mologists tell patients that they have haemorrhages which can lead to blindness and should go to their doctor for a check for better control. Some of these patients arrive in extreme agitation—"I'm going blind." If Mr. X has reported only micro-aneurysms, fleck exudates, and no vessel changes—blindness in younger diabetics being caused more by neovascularization and haemorrhages than by straightforward retinal changes (Whittington, 1961)—I am often able truthfully to reassure the patients that I have seen such minor changes off and on for the last five years, and that with care these may not progress and affect their eyesight: not invariably true, but a very proper white lie, in my opinion, to reduce tension in patients already alerted into full care of their diabetes.

The renal complication is the most threatening, and when increasing renal and vascular complications with added oedema develop into the dreaded Kimmelstiel-Wilson syndrome I usually hope that a quiet uraemic end takes them before they pass through the depression of blindness. Only one death from Kimmelstiel-Wilson disease occurred in this series, and this woman lived so long and actively as to teach me to be very cautious in my prognosis of the duration and value of life even when the blood urea has been over 100 mg./100 ml.

Control Reduces Complications

Contrary opinions have been expressed about this by different authorities, perhaps because it is difficult to gauge and compare control either by periods in hospital or by a frequent check on out-patients. On the other hand, insulin reactions ("hypos"), confirmed by a blood-sugar test or merely from the story of a trusted patient of its timing with a sugar-free urine, are easy to recognize; and it is certain that, apart from actual symptoms, these patients are often in the normal blood-sugar area of non-diabetic metabolism. I have found that such patients among these 90 cases have had few or milder complications, if any. This has been the experience of Sven Johnsson (1960), whose summary I quote: "8 patients who had hypo-

glycaemic coma on more than 20 occasions were all free from proteinuria after 25 years of diabetes mellitus, and 4 had normal ocular fundi and the remainder normal vision and only a few micro-aneurysms." His findings, like mine, suggest that hypoglycaemia—evidence of control—minimizes complications; but I think, from my experience, that the occurrence of 20 comas is carrying hypoglycaemias unnecessarily far.

To understand how periods of control brought about by hypoglycaemia could prevent retinal complications, it is interesting to examine an aetiological suggestion of Ashton (1959) as a basis for further thought and research. "In the metabolic defect of diabetes the retina, being so particularly dependent upon the breakdown of glucose as an energy source and having a higher glycolytic rate than almost any other tissue, is subject to a chronic metabolic disturbance leading gradually to failure of osmotic regulation with the inhibition of water and an increase in retinal turgescence. The resulting rise in tissue tension impedes the capillary circulation, stagnation and anoxia result, and micro-aneurysms form."

This state of "chronic abnormal metabolism" is abolished, and indeed normalized twice a day, by treatment with soluble insulin, properly used, with greater certainty and with less risk of seriously prolonged hypoglycaemia than by any one-dose-a-day treatment.

However, diabetic control, so far as it is possible, can hardly be the whole answer to visual troubles, as there are exceptions in both directions: some, careless and uncontrolled, retain perfect vision; and one of the best-controlled young diabetics I know—my lab. man—went blind from neovascularization trouble without renal or vascular complications (Whittington, 1961), and his case is one of the major puzzles and disappointments of the first 40 years of my practice.

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DIABETES MELLITUS AND INSIPIDUS IN TWO SISTERS

BY

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The occurrence of diabetes mellitus and diabetes insipidus in the same patient is rare. Only 43 cases have been reported previously in the literature available to us; of these, only five have been in children (Natelson, 1954; Rowntree and Poppiti, 1954; Randall *et al.*, 1959; Riggs and Randall, 1960). The familial occurrence of these two diseases has not previously been reported. This article records the case histories of two sisters, each of whom has been shown to have diabetes caused by disorders of both carbohydrate metabolism and the neurohypophysis.

Case 1

The patient was born on May 7, 1951. Thirst and polyuria were first noticed at 4 months, when her mother had difficulty in maintaining a supply of dry napkins.

She was first admitted to Great Ormond Street at the age of 3 years with the complaints of thirst, polyuria, anorexia,

and constipation. The only previous illness was measles at 18 months. On examination her blood-pressure was 110/80 and no abnormal physical signs were found. Tests of renal function showed nothing abnormal. An intravenous pyelogram showed bilateral hydronephrosis and hydroureters. Cystoscopy revealed hypertrophy of the bladder, normal ureteric orifices, and no hypertrophy of the bladder-neck. Skull x-ray films were normal.

