Familial insulin-resistant diabetes, multiple somatic anomalies, and pineal hyperplasia

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West, R. J., Lloyd, J. K., and Turner, W. M. L. (1975). *Archives of Disease in
Childhood,* **50,** 703. **Familial insulin-resistant diabetes, multiple somatic
anomalies, and pineal hyperplasia.** A syndrome comprising unusual facies,
dry skin, acanthosis nigricans, thickened nails, hirsutism, dental precocity and dyspla-
sia, abdominal protuberance, and phallic enlargement is described in 2 sibs. Both
have developed diabetic ketoacidosis with insulin resistance. The elder child, a girl,
had recurrent septic episodes and died at the age of 7·8 years. At necropsy the
pineal gland was hyperplastic, weighing 900 mg. Investigation of the younger sib
over a 4-year period has shown decreasing glucose tolerance, and he was frankly
diabetic with ketoacidosis by the age of 6·8 years. Serum insulin concentrations have
always been grossly raised. Though the mechanism for insulin resistance has not
been definitely established, a functional abnormality of the hypothalamus or pituitary
is postulated to explain the many endocrine features of the syndrome.

The role of the pineal gland in human metabolism
is uncertain; a syndrome in which pineal hyper-
plasia appears to be an integral part may help to
elucidate its function. Such a syndrome was
reported by Rabson and Mendenhall (1956) who
described 3 sibs who initially presented with dental
and skin abnormalities, abdominal distension, and
phallic enlargement. Insulin-resistant diabetes de-
veloped, and the patients died of ketoacidosis and
intercurrent infection during childhood. At nec-
ropsy pineal hyperplasia was found in all 3 children.
5 other children described in published reports had
similar features (Mason and Sly, 1937; Wieder-
mann *et al.*, 1968; Barnes *et al.*, 1974), but
biochemical details are limited. This report
records two further examples of the syndrome, and
speculates on the role of the pineal gland in this
disorder.

Case reports

Case 1. A girl, the first child of healthy unrelated
parents, was born at term after an uneventful pregnancy,
weighing 2 kg. Unusual facies and abdominal disten-
sion were noted from birth. Primary dentition started
at 3 months, and was complete by 1·2 years. Secon-
dary dentition started at the age of 3·5 years and the
teeth were clearly abnormal in appearance. Thickened

finger and toe nails were present from infancy. De-
velopmental progress was normal.

Throughout childhood she had a good appetite but
appeared more thirsty than other children. At the age
of 5, during a routine medical examination, she was found
to have glycosuria with ketonuria, and was admitted to
hospital. On admission height and weight were both
well below the 3rd centile, but she did not appear acutely
ill. She was noted to have unusual facies, hirsutism,
dry skin with acanthosis nigricans of neck and axilla,
thickened nails, dysplastic and carious teeth with greatly
advanced dental age (Fig. 1), and a deeply fissured
tongue. Her abdomen was markedly protuberant and
the clitoris was large but there was no evident organo-
megaly or pubic or axillary hair.

Investigation showed a fasting blood sugar of 155
mg/100 ml and treatment of her diabetes mellitus was
started with soluble insulin, the dose being gradually
increased to 300 IU daily, without any improvement
of ketonuria, polyuria, or lowering of blood sugar.
Insulin antibodies could not be detected. The se-
quential addition of prednisone, chlorpropamide, and
metformin to the insulin therapy did not favourably
influence the hyperglycaemia, and accordingly all anti-
diabetic therapy was discontinued.

Over the next 2 years she remained hyperglycaemic
and ketotic, and her general health gradually deteriorated.
She lost weight, had several episodes of dental sepsis,
and on one occasion ketoacidosis with semi-coma
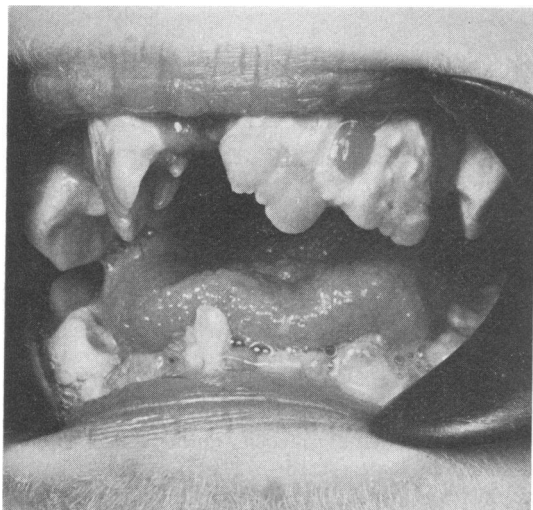required treatment with intravenous fluids.

