Beth Israel Deaconess sent Levine a draft of Karumanchi’s paper on soluble FLT. “I read it once,” Levine told me. “Then I read it a second time. And I thought it was the best piece of work, the most exciting thing that I ever read.”

Several months later, he met with Karumanchi in Boston and agreed to provide his blood and urine specimens and to collaborate on research. “We opened up the bank,” Levine said. Using the N.I.H. specimens, Karumanchi and Levine found that in nearly all the women who had developed preeclampsia the amount of soluble FLT in their blood had been elevated about five weeks before they experienced any symptoms. This meant that physicians might be able to predict which pregnant women would develop the disorder before they became sick, and to monitor them more closely. In February, 2004, Levine and Karumanchi published these findings in *The New England Journal of Medicine*. The article was accompanied by an editorial that noted its importance for most women at risk for preeclampsia, but emphasized that there were some patients with the syndrome whose illness could not be explained solely on the basis of how much soluble FLT was in their blood. Much but not all of the disease’s biology had been unravelled.

Soon after the article appeared, David Haig, a professor of evolutionary biology at Harvard, knocked on the door of Karumanchi’s office and introduced himself. “I loved your paper,” Haig said. For more than a decade, Haig has been elaborating a theory that pregnancy represents a “maternal-fetal conflict,” in which the mother and her fetus compete for oxygen and precious nutrients. “Most pregnancies are successful, but there is a very high frequency of problems,” Haig told me. “Why should that be, since pregnancies are very, very central to fitness? You would think it would be one of the most perfected systems. I think there are so many problems because natural selection so many times is working at cross-purposes on genes in fetuses and genes in mothers.”

Most biologists have assumed that a mother and her fetus have an underlying “harmony of interests,” because the fetus carries its mother’s genes. But “the argument for harmony is

flawed,” Haig has written, “because a mother and fetus do not carry identical sets of genes. . . . An infant’s prospects may be bleak if its mother dies, but children have survived without mothers. Thus, if childbirth threatens the lives of the baby and its mother, the baby may struggle for its own survival, even if this increases the risk to its mother.” In his published articles, Haig cites several instances of maternal-fetal conflict, in which the developing baby’s genes work against the health of the mother. Aside from preeclampsia, the most common is gestational diabetes, which occurs when a pregnant woman, typically during the second trimester, becomes resistant to insulin and has blood-glucose levels in the diabetic range. Women with the condition tend to deliver babies that are larger than average – perhaps, Haig speculates, because the placenta releases hormones into the mother’s bloodstream that, by blocking the effects of insulin, increase the amount of sugar delivered to the fetus.

Haig’s other examples are much rarer. In Beckwith-Wiedemann syndrome, which is sometimes caused when the fetus inherits an extra copy of the eleventh chromosome from its father, the fetus can grow so large that it threatens the mother’s health. (Haig believes that the excessive growth is triggered by a gene called IGF2, which may act to increase the invasive behavior of trophoblasts.) More disturbing is what’s known as a “complete hydatidiform mole,” in which, owing to a gross genetic aberration, a placenta develops without a fetus attached to it. Hydatidiform moles contain two sets of paternal chromosomes and no maternal DNA in the nuclei of their cells. In some cases, the moles become malignant, and the placenta attacks the area beyond the uterus, spreading trophoblast cells into the abdomen and the vital organs. Such moles must be surgically removed or the woman will die.

Haig told me that preeclampsia is not known to occur naturally in any species other than humans. Moreover, he said, unlike the offspring of other primates, human babies are born with thick layers of fat, which represent excess nutrients that the fetus has successfully diverted from the mother. Haig saw in Karumanchi’s research an extreme version of maternal-fetal conflict: the fetus, by releasing soluble FLT into the mother’s bloodstream, causes her vessels to constrict, diverting blood to the placenta at the expense of her organs. “The way the fetus remodels the mother’s arteries is like an open bank account,” Karumanchi said. “Like a credit card with no limit, drawing on all the maternal resources.”

