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## Mutation Can Cause Dangerously High Blood Pressure During Pregnancy

A single mutation in a protein that regulates the body's salt balance can produce dangerously high blood pressure in pregnant women, say researchers from the Howard Hughes Medical Institute (HHMI) at Yale University School of Medicine.

The discovery opens the way to understanding the molecular origins of a form of hypertension that threatens some eight million pregnant women and their infants each year.

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— **Richard P. Lifton**

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In an article published in the July 7, 2000, issue of the journal *Science*, HHMI investigators Richard P. Lifton and Paul B. Sigler and colleagues at Yale University and Albert Einstein College of Medicine report that a mutation renders the mineralocorticoid receptor more sensitive to progesterone, a hormone that is produced in abundance during pregnancy. The *Science* article is dedicated to the memory of Sigler, who died on January 11, 2000.

When the mineralocorticoid receptor is triggered by aldosterone, its normal binding partner, it switches on the cellular machinery that causes kidney cells to reabsorb more salt, ultimately raising blood pressure. Lifton's group found that when women who have the faulty receptor undergo the hundred-fold rise in progesterone that occurs during pregnancy, progesterone overstimulates the receptor, causing salt retention, expansion of blood plasma volume and skyrocketing blood pressure.

"Pregnancy-induced hypertension is an important clinical problem, but nobody has really had a good handle on the biochemical pathways involved in any form of the disorder," said Lifton. "While our study certainly doesn't prove the cause of all cases of such hypertension, we have found the first molecular mechanism by which women can develop severe hypertension in

pregnancy. And that mechanism is an abnormal link between two normal physiologic pathways."

Despite his team's findings, Lifton remains cautious about recommending any immediate changes in how hypertension is treated in pregnant women.

"During normal pregnancy, plasma volume expands substantially. There has always been concern about giving pregnant women medications that would decrease their intravascular volume," he said. "This finding raises the possibility that in a select group of patients with pregnancy-related hypertension, one might consider a carefully controlled clinical trial using salt restriction with diuretic medications." Lifton said that such therapies could first be tested in a genetically altered mouse that bears a similar mutation in the mineralocorticoid receptor gene.

Ironically, the research that yielded the new insight into pregnancy-related hypertension began with a 15-year-old boy. In sequencing DNA from patients with early-onset hypertension, David Geller, a research fellow in Lifton's laboratory, discovered that the boy carried a single mutation in the mineralocorticoid receptor gene.

"At that point, there was no compelling evidence to suggest that the mutation actually was the cause of his hypertension," said Lifton. Thus, the scientists launched both clinical studies of the boy's family and biochemical studies to pinpoint the effects of the mutation.

In tracing the inheritance pattern of the mutated gene, the scientists found that all members of the boy's family who had inherited the mutation had early onset of high blood pressure. And when the scientists used cell culture studies to compare the activity of normal and mutant receptors, they found the mutant receptor to be switched on, even in the absence of a triggering hormone.

"But most surprising was that when we added progesterone, a steroid that normally binds to, but doesn't activate, the mineralocorticoid receptor, we found that it was a potent activator of the mutant receptor," said Lifton. This finding suggested that pregnant women with the mutant receptor would have completely activated receptors, so Lifton and his colleagues next examined the medical histories of those women in the family who had been pregnant.

"When we followed the clinical course of women who had this mutation, we found that they had developed extremely severe hypertension in pregnancy," said Lifton. The researchers found that in all instances the hypertension was so severe that it necessitated preterm delivery.

Molecular characterization of the faulty receptor by Lifton and his colleagues revealed a key aspect of receptor activation that is shared by many related receptors, suggesting a new approach to development of steroid hormone antagonists.

Lifton also believes that further studies may reveal other defects that permit normal hormones of pregnancy to activate the salt reabsorption machinery and cause hypertension. "This finding has opened the door a crack, giving us a first glimpse of a mechanism underlying hypertension in pregnancy," said Lifton. "Knowing that one form of pregnancy-related hypertension can be caused by the abnormal action of a normal hormone, raises the question of whether other forms of hypertension act by a similar mechanism. There's still a long research path to be followed before a disease as complicated as hypertension is understood in satisfactory detail."