blank. Correction is not required for phenolphthalein glucuronide, since spontaneous hydrolysis of the substrate does not occur.

Acid Phosphatase.—The most suitable substrate for this enzyme is *p*-nitrophenyl phosphate (Bessey *et al.*, 1946). The incubating medium contains 0.1 ml. of urine, 1 ml. of *p*-nitrophenyl phosphate (1 mg./1 ml. distilled water), 3.4 ml. of 0.1 *N* acetate buffer of *p*H 4.5, and 0.5 ml. of 0.05 *M* $MgSO_4$. After incubating for 10 minutes at 37° C. 0.1 ml. of 100% NaOH is added to stop the reaction and develop the colour of the free *p*-nitrophenol. The solution is then centrifuged to remove magnesium phosphate and magnesium hydroxide, and the absorbance measured at 400 mμ. Correction factors were applied for the interference absorption produced by urine pigments and *p*-nitrophenyl phosphate. The following reference blanks were therefore used: (1) 0.1 ml. of urine + 1 ml. of distilled water, and (2) 0.1 ml. of distilled water + 1 ml. of *p*-nitrophenyl phosphate.

Alkaline Phosphatase.—The method is identical with that for acid phosphatase except that the 3.4 ml. of acetate buffer is replaced by 3.4 ml. of 0.1 *M* tris + 0.1 *N* HCl buffer of *p*H 8.8.

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Medical Memoranda

Ectopic Pinealoma with Adipsia and Hypernatraemia

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Hypernatraemia has been reported in association with many intracranial lesions, and several different mechanisms for its production have been postulated (Zierler, 1958 ; Welt, 1962 ; Bartter, 1963). The case described below illustrates the major importance of loss of thirst perception in the causation of this syndrome.

CASE REPORT

In 1961, when aged 13, the patient presented at the Hospital for Sick Children, London (Dr. G. H. Newns), with dwarfism. Her development had been normal until the age of 7. Investigations at this time showed plasma cortisol concentrations of 5.6 and 4.6 μg./100 ml., and low urinary 17-hydroxycorticoid excretion. There was no significant response to metyrapone, but there was a response to corticotrophin stimulation. Plasma protein-bound iodine was 4.3 μg./100 ml. Her urine volumes ranged from 1,480 to 3,555 ml., and a diagnosis of hypopituitary dwarfism with diabetes insipidus was made. She was given posterior pituitary snuff and two courses of growth hormone between 1962 and 1965. On this she grew 3.4 cm. (Case 20, Tanner and Whitehouse, 1967). In 1963 she stopped taking pituitary snuff, and in 1965 a random 24-hour urine volume was only 1,240 ml.

In 1966 the vision in the left eye deteriorated and she was readmitted to the Hospital for Sick Children. Air encephalography showed a suprasellar mass. At craniotomy (Mr. K. Till) a tumour, which had destroyed the diaphragma sellae, extended into the posterior fossa, and surrounded the left optic nerve, was removed piecemeal with part of the pituitary gland. Histologically it was a pinealoma.

Cortisone was given to cover the operation but was reduced postoperatively when she was given corticotrophin gel. After operation she had a large diuresis (4–5 l.) and was given vasopressin. She was then transferred to University College Hospital for radiotherapy (Dr. J. N. Godlee), after which corticotrophin injections were stopped.

Two months later she felt tired and depressed. Her plasma sodium concentration was found to be 166 mEq/l. and she was readmitted.

On examination she was afebrile and alert. She was still dwarfed (height 4 ft. 7 in.; 140 cm.) and prepubertal. She was not dehydrated clinically. Her blood pressure was 90/60 mm. Hg lying and 70/40 when standing. Thirst was always denied on direct questioning, and she drank little.

Evidence of Hypopituitarism.—Chronological age 18 years, bone age 12 years. Urinary 17-ketogenic steroids 1.7 mg./24 hr., 17-ketogenic steroids 2.3 mg./24 hr. Plasma cortisol concentration at 9 a.m. 2.3 μg./100 ml. Metyrapone suppression test: urinary 17-ketogenic steroids on control day 2.5 mg./24 hr., on metyrapone 2.5 mg./24 hr. Plasma protein-bound iodine 3.4 μg./100 ml.

Evidence of Diabetes Insipidus.—When untreated the 24-hour urine volume ranged from 1,600 to 2,100 ml. After 15 hours' dehydration urine osmolality was 154 mOsm/kg. H_2O with a plasma osmolality of 336, but when given 20 mU of vasopressin intravenously the urine osmolality rose from 42 to 515 mOsm/kg. H_2O. In four hours 86% of a water load of 20 ml./kg. was excreted. The urine volume rose to 6,250 ml./24 hours with an osmolality of 64 mOsm/kg. when she was given 100 mg. of cortisone acetate. On a replacement dose of 37.5 mg. and vasopressin nasal spray twice daily the urine volume fell to 3,200 ml. with an osmolality of 160 mOsm/kg.

Renal Function.—The creatinine clearance rose from 29 ml./min. (=41 ml./min. corrected to 1.73 sq. m.) when untreated to 62 ml./min. (corrected=88 ml./min.) after nine months on 25 mg. of cortisone acetate; it was not improved by 100 mg. Her urine volume from 9 a.m. to 9 p.m. was 1,900 ml. and from 9 p.m. to 9 a.m. 2,500 ml., but the sodium excretion was not reversed (68 mEq by day and 60 mEq by night). Proteinuria, glycosuria, and amino-aciduria were absent.

