ity of effective treatments for PMS is an important advance. In contrast to the situation a decade ago, there are now treatments for PMS that have stood the test of rigorous trials and that enable us to reduce the considerable suffering of women with this disorder. Although we have not identified the source of the "sensitivity" described by von Feuchtersleben, at least we are finally rediscovering the fact that it exists.

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THE CLINICAL IMPORTANCE OF THE URINARY EXCRETION OF AQUAPORIN-2

THE movement of water across the cell membranes of an organism is of central importance in many functions. The notion that the permeability of some tissues to water is too great to be accounted for by lipid-mediated diffusion has been central to the development of the concept of channel-mediated water transport. Despite the general acceptance of the existence of water-channel proteins, their molecular identification has long remained elusive. The first water-channel protein, originally known as CHIP28 (an acronym for channel-forming integral membrane protein of 28 kd), was discovered during studies of erythrocyte blood-group proteins.[1] Its expression in xenopus oocytes results in a 30-fold increase in osmotic permeability to water but in no increase in permeability to ions.[2]

At present, five structurally related mammalian water-channel proteins have been identified, named aquaporin-1 through aquaporin-5. In view of the large quantity of water filtered and reabsorbed in mammalian kidneys, it is not surprising that aquaporins play an important part in the renal handling of water. Aquaporins 1, 2, and 3 are highly expressed in the kidney,[1,3,4] aquaporin-4 is expressed most abundantly in the brain,[5] and aquaporin-5 is most prominent in salivary, lacrimal, and respiratory tissues.[6] In the kidney, aquaporin-1 (the former CHIP28) is responsible for the constitutively high permeability to water of the proximal tubule and the thin descending limb of Henle's loop.[1] It was therefore surprising that persons homozygous for mutations in the aquaporin-1 gene resulting in the lack of aquaporin-1 water channels were clinically normal.[7] The only explanation for the normal clinical phenotype in such persons seems to be the existence of another mechanism, one capable of compensating for the absence of functional aquaporin-1 proteins.

Aquaporin-2, the vasopressin-regulated water channel in the collecting duct, has a primary role in concentrating the urine. An increase in serum osmolality or a decrease in circulating volume leads to the secretion of arginine vasopressin from the neurohypophysis. The binding of vasopressin to vasopressin V_2 receptors in the principal cells of the cortical collecting duct and cells in the inner medullary collecting duct triggers a cyclic-AMP–dependent chain of events that results in increased reabsorption of water. Aquaporin-2 resides in intracytoplasmic vesicles in these cells. The binding of vasopressin to its receptors promotes the insertion of these aquaporin-2–containing vesicles into the normally watertight luminal membrane, increasing the permeability of the membrane to water. When stimulation by vasopressin is terminated, aquaporin-2 is removed from the luminal membrane by endocytosis of the vesicles. This controlled movement of aquaporin-2–containing vesicles between the luminal membrane and the cytoplasm is known as the "membrane shuttle" mechanism. The efflux of water at the basolateral membrane of collecting-duct cells appears to be mediated by aquaporin-3.[4]

The link between aquaporin-2 and the regulation of the renal excretion of water by vasopressin was firmly established when it was discovered that the aquaporin-2 gene is mutated in patients with congenital nephrogenic diabetes insipidus. This hereditary renal disease is characterized by insensitivity of the collecting-duct cells to the antidiuretic effect of vasopressin. As a result, the kidney loses its concentrating ability and the patient excretes large volumes of hypotonic urine, a condition that may lead to severe dehydration. In most families, nephrogenic diabetes insipidus is caused by a mutation in the gene for the vasopressin V_2 receptor on the X chromosome, resulting in an X-linked recessive mode of inheritance. In some patients, however, nephrogenic diabetes insipidus is inherited as an autosomal trait. Recently, mutations in the autosomal gene coding for aquaporin-2 were found in four patients with neph-

rogenic diabetes insipidus.[8] Expression studies in xenopus oocytes showed that the mutated water channels are indeed nonfunctional.

