TABLE

Necropsy Findings in 7 Cases with Congenital Abnormalities of Both Pituitary and Adrenal Glands

Author	Sex	Pituitary	Adrenals*	Testes	Penis	Ovaries	Thyroid
Blizzard and Alberts (1956)	M	Absent	Hypoplastic	Hypoplastic	Small	—	Hypoplastic
Brewer (1957)	F	Absent	Hypoplastic	—	—	Hypoplastic	Hypoplastic
Reid (1960)	M	Absent	Hypoplastic	Hypoplastic	Normal	—	Hypoplastic
Present case	M	Absent	Hypoplastic	Normal	Small	—	Normal
Dunn (1966)	F	Absent	Absent	—	—	Not recorded	—
Mosier (1956)	F } F } Twins	Hypoplastic Not recorded	Hypoplastic Hypoplastic	— —	— —	Normal Not recorded	Hypoplastic Not recorded

*All adrenals found to be devoid of fetal cortex.

medulla was also more abundant and better developed than is usual in the newborn. The thyroid was normal macroscopically and microscopically. The testes lay in the inguinal canals and were of normal size. Their histological appearance was probably within normal limits, though there was a moderate amount of loose connective tissue between the tubules. Interstitial cells were present, but not abundant.

Comment

The cause of this rare syndrome is unknown. The pituitary gland probably develops normally at first and subsequently atrophies, for the pituitary gland is required for early masculinization of the external genitalia, at least in experimental animals (Jost, 1953). The small size of the penis may reflect inadequate pituitary activity later in fetal life.

Normal development of the male genitalia in fetal life also depends on adequate adrenal and testicular function. Inadequate adrenal function, which occurs in the variety of congenital adrenal hyperplasia due to 3- β -ol-dehydrogenase deficiency, causes hypospadias and incomplete fusion of the labioscrotal folds (Hamilton and Brush, 1964). Inadequate testicular function leads to the development of the internal and external genitalia along female lines, regardless of chromosomal sex (Jost, 1953).

It is interesting that, despite the small size of the adrenal glands in our subject, adrenal activity in fetal life was sufficient to promote development of the external genitalia, and, after birth, to prevent hypoglycaemia and hyponatraemia from occurring.

Adrenal hypoplasia is presumably due to lack of adrenocorticotrophic hormone, for it is always found in association with pituitary hypoplasia in anencephaly (Potter, 1961). The thyroid gland may also be hypoplastic (Table) due to lack of thyroid stimulating hormone.

Summary

A male infant with a very small penis, who died

at 48 hours of age, is described. At necropsy no pituitary gland was found, and the adrenal glands were hypoplastic. The finding of a very small penis may prove to be an external marker of a lethal congenital abnormality.

We thank Dr. Paul Rayner for helpful advice.

REFERENCES

Blizzard, R. M., and Alberts, A. (1956). Hypopituitarism, hypoadrenalism, and hypogonadism in the newborn infant. *Journal of Pediatrics*, **48**, 782.
Brewer, D. B. (1957). Congenital absence of the pituitary gland and its consequences. *Journal of Pathology and Bacteriology*, **73**, 59.
Dunn, J. M. (1966). Anterior pituitary and adrenal absence in a live-born normocephalic infant. *American Journal of Obstetrics and Gynecology*, **96**, 893.
Hamilton, W., and Brush, M. G. (1964). Four clinical variants of congenital adrenal hyperplasia. *Archives of Disease in Childhood*, **39**, 66.
Jost, A. (1953). Problems of fetal endocrinology: the gonadal and hypophyseal hormones. *Recent Progress in Hormone Research* **8**, 379.
Mosier, H. D. (1956). Hypoplasia of the pituitary and adrenal cortex: report of occurrence in twin siblings and autopsy findings. *Journal of Pediatrics*, **48**, 633.
Potter, E. L. (1961). *Pathology of the Fetus and Infant*, 2nd ed., p. 331. Year Book Medical Publishers, Chicago.
Reid, J. D., (1960). Congenital absence of the pituitary gland. *Journal of Pediatrics*, **56**, 658.

M. W. MONCRIEFF,* D. S. HILL,† J. ARCHER, and L. J. H. ARTHUR
Children's Hospital, Derby.

*Correspondence to Dr. M. W. Moncrieff.
†Present address: Jessop Hospital for Women, Sheffield.

