

JUNE 30, 1998

Seeking Clues to High Blood Pressure

Some people can pour table salt on their meals for years without suffering negative consequences. For others, habitual use of salt is poisonous, causing blood pressure to skyrocket and increasing the risk of heart disease, stroke or kidney failure.

Physicians want to know who is at the mercy of salt and why?

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— **Theodore Kurtz**

Richard Lifton, a Hughes investigator at Yale University, thinks the answer is to be found in each person's genes. In studying newborn infants with a genetic disorder that causes low blood pressure, Lifton's research team traced the cause of the disorder to an abnormal protein that helps to process sodium in the kidney.

Absence of the protein leads to a rare but mild low blood pressure disorder in newborns that results in loss of salt from the blood. Studying how this protein, the mineralocorticoid receptor (MLR), regulates sodium channels in the kidney may offer more general clues about how blood pressure is controlled by the kidney.

The research may also explain how hypertension develops in the 50 million Americans with the disease. "Our studies raise the question of whether more common variants of the same gene could be responsible for more modest effects on blood pressure in the general public," says Lifton, whose report appears on the July, 1998, issue of *Nature Genetics*. "It's another piece of the puzzle."

Lifton and his colleagues have now identified nine genes that play a role in the biological "pathway" used by kidneys to maintain a balance of salt and water in the blood and body. Too much salt in the blood results in a higher volume of blood fluid, which increases pressure on the circulatory system and causes hypertension. Too little salt in the blood reduces the volume of blood

serum, resulting in low blood pressure.

The trail leading to MLR began when Lifton's team studied five families in which children were born with a dominant form of pseudohypoaldosteronism type 1 (PHA1), a potentially deadly disease of newborns. Since Lifton's group had shown that PHA1 families with a recessive form of the disease had mutations in a sodium channel, Lifton assumed that they would find that PHA1 was caused by different mutations in that same channel.

To their surprise, however, the culprit was found to be MLR, the regulator of these sodium channels. MLR mutations were found both in families in which the mutant gene was transmitted from affected parents to their children. MLR was also mutated spontaneously in a child born to two parents who did not have PHA1.

Lifton notes that patients with MLR mutations who survive the neonatal period improve clinically with age. They are usually free of symptoms by age 10, but they continue to show biochemical signs of the disease. These findings indicate the important role of MLR in regulating of blood pressure, Lifton says. "It raises the possibility that there may be more common and more subtle abnormalities not only in this gene but in other genes along this pathway that accounts for many variations in blood pressure regulation," he says.

Theodore Kurtz, an expert in hypertension at the University of California, San Francisco, calls Lifton's study "outstanding" because of its widespread implications. "The results dovetail perfectly with a series of other compelling studies by Lifton and colleagues indicating that genetic variation in the kidney's ability to regulate blood pressure. These studies will be key to understanding why hypertension runs in families and why people vary in their blood pressure response to changes in dietary salt," Kurtz said.