In this issue of the *Journal,* Kanno et al.[9] report that aquaporin-2 is detectable in urine in both soluble and membrane-bound forms and that the urinary excretion of aquaporin-2 reflects the physiologic regulation of aquaporin-2 water channels by vasopressin. Thus, dehydration or infusion with the V_2 analogue desmopressin (1-desamino-8-D-arginine vasopressin, or DDAVP) significantly increased the urinary excretion of aquaporin-2 in normal subjects. The authors suggest that this increase results from increased delivery of aquaporin-2 to the luminal membrane. In five patients with vasopressin deficiency (central diabetes insipidus), the basal urinary excretion of aquaporin-2 was very low during water restriction but was four to six times higher after the subcutaneous injection of vasopressin, a finding consistent with the presence of an intact urine-concentrating mechanism in the kidney. The increase in the urinary excretion of aquaporin-2 after the injection of vasopressin in the patients with central diabetes insipidus probably resulted from increased expression of aquaporin-2 in the kidney medulla. In patients with either X-linked or autosomal nephrogenic diabetes insipidus, however, there was no increase in the urinary excretion of aquaporin-2 in response to desmopressin. The authors conclude that such excretion can be used as an index of the action of vasopressin and may help in differentiating between nephrogenic and central diabetes insipidus. The demonstration of aquaporin-2 in the urine of humans is of interest because it indicates that some particulate aquaporin-2 is secreted into the lumen, a possibility not considered in the membrane-shuttle hypothesis.

The conclusion that measuring urinary aquaporin-2 excretion may aid in the differential diagnosis of congenital diabetes insipidus may be somewhat exaggerated. In most patients nephrogenic and central diabetes insipidus can be differentiated easily by measuring urinary osmolality in response to the intranasal administration of desmopressin. Patients with congenital nephrogenic diabetes insipidus have no increase in urinary osmolality after the administration of desmopressin, whereas patients with central diabetes insipidus have a substantial increase. Therefore, the measurement of aquaporin-2 excretion is not necessary, and in addition it is too complicated at present for routine clinical use.

Nevertheless, the possibility of using urinary excretion of aquaporin-2 as an index of the action of vasopressin in the kidney is exciting in view of the recent observations that the long-term treatment of rats with lithium causes a marked decrease in the expression of the aquaporin-2 protein in medullary collecting-duct cells and that it results in severe nephrogenic diabetes insipidus.[10] Thus, lithium-induced nephrogenic diabetes insipidus may be due to the decreased availability of aquaporin-2 water channels. It would be interesting to know whether there is a decrease in the urinary excretion of aquaporin-2 in patients receiving prolonged lithium treatment, because nephrogenic diabetes insipidus develops in approximately 20 percent of patients who receive lithium for affective disorders. If so, measuring the urinary excretion of aquaporin-2 would be an elegant method of examining whether other forms of secondary nephrogenic diabetes insipidus, such as those caused by tetracyclines, hypokalemia, hypercalcemia, juvenile nephronophthisis, or postobstructive diuresis, are also associated with reductions in either the expression of aquaporin-2 or its delivery to the luminal membrane.

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SIGNALING PATHWAYS AND *c-fos* TRANSCRIPTIONAL RESPONSE — LINKS TO INHERITED DISEASES

INTRACELLULAR signal-transduction pathways have central roles in processes such as growth, development, cellular differentiation, and neurotransmission. Alterations in the levels of various substances involved in signal-transduction pathways have profound effects on cellular functions, and many inherited diseases are caused by mutations that affect key components of signaling pathways.[1]

There are two major signal-transduction pathways, one using cyclic AMP (cAMP) and the other diacylglycerol. Each pathway is characterized by its specific protein kinase, protein kinase A and protein kinase C, respectively. The fine modulation of gene expression is achieved by the complex interactions between membrane receptors and the cytoplasmic constituents of cells. Among these constituents, the products of onco-