FIG. 1.—*Case 1. Dysplastic and carious teeth at the age of 7 years.*

dental abscess, pneumonia, and ischiorectal abscess. At the age of 7·8 years she died at home after a short diarrhoeal illness.

Post-mortem examination showed distension of the whole of the small intestine, and of the ascending colon. There was a small amount of peritoneal fluid. The liver was slightly enlarged. Spleen, pancreas, adrenals, and kidneys appeared normal. The ovaries were enlarged and somewhat cystic, but the uterus and adnexa were normal. The appearance of the brain was normal and the pituitary gland was of normal size. The pineal gland was grossly enlarged, weighing 900 mg (normal <150 mg). On microscopical examination, the pancreas showed conspicuous hyalinization of the islets. The adrenals showed well-marked compact cell change. The ovaries were histologically normal, as were sections of myocardium, skeletal muscle, brain, stomach, jejunum, caecum, spleen, thyroid, and uterus. The lungs showed alveolar congestion, and in the liver there was some vacuolation of the parenchymal cells and dilatation of the sinusoids. There was hyalinization of some of the afferent arterioles of the kidney. The pituitary was normal in size, with normal proportions of the various cell types. The pineal, though enlarged, showed no histological abnormalities (Fig. 2).

At the age of 6·8 years she was admitted to The Hospital for Sick Children, London, for further study. On examination she weighed 11·5 kg and was grossly wasted, with no apparent subcutaneous fat. The somatic features were as already described and her dental age was assessed at around 12 years. Investigations showed Hb 14·5 g/100 ml, WBC 12 900/mm³ with 70% neutrophils. Serum sodium was 119 mEq/l, potassium 2·7 mEq/l, chloride 97 mEq/l, bicarbonate 9 mmol/l, and urea 26 mg/100 ml. Fasting blood glucose was 235 mg/100 ml, plasma calcium 8·0 mg/100 ml, inorganic phosphorous 1·3 mg/100 ml, alkaline phosphatase 38 KA units, and total serum protein 6·8 g/100 ml. Serum transaminases were normal. Urine volumes varied between 5–6 l daily, and contained 100–200 g glucose, and about 90 mEq sodium and 45 mEq potassium. There was a generalized amino-aciduria. Chest x-ray was normal, the bones were somewhat porotic and bone age was 5 years. Barium meal showed widening of the jejunum with coarse mucosal folds. Faecal fat was 4·5 g/day (mean of 5 days). Results of special investigations are given separately.

The electrolyte abnormality was treated with sodium bicarbonate and potassium supplements, and serum values gradually returned to normal, as did plasma calcium and inorganic phosphorus; the aminoaciduria improved. Insulin, both beef and pork, was given in doses up to a total of 1000 IU daily without apparent effect and the subsequent addition of metformin 1·5 g/day was also without effect. Trials of fructose and xylitol as alternative dietary carbohydrate were without benefit. She was discharged on electrolyte and alkali supplements only. Subsequent progress was complicated by episodes of infection, including otitis media,

Case 2. A boy, the brother of Case 1, was born at term weighing 2·3 kg. His facial appearance was similar to his sister's; primary dentition started at 4 months and secondary dentition at 3 years. Roughness of the skin was noted at the age of 9 months and thickened nails at 1·5 years. In view of the similarity to his sister he was investigated at The Hospital for Sick Children at the age of 3·1 years.

On examination the facial resemblance to his sister was obvious (Fig. 3). He was, however, well nourished, with both height and weight between the 3rd and 10th centiles. His skin was dry, moderately hirsute, and with acanthosis nigricans of neck, axillae, and cubital fossae. The nails were thickened, the teeth were dysplastic and carious, and the dental age advanced. The tongue was fissured, the abdomen was somewhat protuberant, and there was penile enlargement but no pubic hair or testicular enlargement. Urine analysis showed occasional glycosuria, but there was no polyuria or polydypsia, and hyperglycaemia could not be shown. Results of special investigations are given later.

