TABLE 404-1 CAUSES OF DIABETES INSIPIDUS

Pituitary diabetes insipidus
- Acquired
  - Head trauma (closed and penetrating) including pituitary surgery
  - Neoplasms
    - Primary
      - Craniopharyngioma
      - Pituitary adenoma (suprasellar)
      - Dysgerminoma
      - Meningioma
    - Metastatic (lung, breast)
    - Hematologic (lymphoma, leukemia)
  - Granulomas
    - Sarcoidosis
    - Histiocytosis
    - Xanthoma disseminatum
  - Infectious
    - Chronic meningitis
    - Viral encephalitis
    - Toxoplasmosis
  - Inflammatory
    - Lymphocytic infundibuloneurohypophysitis
    - Granulomatosis with polyangiitis (Wegener's)
    - Lupus erythematosus
    - Scleroderma
  - Chemical toxins
    - Tetrodotoxin
    - Snake venom
  - Vascular
    - Sheehan's syndrome
    - Aneurysm (internal carotid)
    - Aortocoronary bypass
    - Hypoxic encephalopathy
  - Idiopathic
- Congenital malformations
  - Septo-optic dysplasia
  - Midline craniofacial defects
  - Holoprosencephaly
  - Hypogenesis, ectopia of pituitary
- Genetic
  - Autosomal dominant (AVP-neu*rophysin gene)*
  - Autosomal recessive
  - Type A *(AVP-neurophysin gene)*
  - Type B *(AVP-neurophysin gene)*
  - Type C *(Wolfram's [4p-WFS 1] gene)*
  - X-linked recessive (Xq28)

Gestational diabetes insipidus
- Pregnancy (second and third trimesters)

Nephrogenic diabetes insipidus
- Acquired
  - Drugs
    - Lithium
    - Demeclocycline
    - Methoxyflurane
    - Amphotericin B
    - Aminoglycosides
    - Cisplatin
    - Rifampin
    - Foscarnet
  - Metabolic
    - Hypercalcemia, hypercalciuria
    - Hypokalemia
  - Obstruction (ureter or urethra)
  - Vascular
    - Sickle cell disease and trait
    - Ischemia (acute tubular necrosis)
  - Granulomas
    - Sarcoidosis
  - Neoplasms
    - Sarcoma
  - Infiltration
    - Amyloidosis
  - Idiopathic
- Genetic
  - X-linked recessive *(AVP receptor-2 gene)*
  - Autosomal recessive *(AQP2 gene)*
  - Autosomal dominant *(AQP2 gene)*

Primary polydipsia
- Acquired
  - Psychogenic
    - Schizophrenia
    - Obsessive compulsive disorder
  - Dipsogenic (abnormal thirst)
    - Granulomas (sarcoidosis)
    - Infectious (tuberculous meningitis)
    - Head trauma (closed and penetrating)
    - Demyelination (multiple sclerosis)
    - Drugs
    - Idiopathic
    - Iatrogenic

In pituitary and nephrogenic DI, the severity of the defect in AVP secretion or action varies significantly from patient to patient. In some, the defect is so severe that it cannot be overcome by even an intense stimulus such as nausea or severe dehydration. In others, the defect in AVP secretion or action is incomplete, and a modest stimulus such as a few hours of fluid deprivation, smoking, or a vasovagal reaction can raise urine osmolarity as high as 800 mosmol/L. However, even when the defects are partial, the relation of urine osmolarity to plasma AVP in patients with nephrogenic DI **(Fig. 404-3*A*)** or of plasma AVP to plasma osmolarity and sodium in patients with pituitary DI **(Fig. 404-3*B*)** is subnormal.

In primary polydipsia, the pathogenesis of the polydipsia and polyuria is the reverse of that in pituitary, nephrogenic, and gestational DI. In primary polydipsia, an abnormality in cognition or thirst causes excessive intake of fluids and an increase in body water that reduces plasma osmolarity/sodium, AVP secretion, and urinary concentration. Dilution of the urine, in turn, results in a compensatory increase in urinary free-water excretion that usually offsets the increase in intake and stabilizes plasma osmolarity/sodium at a level only 1–2% below basal. Thus, hyponatremia or clinically appreciable overhydration is uncommon unless the polydipsia is very severe or the compensatory water diuresis is impaired by a drug or disease that stimulates or mimics the antiduretic effect of endogenous AVP. A rise in plasma osmolarity and sodium produced by fluid deprivation or hypertonic saline infusion increases plasma AVP normally. However, the resultant increase in urine concentration is often subnormal because polyuria per se temporarily reduces the capacity of the kidney to concentrate the urine. Thus, the maximum level of urine osmolarity achieved during fluid deprivation is often indistinguishable from that in patients with partial pituitary or partial nephrogenic DI.

Differential Diagnosis When symptoms of urinary frequency, enuresis, nocturia, and/or persistent thirst are present in the absence of glucosuria, the possibility of DI should be evaluated by collecting a 24-h urine on ad libitum fluid intake. If the volume exceeds 50 mL/kg per day (3500 mL in a 70-kg male) and the osmolarity is below 300 mosmol/L, DI is confirmed and the patient should be evaluated further to determine the type in order to select the appropriate therapy.

The type of DI can sometimes be inferred from the clinical setting or medical history. Often, however, such information is lacking, ambiguous, or misleading, and other approaches to differential diagnosis are needed. If basal plasma osmolarity and sodium are within normal limits, the traditional approach is to determine the effect of fluid deprivation and injection of antidiuretic hormone on urine osmolarity. This approach suffices for differential diagnosis *if* fluid deprivation raises plasma osmolarity and sodium above the normal range *without* inducing concentration of the urine. In that event, primary polydipsia and partial defects in AVP secretion and action are excluded, and the effect on urine osmolarity of injecting 2 μg of the AVP analogue, desmopressin, indicates whether the patient has severe pituitary DI or severe nephrogenic DI. However, this approach is of little or no diagnostic value if fluid deprivation results in concentration of the urine because the increases in urine osmolarity achieved both before and after the injection of desmopressin are similar in patients with *partial* pituitary DI, *partial* nephrogenic DI, and primary polydipsia. These disorders can be differentiated by measuring plasma AVP during fluid deprivation and relating it to the concurrent level of plasma and urine osmolarity (Fig. 404-3). However, this approach does not always differentiate clearly between partial pituitary DI and primary polydipsia unless the measurement is made when plasma osmolarity and sodium are at or above the normal range. This level is difficult to achieve by fluid deprivation alone once urinary concentration occurs. Therefore it is usually necessary to give a short infusion of 3% saline condition (0.1 mL/kg body weight per minute for 60 to 90 minutes) and repeat the measurement of plasma AVP.

A simpler but equally reliable way to differentiate between pituitary DI, nephrogenic DI, and primary polydipsia is to measure basal plasma