Karumanchi believes that women who have closely spaced pregnancies have a lower risk of developing preeclampsia because the blood vessels in their uteruses don’t have a chance to return to their pre-pregnancy shape. They are able to supply relatively robust amounts of blood to the fetus early in pregnancy, thus minimizing the likelihood of oxygen deprivation and the need for the placenta to produce soluble FLT. “People in the field say that the uterine vessels can be thought of as a panty-hose stocking,” Karumanchi said. “Once you expand them, it takes a long time for them to return to their original shape.”

**I**n the past three years, at least fifteen groups of researchers have reproduced Karumanchi’s main findings, and several drug companies are now trying to turn his insights into diagnostic tests and therapies. Scios, a division of Johnson & Johnson, produces a version of VEGF – it was originally developed as a treatment for cardiovascular disease – and in 2003 the company negotiated with Beth Israel Deaconess for the rights to market the drug to women with



preeclampsia. (The hospital has applied for a patent on methods of diagnosing and treating the disease; Karumanchi, Sukhatme, and Susan Maynard, a nephrologist who assisted Karumanchi in his research, will receive a percentage of any revenues.)

It's still not clear why some women develop preeclampsia and others don't. Phyllis August, a nephrologist at New York-Presbyterian Hospital, in Manhattan, who specializes in pregnancy and hypertension, believes that the explanation may be found in the underlying health of the mother's blood vessels. Women who already suffer from medical conditions involving their blood vessels – such as diabetes, hypertension, kidney disease, or abnormalities of their clotting proteins – seem to be more susceptible to preeclampsia, August said.

Karumanchi suspects that women whose vessels are normal but who nevertheless develop the disease may have inherited a predisposition to the disorder. He is collaborating with Levine to study the DNA of hundreds of women in the hope of discovering the genetic basis of preeclampsia, and he has continued to seek corroboration for his theory about soluble FLT's role in triggering the disease. One tantalizing piece of evidence comes from a rare genetic syndrome called trisomy 13, in which a fetus receives three copies of the thirteenth chromosome. The syndrome, which is ultimately fatal, can be diagnosed early in pregnancy, through amniocentesis, and most women with affected fetuses choose abortion. Of the women who decide to carry such fetuses to term, the incidence of preeclampsia is more than twenty-five per cent. It turns out that the gene for soluble FLT is on the thirteenth chromosome, and Karumanchi, in a paper that he published last year, showed that women carrying fetuses with trisomy 13 also have large amounts of the protein in their bloodstreams.

For several decades, epidemiological studies have shown that pregnant women who smoke have a low incidence of preeclampsia, and recently Karumanchi and Levine found that the placentas of such women produce less soluble FLT than the placentas of nonsmokers do. "It may be that nicotine or carbon monoxide reduces production of soluble FLT by the placenta," Karumanchi told me.

Last year, Karumanchi reviewed the data from his initial microarray studies and identified a second protein that could damage endothelial cells: endoglin. He found that women with severe preeclampsia had markedly elevated amounts of endoglin in their bloodstreams. (Women with mild disease had less.) When Karumanchi gave both soluble FLT and endoglin to pregnant rats, the animals developed features of severe preeclampsia: their livers were damaged and their red blood cells and platelets were decimated. "There seems to be a family of synergistic proteins – soluble FLT and endoglin are two of them," Karumanchi said. "I think these two account for nearly all the symptoms in preeclampsia." Karumanchi's paper on endoglin appeared in the June issue of *Nature Medicine*. (He and Levine have also found that women who smoke have lower levels of endoglin between the tenth and twentieth weeks of pregnancy.)

Drug-based therapies for preeclampsia may still be years away. But, when I spoke to Karumanchi a few weeks ago, he sounded optimistic. He told me that Scios had recently announced that it could reverse symptoms of preeclampsia in rats by administering its VEGF drug – the first step toward testing it in humans. He also mentioned that several other companies

have begun work on a diagnostic test that would allow doctors to measure women's levels of soluble FLT and PlGF early in pregnancy, and thus to predict whether they are likely to develop preeclampsia. "In the last decade, seven hundred mothers died of preeclampsia in the United States," Karumanchi said. "I don't see any more experiments that need to be done. Now is the moment; we've got to grab it and run with it. My feeling is that it would be almost a crime not to try it."