When reviewed at the age of 4·9 years his clinical condition was essentially unchanged. By 6·8 years, however, he had developed increased thirst and polyuria though he remained well nourished. His dental age was around 14 years. Urine volume varied between 3–4 l daily, and contained approximately 200 g glucose/24 h. Fasting blood glucose varied between 200 and 260 mg/100 ml. He was ketonuric and mildly hypokalaemic, but was not acidotic. Hypokalaemia was corrected by oral potassium supplements but neither insulin nor oral hypoglycaemic drugs have been used.

At the time of writing he was 7·5 years old; there has been no major clinical progression of his disease.
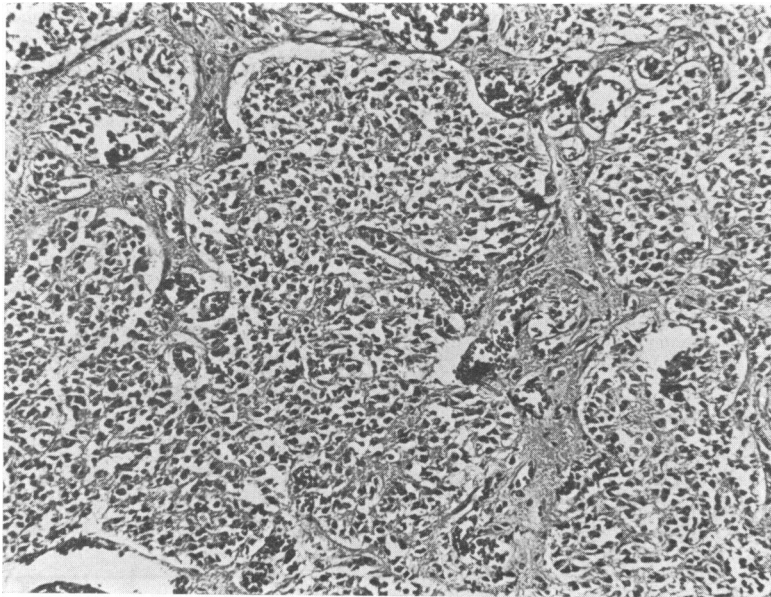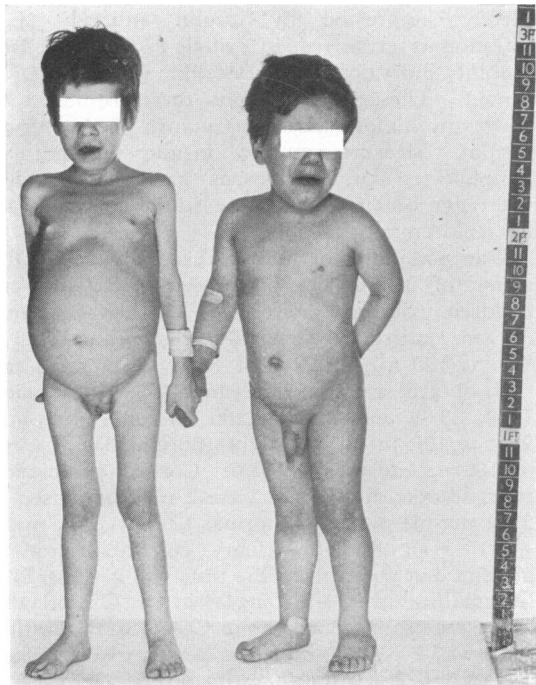
FIG. 2.—*Case 1. Microscopy of the pineal gland.*

FIG. 3.—*Cases 1 and 2. Two sibs showing facial resemblance, abdominal protrusion, and phallic enlargement in both girl and boy.*

Special investigations

Glucose tolerance tests. Glucose tolerance tests (GTT), using oral glucose (1·75 g/kg body weight to a maximum of 50 g) and measuring blood glucose and serum insulin at 0, 30, 60, 90, 120, and 150 minutes, were performed on both children and their parents; plasma nonesterified fatty acids (NEFA) were measured in most tests. Glucose was measured on venous blood by an autoanalyser glucose oxidase method, serum insulin by a double binding radioimmunoassay, and plasma NEFA by the method of Fosbrooke and Tamir (1968). In Case 1 the test was done at the age of 7·3 years, 2 months after discontinuing insulin therapy. In Case 2, tests were performed at 3·1, 4·9, and 6·8 years.