From the results of "pitressin" and water-deprivation tests the patient was considered to have diabetes insipidus. Treatment with intranasal pitressin was begun and improvement of symptoms was striking. Intramuscular aqueous pitressin tannate, 1 unit b.d., was substituted later, and this gave adequate control. A second intravenous pyelogram four months later showed considerably less dilatation of the ureters and no good evidence of hydronephrosis. As the child grew older the pitressin had to be increased to 10 units of pitressin tannate in oil, given every other day.

At the age of 9 years the child developed an abscess at an injection site and was admitted to hospital. On routine examination of the urine glycosuria was discovered, and further investigations showed that she had diabetes mellitus as well as diabetes insipidus. The diabetes mellitus was controlled on an unrestricted diet and 32 units of insulin zinc suspension (I.Z.S.) daily.

In April, 1962, at the age of 11 years, the child's vision began to deteriorate. There were no associated neurological symptoms. She was admitted to Great Ormond Street in June for further investigations.

The patient was fair-haired and of asthenic build. Her height was 139 cm. and weight 30.5 kg. These figures fall on the 25th percentile (Tanner's charts). Her visual acuity was 6/18 in both eyes. The visual fields were normal. The optic disks showed bilateral optic atrophy, but the fundi were otherwise normal. The blood-pressure was 115/80. No other abnormal physical signs were detected.

After her admission it was found that considerable glycosuria was present. She was placed on a diet of 160 g. of carbohydrate a day with unrestricted protein and fats. The insulin dose was gradually increased to 64 units of I.Z.S. daily, at which stage the glycosuria was eliminated, and it became possible to begin investigations.

Soon after her admission the pitressin therapy was discontinued. A dramatic change in the degree of polyuria was noted. Whereas on pitressin every other day her urine volume varied from 2 to 4 l./day with a specific gravity of 1010, without pitressin the urine volume rose to 8 to 12 l./day (see Fig. 1), and the specific gravity fell to 1000.

FIG. 1.—Case 1. Daily urinary volume. *On these days pitressin was used prior to general anaesthesia for renal biopsy, etc.

Renal-function Tests.—Repeated urine analyses were negative for albumin and cells. The blood urea on several occasions was 29 mg./100 ml. Urea clearance, using the maximal formula, was 50 and creatinine clearance was 122 ml./min./1.73 sq. m. The urinary amino-acid excretion pattern was normal. An intravenous pyelogram was performed after pitressin had been given to prevent dehydration. The x-ray films showed bilateral hydronephrosis and hydroureters. A micturating cystogram showed a bladder capacity of 350 ml., a regular smooth bladder outline, and no ureteric reflux, either at rest or on micturition. On cystoscopy the bladder-neck appeared normal. Retrograde pyelograms showed a moderate degree of dilatation of the urinary tract on both sides (Fig. 2). Tissue obtained by renal biopsy (needle) showed changes consistent with early diabetic glomerulosclerosis, but the renal tubules were normal.

Pituitary-function Tests.—A water-deprivation test was performed. Within two and a half hours her weight fell by 2 kg. and she became severely dehydrated clinically. Her urine output remained constant at first and then fell markedly, while her serum sodium rose to 153 mEq/l. The test had to be discontinued at this stage (see Table). Skull x-ray films showed no abnormal calcification or lesion of the pituitary fossa or

calvarium. The bone age at the wrist was consistent with her chronological age. The cerebrospinal fluid was normal and a lumbar air encephalogram demonstrated no abnormality of

Water-deprivation Tests

Case	Time	Weight		Serum Sodium	
		Before	After	Before	After
1	2½ hours	32.4 kg.	30.2 kg.	149 mEq/l.	153 mEq/l.
2	6 "	51.8 "	50.0 "	139 "	150 "

FIG. 2.—Case 1. Retrograde pyelogram.

FIG. 3.—Case 1. Pitressin test.

the ventricular system. The pitressin test was carried out. The recommended dose of 5 units of pitressin tannate in oil per 70 kg. body weight—that is, 2 units for this patient—produced no effect. The test was repeated using 6 units, with

doubtful results. With 10 units the urine volume fell from about 400 ml./hour to the lowest level of 20 ml./hour, and the specific gravity of the urine rose to a maximum of 1023. No glycosuria was present throughout the test (see Fig. 3).