**Failure to Detect the Carrier
in Congenital Nephrogenic
Diabetes Insipidus**

Congenital nephrogenic diabetes insipidus is known to give rise to stunting of growth and possible mental retardation. Prolonged polyuria may result in urinary tract dilatation and hydrone-

phrosis. The need for accurate genetic counselling in affected families thus becomes apparent. Unfortunately, there is no agreement as to the mechanisms of inheritance. Most writers have felt a sex-linked gene to be involved (Forssman, 1945; Carter and Simpkins, 1956; West and Kramer, 1955; Emery, 1971). Cannon (1955) reported a large family in which 5 affected males had 6 affected sons, and he proposed that the trait was an autosomal dominant with almost complete penetrance in the male and with a variable degree of expressivity in the female. Robinson and Kaplan (1960) reviewed the previous literature and agreed with his proposal.

While males are usually severely affected, female patients or 'carriers'—and a distinction between these two states may be difficult—are generally less severely affected, and additionally show a great deal of variability in their symptoms or measurable concentration defect. Carter and Simpkins (1956), assuming a sex-linked gene, investigated 4 mothers of 4 male patients and found a urinary concentration defect in that after a 12-hour overnight thirst the urine SG did not rise above 1.018, equivalent to a urine osmolality of approximately 750 mOsm/kg from the figures of Edelmann *et al.* (1967). They concluded that the failure to achieve SG 1.018 on three such occasions indicated a heterozygous state, but they did not exclude the possibility that experience with subsequent families might show that some carriers could not be detected. Nevertheless, Fraser Roberts writes in a current textbook of genetics 'the gene is sex-linked, the heterozygous women can almost invariably or perhaps always be recognized by their failure to produce a normally concentrated urine' (Roberts, 1970). We wish to briefly record an instance where the possibility envisaged by Carter and Simpkins did in fact arise and where genetic advice was given and subsequently proven to be inaccurate.

Methods

Affected males were thirsted to a 5% loss of body weight and the subsequent specimen of urine examined. Carriers were thirsted overnight for 12 hours at home; the overnight sample of urine was discarded and the subsequent specimen retained for examination. Urine osmolality was estimated on 0.2 ml specimens by the 'Advanced' osmometer.

Case Reports

Case 1. A male, born 1 November 1967, was admitted to hospital on account of weight loss and vomiting at age 14 days. He was found to be dehydrated with serum electrolytes as follows: sodium 162 mEq/l.; potassium 6.6 mEq/l.; chloride 132 mEq/l.; CO_2CP 13.4 mEq/l.; BUN 53 mg/100 ml; glucose 58 mg/100 ml.

Urinalysis showed no abnormal constituents, but 24-hour collections of urine showed a daily output of between 500 and 600 ml with an osmolality of 136 mOsm/kg. After thirsting, the urine osmolality rose only to 150 mOsm/kg, while the injection of 0.4 IU pitressin tannate in oil had a similar lack of response. A diagnosis of congenital nephrogenic diabetes insipidus was made and he was treated with low solute feeds and 5% glucose. Adequate hydration was difficult to maintain and he remained in hospital until the age of 11 weeks when he succumbed to an *Esch. coli* septicaemia with peritonitis and meningitis.

Case 2. A male, born 26 July 1969, the cousin (mother's sister's son) of Case 1. This patient was referred to hospital at the age of 12 days on account of weight loss. He was found to be dehydrated and in view of the family history was immediately thought to have congenital nephrogenic diabetes insipidus. The electrolytes on admission were: sodium 162 mEq/l.; potassium 4.2 mEq/l.; chloride 140 mEq/l.; CO_2CP 12.1 mEq/l.; BUN 48 mg/100 ml. The urine had no abnormal constituents but after rehydration he began to secrete between 1500 and 2500 ml urine per 24 hours at a concentration never greater than 150 mOsm/kg. There was no significant response to thirsting nor to pitressin. Subsequent progress during management with low solute feeds and extra water as required has been poor. When aged 16 months he weighed only 6.8 kg and had required many admissions for rehydration.

Case 3. The 28-year-old mother of Case 1. She has enjoyed good health throughout life and the urine concentrating ability was measured only after the death of her son when genetic advice had been requested. Morning urine specimens were measured on three occasions, the concentrations being 868, 964, and 983 mOsm/kg. Her serum osmolality was 274 mOsm/kg, while blood urea and electrolytes were within normal limits.

Case 4. The 24-year-old mother of Case 2 and sister of Case 3. This girl has at no time experienced symptoms of polyuria or polydipsia, even during pregnancy. After the overnight thirst on three occasions, her urine concentrations were 619, 526, and 676 mOsm/kg respectively. The serum osmolality was 282 mOsm/kg and blood urea and electrolytes were within normal limits.