Measurement of serum insulin in Case 1 was complicated by the presence of antibody, presumably induced by exogenous insulin. Fractionation of two of the serum samples through a G100 Sephadex column removed the antibody and enabled an approximate result to be obtained. In Case 2 antibodies were not present in the serum. The results of the GTTs are shown in the Table. In Case 1 there was marked hyperglycaemia throughout the test, and serum insulin at 0 and 60 minutes was high; the response of plasma NEFA was normal. In Case 2 the first GTT showed normal glucose tolerance, but extremely high serum insulin con-

TABLE

Results of oral glucose tolerance tests in patients and parents

Subject	Age (yr)	Estimation	Minutes after glucose					
			0	30	60	90	120	150
Case 1	7·3	Glucose (mg/100 ml)	265	387	370	310	286	246
		Insulin (μU/ml)*	212	–	440	–	–	–
		NEFA (mEq/l)	1·56	0·70	0·84	0·72	0·62	1·77
Case 2	3·1	Glucose (mg/100 ml)	42	154	144	122	109	84
		Insulin (μU/ml)	556	3208	3136	2875	3187	2656
		NEFA (mEq/l)	1·98	1·93	0·53	0·44	0·58	0·88
	4·9	Glucose (mg/100 ml)	90	232	250	231	174	104
		Insulin (μU/ml)	1050	4050	3125	4300	3350	1600
		NEFA (mEq/l)	0·88	0·50	–	0·29	0·26	0·47
	6·8	Glucose (mg/100 ml)	259	460	469	362	218	252
		Insulin (μU/ml)	498	535	725	909	393	288
Mother	30	Glucose (mg/100 ml)	61	101	98	90	67	51
		Insulin (μU/ml)	48	310	312	240	115	69
Father	32	Glucose (mg/100 ml)	78	128	103	34	55	74
		Insulin (μU/ml)	16	130	136	23	8	11
		NEFA (mEq/l)	0·45	0·19	0·17	0·26	0·47	0·71

*After removal of circulating antibody.
NEFA, plasma nonesterified fatty acids.

centrations. The second and third tests showed progressively impaired glucose tolerance; in the third test serum insulin values were still markedly raised though somewhat lower than previously. Plasma NEFA response was normal in the two tests where it was measured.

The mother had normal glucose tolerance but somewhat raised serum insulin values throughout the test. The interpretation of these results is hampered by the fact that she was at the time taking Ovulen 50 (Searle) for contraceptive purposes; it seems unlikely, however, that this drug was the sole cause of the hyperinsulinaemia (Wynn and Doar, 1969). The father had a normal response to oral glucose for all 3 variables measured (Table).

Investigation of insulin resistance. Investigation of Case 1 was hampered by the presence of antibodies and the very poor clinical condition with evidence of many secondary metabolic abnormalities. Most investigations have therefore been carried out on Case 2 who never received exogenous insulin and whose general clinical state was good at the time of testing. Measurement of his serum insulin by radioimmunoassay has always shown grossly raised values, and no antibody or proinsulin has been detected on any occasion. Bioassay of serum insulin, using isolated fat cells (Dr. O. Sovik) gave a value of 5133 μU/ml, compared with immunoreactive serum insulin of 5850 μU/ml on the same

sample. Insulin activity in this sample was completely suppressed by insulin antibody. Gel filtration of serum yielded a single insulin peak with mobility indentical with crystalline insulin (Dr. O. Sovik). These investigations therefore failed to show any abnormality of structure of the serum insulin. Measurement of insulin binding of lymphocytes (Dr. N. Lazarus) gave values within the range obtained for obese adults (normal data for children not available).