Hypertonic-saline tests (Hickey-Hare or Carter-Robbins) were also performed. The child drank 600 ml. of water five minutes before the tests were made. The rate of urine output remained constant before, during, and after the infusion of hypertonic saline, indicating no pituitary response to hyperosmolarity of the blood (see Fig. 4).

FIG. 4.—Hypertonic saline tests. In both patients urinary specific gravity remained constant at 1001 throughout the test.

Other Tests.—These included a serum calcium estimation, which was 9.6 mg./100 ml., and serum phosphate, which was 5.1 mg./100 ml. The Heaf test and blood Wassermann reaction were negative. Her haemoglobin was 14.3 g./100 ml. The blood film showed normal red cells, white cells, and platelets.

Treatment.—The child was given 10 units of pitressin tannate in oil every other day. Her urine output fell to 2–3 l./day and the specific gravity rose to 1010. There was no change in the requirements for management of the diabetes mellitus.

Case 2

This child, the elder sister of Case 1, was born on March 13, 1948. She remained well until 5 years of age, when glycosuria was observed during her admission to hospital for tonsillectomy. In retrospect it appeared that polyuria had been present for some time. Further investigations showed that she had diabetes mellitus, and insulin treatment was started. Despite adequate control of the child's urinary sugar, polyuria continued to increase. At the age of 7 years, by which time it was known that her younger sister had diabetes insipidus, the patient was admitted to another hospital for further investigation. A diagnosis of diabetes insipidus was made. She was treated with pitressin tannate in oil, 5 units on alternate days. By the age of 12 years this dose had to be increased to 10 units on alternate days in order to control the degree of polyuria.

In June, 1962, at the age of 14 years, she was admitted to Great Ormond Street with her younger sister.

Examination showed her to be a moderately obese, short, dark-haired girl. Her weight was 55.3 kg.—that is, on the 75th percentile—and her height was 150 cm.—that is, on the 10th percentile (Tanner's charts). Her blood-pressure was 110/80. Her visual acuity was 6/9 in both eyes. Visual fields and optic fundi and disks were normal. No abnormal physical signs were detected.

Considerable glycosuria was present on admission. She was placed on a diet of 200 g. of carbohydrate per day with unrestricted protein and fats. After her admission blood-sugar

estimations taken throughout the day fluctuated between 250 and 360 mg./100 ml. A twice-daily regimen of soluble insulin 30 units and isophane insulin 36 units, given morning and evening, was required to eliminate the glycosuria.

The pitressin therapy was discontinued soon after admission. The urine volume rose from 2–3 to 8–10 l./day (see Fig. 5), and the specific gravity fell from 1015 to 1002.

Renal-function Tests.—Repeated urine analysis was negative for cells and protein. Blood urea was 35 mg./100 ml. on several occasions. Urea clearance, using the maximal formula, was 54 and creatinine clearance 63 ml./min./1.73 sq. m. The urinary amino-acid-excretion pattern was normal on chromatography. An intravenous pyelogram was normal. A micturating cystogram showed a bladder capacity of 400 ml. There was a normal bladder outline, with no ureteric reflux and no obstruction of the bladder-neck. A needle biopsy of the kidney showed normal glomeruli and tubules on microscopy.

FIG. 5.—Case 2. Daily urinary volume. *On these days pitressin was used prior to general anaesthesia for renal biopsy, etc.

FIG. 6.—Case 2. Pitressin test.

Pituitary-function Tests.—X-ray films of the skull showed no abnormal calcification nor any lesion of the pituitary fossa or calvarium. The bone age at the wrist was consistent with the chronological age. A water-deprivation test was performed. After six hours the child was clinically dehydrated and her weight fell by 2 kg., her urinary output fell to 120 ml. per hour, and the specific gravity of the urine rose from 1002 to 1015. During the test the serum sodium concentration rose from 139 to 150 mEq/l. (see Table). A pitressin test was performed; 10 units of pitressin tannate in oil was given. The

hourly urine volume fell markedly and the specific gravity rose to 1016 after six hours and remained at that level. The test was discontinued because the patient became hypoglycaemic (see Fig. 6).