Case 5. The 49-year-old grandmother of Cases 1 and 2, and mother of Cases 3 and 4. Throughout her life this woman had experienced symptoms of polyuria, nocturia, and polydipsia, but had never sought medical advice. During the previous 5 years she had developed signs and symptoms of hypertensive heart disease and during investigation was found to have a normal urinalysis and a normal intravenous pyelogram. Urine osmolality after an overnight thirst was on two occasions 221 and 140 mOsm/kg. Serum osmolality was 310 mOsm/kg; serum sodium 151 mEq/l.; potassium 4.1

mEq/l.; chloride 107 mEq/l.; CO_2CP 26.7 mEq/l.; BUN 14.7 mg/100 ml. She became much upset over the genetic implications and we acceded to the request of her family not to carry investigations further.

Discussion

Investigation of Case 3 has confirmed that a female carrier of congenital nephrogenic diabetes insipidus may not be detectable by some currently accepted criteria. On the basis of her normal urinary concentration she was initially reassured that the disease would not recur in any subsequent children and it was concluded that Case 1 had resulted from a mutation. Subsequently the appearance of the disease in Case 2 and the discovery of the concentrating defects in Cases 4 and 5 led to a rapid reappraisal, and counselling appropriate to the assumption of X-linked inheritance has now been given.

The family tree (Fig.) emphasizes that genetic counselling in congenital nephrogenic diabetes insipidus with respect to suspected carriers should depend not only on the results of an overnight thirst, but also on a wider investigation of the immediate family. Such investigation may result in the discovery of hitherto unrecognized patients who are carriers and appropriate advice may be given. These cases are similar to previously reported families in that males have been severely affected while female 'carriers' show a marked variability of affliction. Such variability may result from the randomization of the X chromosome according to the Lyon hypothesis, but is equally in keeping with the views of Cannon (1955) and Robinson and Kaplan (1960) as mentioned above.

Summary

A further example of a family containing several cases of congenital nephrogenic diabetes insipidus is described. It appears that currently accepted

methods of carrier detection are not wholly satisfactory and recourse must always be had to examination of the whole family before appropriate genetic advice is given.

REFERENCES

- Cannon, J. F. (1955). Diabetes insipidus: clinical and experimental studies with consideration of genetic relationships. *Archives of Internal Medicine*, **96**, 215.
Carter, C., and Simpkins, M. (1956). The 'carrier' state in nephrogenic diabetes insipidus. *Lancet*, **2**, 1069.
Edelmann, C. M., Jr., Barnett, H. L., Stark, H., Boichis, H., and Soriano, J. R. (1967). A standardized test of renal concentrating capacity in children. *American Journal of Diseases of Children*, **114**, 639.
Emery, A. E. H. (1971). *Elements of Medical Genetics*, 2nd ed., p. 194. Livingstone, Edinburgh.
Forssman, H. (1945). On hereditary diabetes insipidus with special regard to a sex-linked form. *Acta Medica Scandinavica*, Suppl. **159**.
Roberts, J. A. F. (1970). *An Introduction to Medical Genetics*, 5th ed., p. 188. Oxford University Press, London.
Robinson, M. G., and Kaplan, S. A. (1960). Inheritance of vasopressin-resistant ('nephrogenic') diabetes insipidus. *American Journal of Diseases of Children*, **99**, 164.
West, J. R., and Kramer, J. G. (1955). Nephrogenic diabetes insipidus. *Pediatrics*, **15**, 424.

W. S. UTTLEY* and D. THISTLETHWAITE
Department of Child Life and Health, University of Edinburgh, and the Royal Hospital for Sick Children, Edinburgh, Scotland.

*Correspondence to Dr. W. S. Uttley, Department of Child Life and Health, University of Edinburgh, Edinburgh.

Hyperlipidaemia During Persistent Peritoneal Dialysis

The technique of peritoneal dialysis is well established as the dialytic method of choice in children. In the present case an infant with anuria survived for 99 days by peritoneal dialysis alone: an unusual finding of hyperlipidaemia was observed during her clinical course.

Case Report

A 10-month-old girl of Japanese extraction was referred to us because of anuria after nephrectomy of the left side was performed in another hospital for a severe congenital hydronephrosis. On admission, clinical and laboratory findings were those of uraemia, and therefore peritoneal dialysis was performed immediately. No artificial kidney suitable for the infant was available, so peritoneal dialysis was conducted every day except on Sunday for 99 days, while awaiting cadaver transplantation. On the 5th day after admission the right kidney was found to be non-functional and multicystic after an open renal biopsy. During the treatment serum urea varied from 60 to 99 mg/100 ml, serum sodium from 125 to 140 mEq/l., potassium from 3.6 to 5.8 mEq/l., chloride from 89 to 101 mEq/l., calcium from 7.2 to 8.7 mg/100 ml, and phosphorus from 8.6 to 9.7 mg/100 ml. Several antihypertensive drugs were used to maintain the blood pressure within

FIG.—Pedigree of affected family showing urinary concentration (mOsm/kg) average after thirsting.