The possibility of hormonal antagonism to the action of insulin has been investigated in both children. Serum cortisol in Case 1 was normal (9 a.m. cortisol 14·0 μg/100 ml; normal 17·3 ± 7·8 μg/100 ml, mean ± 1 SD). In Case 2 the cortisol level was sometimes high, the values being 13·4, 28·0, and 28·5 μg/100 ml for 9 a.m., and 9·6 μg/100 ml at midnight (normal 3·1 ± 1·2 μg/100 ml, mean ± 1 SD). Cortisol production rate (isotopic dilution) in Case 2 was also raised at 23·2 mg/m^2 per 24 h (normal 12·3 ± 2·8, mean ± 1 SD), though urinary cortisol excretion, measured at about the same time was 0·8 mg/24 h (normal for age 0·4-3·2 mg/24 h, Dr. C. Forsyth).

Plasma growth hormone in Case 1 in the fasting state was 7 μU/ml, and in Case 2 varied between 3·3 and 6·2 μU/ml (3 estimations). In Case 2 the response to oral Bovril (Jackson, Grant, and Clayton, 1968) was subnormal with a maximum value of 8·2 μU/ml (normal rise of at least 7 μU/ml);

however, on one occasion during a GTT a growth hormone level of > 40 μU/ml was recorded.

Plasma glucagon (Dr. S. Bloom) in Case 2 at a time when he was hyperglycaemic (blood glucose 300 mg/100 ml) was 97 pg/ml (normal adults 10–59 pg/ml). No direct estimations of catecholamines were made; urinary VMA in Case 2 was 1·9 mg/24 h (normal up to 3·3 mg/24 h).

Other endocrine investigations. In Case 1 protein-bound iodine was 5 μg/100 ml (normal 2·5–6·6 μg/100 ml). Urinary ketosteroid excretion was 2·6 mg/24 h, and hydroxycorticoid excretion was 7·4 mg/24 h (both mean of 3; normal ketosteroids 1·4 ± 0·7, mean ± ISD, hydroxycorticoids 0·6–6·4 mg/24 h).

In Case 2 it was possible to assay a number of pituitary hormones in addition to growth hormone; normal results were obtained for serum thyroid stimulating hormone (1·8 μU/ml, Dr. B. Ormston), ACTH (9 a.m. 33 pg/ml, midnight <12 pg/ml, Dr. L. Rees), FSH (<16 pg/ml, Dr. L. Rees), and prolactin (11·2 ng/ml). Urinary leutinizing hormone was raised at 9·5 IU/24 h (mean of 2; normal 1·37 ± 0·45 IU/24 h mean ± ISD); urinary follicle stimulating hormone was <0·5 IU (mean of 3; normal <1 IU/24 h).

Serum thyroxine was normal (9·3 and 6·9 μg/100 ml), as was plasma testosterone (Dr. B. Rudd). Urinary 17-ketosteroids at age 4·9 years were 2·9 mg/24 h (normal for age 0·8 ± 0·5, mean ± 1 SD), and at age 6·9 were 2·8 mg/24 h (normal for age 1·4 ± 0·7 mg/24 h). Urinary dehydro-epiandrosterone (Dr. C. Forsyth) was high at 37 μg/24 h (normal for age up to 18 μg/24 h), whereas aetiocholanolone, androsterone, 11-deoxy-17-ketosteroids, and corticosterone excretions were normal.

Investigation of pineal gland. An attempt to study the pineal gland was made in Case 2. An EMI scan of the brain at the age of 7 years showed a normal sized pineal and there was no distortion or enlargement of the ventricular system. Urinary 5-hydroxy-indole-acetic acid (formed during melatonin synthesis) excretion was not raised (Dr. K. Blau). Administration of oral melatonin in dosage up to 200 mg/day for 12 days did not improve the diabetic state (Fig. 4), though the recognized side effects of drowsiness and slurring of speech occurred.