A hypertonic saline test (Hickey-Hare or Carter-Robbins) was carried out, the child having drunk 1,000 ml. of water within the five minutes before the test was started. There was no significant alteration in the rate of urine output or in the specific gravity of urine during the period of infusion or the succeeding half-hour, indicating a lack of pituitary response to hyperosmolarity of the blood (see Fig. 4).

Other Tests.—Her haemoglobin was 13.5 g./100 ml. Red cells, white cells, and platelets were normal. The blood Wassermann reaction was negative. Serum electrolytes were normal. Serum calcium was 9.2 mg./100 ml. and serum phosphate 4.4 mg./100 ml.

Treatment.—The patient was put back on pitressin tannate in oil, 10 units every other day. The daily urine output fell to 2–3 l./day and the specific gravity rose to 1015. There was no change in the requirements for management of the diabetes mellitus.

Genetics.—The family tree is shown in Fig. 7.

Fig. 7.—Family tree.

Discussion

These two sisters each have two of the diseases causing polyuria—that is, diseases due to deficient production of antidiuretic hormone and to inability to metabolize glucose properly. The association of diabetes mellitus and insipidus is excessively rare in childhood. Of the 43 cases reported to date, 38 have been in adults, and in the majority of these the diabetes insipidus has been caused by a tumour, granuloma, or other lesion. Only five cases have occurred in children, and only two of these are well documented. Allan and Rowntree (1931) report a case in which the diabetes insipidus came on after encephalitis in a child who already had diabetes mellitus. A case of diabetes mellitus and idiopathic diabetes insipidus was reported by Lowrey and Arbor (1960) in a 7-year-old girl. Two cases were reported at the recent International Paediatric Congress at Lisbon (Chute *et al.*, 1962). The first patient was a well-controlled diabetic. During a bout of ketosis he developed diabetes insipidus and died four days later.

At necropsy there was a haemorrhagic softening of the hypothalamus and corpus callosum. Microscopy showed a necrotizing arteritis of small vessels in that region. In the second patient both disorders developed within a few weeks of a blow to the head. She developed optic atrophy, and this increased in severity. An arachnoiditis in the pituitary-hypothalamic area appeared to be the cause of the disorder.

We were unable to find any reports of the two disorders occurring in several members of one family. Thus our two

sisters, who developed both diabetes mellitus and diabetes insipidus before the age of 9 years, represent the sixth and seventh cases in children.

In both cases the diabetes mellitus was established by the elevated blood sugar, the glycosuria, and episodes of ketosis. In Case 1 the mid-afternoon blood sugar after control was 170 mg./100 ml. In Case 2, after control, the blood sugar fluctuated between 110 and 170 mg./100 ml. during the day and night.

The diabetes insipidus was established, firstly, by failure of the kidney to conserve water when the patients were deprived of fluid, and this led to the rapid onset of clinical dehydration. Secondly, the rate of urine output remained constant when the blood osmolarity was raised by the intravenous injection of hypertonic saline. Thirdly, there was a satisfactory response to pitressin, as shown by a reduction in the urine output and a rise in its specific gravity.

Functionally, the kidneys of both girls appeared to be normal except for the hydronephrosis demonstrated by radiography in Case 1. Silverstein and Tobian (1961) suggest in their reported case that in diabetes insipidus the urinary bladder capacity is inadequate for the degree of urine produced, and that there is an accumulation of fluid in the ureters and pelves of the kidneys, leading to hydro-ureters and hydronephrosis if the polyuria is present for years. Weller *et al.* (1950) suggest that these changes are the results of efforts at compensation for large urinary volumes.

The early diabetic changes in the glomeruli demonstrated in the renal biopsy of Case 1 are also of interest because they were found in a child of 11 years with a known history of diabetes mellitus of only two years. It may be noted that during this period her glycosuria was poorly controlled.

Hereditary diabetes insipidus can be transmitted in several ways. Forssman (1945) has shown that it may occur as a sex-linked gene, on the X chromosome as in haemophilia and colour-blindness. It may also occur from autosomal dominant transmission (Martin, 1959). It is probable that in our patients the transmission was mediated as an autosomal recessive gene.