Other Investigations.—Urinary aldosterone excretion was 4.3 μg./24 hr. At maximum dehydration it was 3.8 μg./24 hr. When the plasma sodium concentration was 154 mEq/l. the plasma volume was 1,530 ml. (predicted volume=1,660 ml.).

Hypernatraemia and Hyperosmolality.—The plasma sodium concentration was 166 mEq/l. and the plasma osmolality 336 mOsm/kg. H_2O when untreated, but the sodium fell to 146 mEq/l. when a forced water intake and 25 mg. of cortisone acetate were given.

Discussion

The plasma sodium concentration is maintained within a narrow range by regulation of water excretion, mediated by antidiuretic hormone, and of water intake activated by the sensation of thirst. In a few recorded cases of hypernatraemia the administration of water has failed to reduce the plasma sodium concentration to within the normal range; the water is merely excreted. These patients are without clinical features of dehydration, have a normal circulating volume, and are capable of secreting and responding to antidiuretic hormone. It is assumed that the critical level for the osmoreceptor response has been set abnormally high, and so this phenomenon has been termed "essential hypernatraemia" (Welt, 1962). A variant with a contracted extracellular space has recently been described (Goldberg *et al.*, 1967). This explanation does not apply to our patient, as she was incapable of secreting antidiuretic hormone, and increase of water intake of sufficient degree eventually led to reduction of plasma sodium concentration to within the normal range.

Hypernatraemia does not develop in patients with diabetes insipidus unless their thirst perception is lost. The presence of a "thirst centre" in the brain was first postulated by Nothnagel in 1881. He observed that a man kicked in the head by a horse developed extreme thirst within half an hour. Evidence for an area in the hypothalamus controlling thirst has been provided by the classical physiological methods of localized electrical stimulation and placing discrete lesions (Fitzsimons, 1966). Lesions in the hypothalamus may destroy a thirst centre or interrupt pathways passing through this area.

Patients with lesions in the hypothalamus sometimes provide a clinical replica of these experiments—for example, the patient described by Kourilsky *et al.* (1942) who lost her intense thirst as soon as an arachnoid cyst impinging on the hypothalamus was punctured.

Hyperosmolality of the plasma is the chief stimulus to the thirst centre, the cells of which presumably act as osmoreceptors. They are situated in the vicinity of the osmoreceptors of Verney (1947) and of the paraventricular nuclei responsible for the secretion of vasopressin.

Adipsia is not uncommon in patients with so-called ectopic pinealomas, but in most recorded cases the loss of thirst has been permanent (Leaf, 1962; Avioli *et al.*, 1962; Linquette *et al.*, 1967). Return of thirst after the administration of cortisone in patients hypophysectomized for breast cancer has been reported (Decourt *et al.*, 1957), as has the return of thirst in an adipsic patient with Hand–Schüller–Christian syndrome after radiotherapy (Kastin *et al.*, 1965). However, absence of thirst persisted when prednisone was given in the case described by Avioli *et al.* (1962).

The administration of cortisone acetate to our patient, which increased the daily urine volume to six litres, was also followed by a return of thirst, so that she was able to maintain plasma sodium concentration within normal limits on a voluntary intake. On two later occasions when cortisone replacement was inadequate thirst was again lost and hypernatraemia ensued, but increase of replacement therapy once more resulted in a return of thirst. This relation between thirst and the administration of steroids is of interest. Patients with anterior pituitary insufficiency are not thirsty or hungry and pass small urine volumes, in part because of the low solute load and in part because of reduced glomerular filtration rate. They also tend to have hyponatraemia, and so have no osmotic stimulus to thirst perception. The hypernatraemia of our patient should have been a stimulus to make her drink, and yet she was adipsic until given cortisone acetate. One possible explanation is that the adipsia resulted from damage to thirst centres in the anterior hypothalamus by oedema secondary to the presence of remnants of tumour or to damage by radiotherapy, and that the extent of the oedema was reduced when cortisone was given. Alternatively, the presence of cortisone may increase the sensitivity of the thirst centre or in some way be necessary for the functioning of the centre. The latter explanation seems more likely because she continued to lose thirst when steroid-deficient even two years after her operation.

Unexpectedly aldosterone production did not rise after fluid deprivation, normally a stimulus to increased aldosterone secretion. Various explanations can be offered. Corticotrophin is a known trophic hormone for aldosterone secretion. The level of aldosterone secretion is reduced in patients with hypopituitarism, but only to the extent of 60% of normal (Ross *et al.*, 1960). Our patient's urinary aldosterone excretion was only about 25% of normal, and it failed to rise despite the presence of diabetes insipidus.

The pineal gland has been stated to secrete a substance which stimulates aldosterone secretion (Farrell, 1959), but pinealectomy does not diminish the aldosterone response to sodium deprivation (Wurtman *et al.*, 1960), and patients with calcified pineal glands have normal aldosterone secretion.

The hypernatraemia itself may have been the cause. The cells of the juxtaglomerular apparatus may function as osmoreceptors (Fisher *et al.*, 1965). There is experimental evidence that aldosterone secretion is decreased when the plasma sodium concentration is raised experimentally (Coghlan *et al.*, 1960; Davis *et al.*, 1963), but no information appears to be available for man. Our patient may demonstrate the human counterpart of these experiments.

The contracted plasma volume should be a stimulus to aldosterone secretion, and this has been noted in some hypernatraemic patients (Kennedy *et al.*, 1962; Bartter, 1963), but was not found in our patient. It is of interest to compare this response with that present in hyponatraemic patients with an expanded plasma volume, where aldosterone secretion is also low (Ross, 1963). This indicates that plasma sodium concentration and plasma volume are independent variables concerned with the regulation of aldosterone secretion.

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