Discussion

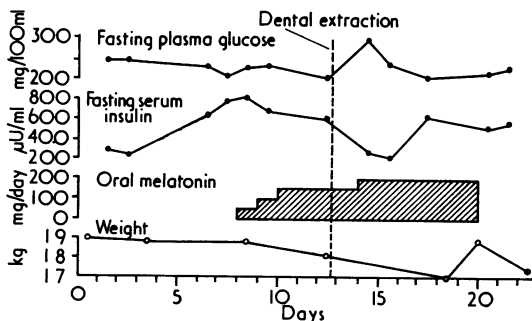Our patients most closely resemble the family reported by Rabson and Mendenhall (1956) and

FIG. 4.—*Case 2. Effect of melatonin on fasting plasma glucose, serum insulin, and body weight.*

the patient of Mason and Sly (1937). From these 6 patients the characteristic features of the syndrome appear to be low birthweight, dry skin, thickened nails, hirsutism, acanthosis nigricans, dental precocity and dysplasia, abdominal protuberance, phallic enlargement, and insulin-resistant diabetes mellitus with ketosis developing during childhood, and association with frequent septic episodes. All 3 children described by Rabson and Mendenhall (1956) and Case 1 of our family died in mid-childhood, necropsy showing marked pineal hyperplasia. No follow-up of the patient of Mason and Sly (1937 is available after the age of 2 years.

The brother and sister described by Wiedemann et al. (1968) did not have abdominal distension or phallic enlargement, and were still living at the ages of 13 and 11, respectively; the 2 sisters described by Barnes et al. (1974) did not have abnormal teeth or nails, and are surviving at the ages of 23 and 11 years. However, as both these sibships have many similarities to the other 6 patients, they may represent less severe variants of the syndrome. The syndrome appears to show autosomal recessive inheritance, and the 2 sisters described by Barnes et al. (1974) were daughters of a first-cousin marriage. The raised serum insulin found in the mother of our patients may be a biochemical indication of her heterozygous status.

The mechanism of the insulin resistance has not yet been established. Insulin antibodies were not present in Case 2, or intially in Case 1. Growth hormone, cortisol, glucagon, and adrenalin were not present in amounts likely to cause insulin resistance. Suppression of plasma NEFA by oral glucose in both our patients suggested that adipose tissue at least was not totally resistant to the action of insulin. Nevertheless, some form of tissue resistance cannot be completely excluded.

The role of the pineal gland in this syndrome can

only be speculative. In man the only pineal hormone definitely identified is melatonin (n-acetyl-methoxy-tryptamine), which is known to suppress gonadal development by acting on the hypothalamus to inhibit the liberation of gonado-trophic-releasing factors (Kappers, 1971). Rabson and Mendenhall (1956) suggested that the pineal hyperplasia in their patients might be associated with defective production of pineal hormones, in a manner analogous to the situation in congenital adre-nal hyperplasia. This could explain the phallic enlargement, but for such a mechanism to explain insulin resistance as well it would be necessary to postulate either that pineal deficiency itself induced insulin resistance or that there was excessive production of another pineal hormone which was antagonistic to insulin. Destruction of the pineal gland by tumour has induced sexual precocity (Pelizzi, 1910) but insulin resistance has never been reported. The failure of exogenous mela-tonin to influence either blood glucose or serum insulin in Case 2 makes it unlikely that pineal hypofunction, at least in respect of melatonin production, can be the cause of this syndrome.

The phallic enlargement, present in all 6 typical patients, suggests the action of an androgen, and if excessive production of such a hormone is not due to failure of pineal inhibition, the primary abnor-mality may be in either the hypothalamus or the anterior pituitary, or the adrenal. There is no evidence to support a primary adrenal abnormality. However, a primary abnormality in the hypothala-mus or pituitary is a possibility. Louis and Conn (1972) have described a diabetogenic polypeptide which they have isolated from human pituitaries which is distinct from previously recognized pituitary hormones and, if there was disturbance of function of hypothalamus or pituitary, production of such a hormone could explain the diabetes and insulin resistance; excess FSH production could lead indirectly to the phallic enlargement, and pineal hyperplasia might be explained by feedback mechanisms attempting to inhibit this FSH. The failure to show pineal hyperplasia in our second

patient may be due to the limitations of EMI scanning, or may simply reflect the stage of his disease. Serial studies are clearly indicated.

A unifying hypothesis to explain all the somatic and metabolic features in this syndrome is not yet possible. The extremely high circulating insulin concentrations present from an early age may possibly play some part in the development of the dental, skin, and nail abnormalities.

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