The combination of optic atrophy with diabetes insipidus in Case 1 led us to suspect a localized lesion. We were unable to demonstrate any space-occupying lesion. One might postulate, therefore, that there is a degenerative process in the region of the supraopticohypophysial tract. Such a process could spread to involve the optic tract. The associated diabetes mellitus in the same patient is difficult to explain in terms of such a single degenerative lesion. Although it is possible to speculate on ways in which a hypothalamic lesion might cause diabetes mellitus it seems probable that the two diseases coexist in these children through the chance coincidence of two unrelated genes.

Summary

Two sisters, both suffering from diabetes mellitus and diabetes insipidus, are described. The familial occurrence of these two diseases has not previously been reported. The older girl developed diabetes mellitus at 9 years of age, the younger one at 5 years. The diagnosis of diabetes insipidus was confirmed by positive "pitressin" tests and by the absence of a normal response to infusion with hypertonic saline. Both children responded well to injections of pitressin tannate in oil.

Genetically there was nothing in the family history to suggest a sex-linked transmission of the diabetes insipidus. In these patients the inheritance was probably mediated by an autosomal recessive gene.

No evidence of a space-occupying lesion was found in either child. It was not possible to explain the presence of both diseases on the basis of a single anatomical lesion. It was concluded, therefore, that the two diseases coexisted through the chance coincidence of two unrelated genes.

We wish to thank Dr. B. W. Powell, of Peterborough, for referring the patients to us, and also the medical illustrations department at this hospital for helping us with the diagrams.

MULTIPLE EPIPHYSIAL DYSPLASIA

BY

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The term of "epiphysial dysplasia" was suggested by Fairbank (1935) for a group of cases characterized by irregularity in density and outline of several of the developing epiphyses, dwarfism, and stubby digits. Since his account of this condition many further cases have been reported. Nevertheless, multiple epiphysial dysplasia is uncommon enough to make the following cases of interest.

This report of six cases in one family, with strong presumptive evidence of other affected members, follows the pattern of simple dominant inheritance. However, there was considerable variation in the severity and locality of the affection.

Genealogy.—The family tree is shown here. Male members I2, II4, and III7 are known to have suffered

Her brother (V 5) aged 11 was found to have epiphysial dysplasia, affecting ankles, hips, and upper humeral epiphyses. The knee-joints were normal.

The father of these children (IV 4), aged 49, was thought to have had rickets at the age of 2, and at 14 he had corrective osteotomy for genu valgum. He has led an active and

Details of Cases Examined

	III 1	IV 2	IV 4	V 3	V 5	V 6
Age	75	45	41	25	11	9
Shoulders	Normal	Normal	Normal	Normal	MED	Normal
Hips	MED	MED	MED	MED	"	MED
Knees	"	"	"	"	Normal	"
Ankles	Normal	"	"	"	MED	"
Spine	"	"	"	"	"	"
Symptoms	None	Osteo-arthritis of right hip	Painful knock-knees as a child relieved by osteotomy	Childhood only	Flat-feet	Painful knock-knees relieved by osteotomy

MED = Multiple epiphysial dysplasia.

symptom-free life in the Navy since. Radiographs of his knees and ankles showed marked epiphysial dysplasia.

His father (III 2) was also thought to have suffered from rickets at the age of 2. He too was a naval officer, and had no trouble in later life.

The case of V 3 was reported by Fairbank (1947), and a radiograph is illustrated in Fig. 297 of that paper. Although he suffered from symptoms in early life, he is now 25 and has been symptom-free for 10 years.

Summary

Six further cases of multiple epiphysial dysplasia in one family are reported, with probable affection in six other cases not available for examination.

The disability of those affected, even in the presence of marked radiological changes, may be negligible; and the regularity of dominant gene inheritance may be demonstrable only by radiology.

Unlike the family described by Weinberg *et al.* (1960), there was a haphazard distribution of the affected joints. The shoulders were affected in only one case (V 5), and in this patient the knee-joints escaped.

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The family tree.

from a hereditary bone condition (almost certainly epiphysial dysplasia) which had affected previous generations of the family. In generation III four members out of seven were affected. Only one of these (III 1) was examined, however. In generation IV there were two affected members, and in generation V three were traced.

Case Histories

V 6, a girl aged 9, was referred with painful knock-knees. She presented the typical "dumpy" bodily habitus of epiphysial dysplasia, with affection of the knees, hips, ankles, and vertebral column. After a year's observation corrective osteotomy was performed with complete relief of symptoms.