

10.5 ± 2.3 on SMA. Gas-liquid chromatography of the faecal fat in 2 of 3 infants showed that C16:0 was responsible for most of the excess fatty acid when they were fed Cow and Gate V formula.

We are grateful to Professor J. A. Davis for encouragement, Dr. E. M. Widdowson for helpful discussion, and Dr. A. H. Gowenlock in whose department the estimations of faecal fat were performed.

REFERENCES

- Fomon, S. J., Ziegler, E. E., Thomas, L. N., Jensen, R. L. and Filer, L. J., Jr. (1970). Excretion of fat by normal full-term infants fed various milks and formulas. *American Journal of Clinical Nutrition*, **23**, 1299.
- Gompertz, S. M., and Sammons, H. G. (1963). The origin of faecal lipids. *Clinica Chimica Acta*, **8**, 591.
- Holt L. E., Jr., Tidwell, H. C., Kirk, C. M., Cross, D. M., and Neale, S. (1935). Studies in fat metabolism. I. Fat absorption in normal infants. *Journal of Pediatrics*, **6**, 427.
- van de Kamer, J. H., Huinink, H. ten Bokkel, and Weijers, H. A. (1949). Rapid method for the determination of fat in feces. *Journal of Biological Chemistry*, **177**, 347.
- Matthys, F., Christophe, A., and Verdonk, G. (1972). A combined thin layer-gas chromatographic method for the analysis of fatty acid-containing stool fractions. *Clinica Chimica Acta*, **36**, 341.
- Southgate, D. A. T., Widdowson, E. M., Smits, B. J., Cooke, W. T., Walker, C. H. M., and Mathers, N. P. (1969). Absorption and excretion of calcium and fat by young infants. *Lancet* **1**, 487.
- Tidwell, H. C., Holt, L. E., Jr., Farrow, H. L., and Neale, S. (1935). Studies in fat metabolism. II. Fat absorption in premature infants and twins. *Journal of Pediatrics*, **6**, 481.
- Varley, H. (1967). *Practical Clinical Biochemistry*, 4th ed., p. 423. Heinemann, London.
- Watson, W. C. (1965). Intestinal hydrogenation of dietary fatty acids. *Clinica Chimica Acta*, **12**, 340.
- Williams, M. L., Rose, C. S., Morrow, G., Sloan, S. E. III, and Barnes, L. A. (1970). Calcium and fat absorption in neonatal period. *American Journal of Clinical Nutrition*, **23**, 1322.

R. D. G. MILNER*, Y. DEODHAR, C. R. CHARD, and ROWENA M. GROUT

Department of Child Health, University of Manchester, and Willink Biochemical Genetics Laboratory, Royal Manchester Children's Hospital.

*Correspondence to Dr. R. D. G. Milner, Room 61, Research Floor, St. Mary's Hospital, Manchester M13 0JH.

Urinary 3'5' cyclic AMP Diagnostic test in pseudohypoparathyroidism

Pseudohypoparathyroidism is characterized by end-organ resistance to parathyroid hormone (PTH). There is evidence that this unresponsiveness is located in the renal cortex and involves failure of the hormone to activate adenylate cyclase, the enzyme which forms adenosine 3'5'-cyclic phosphate (cyclic AMP). In normal subjects

infusion of PTH leads to a dose-dependent increase in urinary cyclic AMP (Chase, Melson, and Aurbach, 1969; Kaminsky *et al.*, 1970; Greenberg, Karabell, and Saade, 1972). In patients with pseudohypoparathyroidism, infusion of the hormone fails to alter urinary levels of the cyclic nucleotide (Chase *et al.*, 1969; Greenberg *et al.*, 1972). It has been suggested (Chase *et al.*, 1969) that measurement of urinary cyclic AMP in response to infusion of PTH may be a sensitive index for establishing the diagnosis of this disease. The present report describes 2 children diagnosed as having pseudohypoparathyroidism in whom urinary cyclic AMP levels failed to rise after infusion of PTH.

Case reports

Case 1. A white male, aged 2 years 9 months, was admitted to Vancouver Children's Hospital for assessment of obesity, subcutaneous calcifications, and delay in behavioural development. He had been previously examined (at age 14 months) for delayed behavioural development and at that time was found to have multiple subcutaneous nodules in the scalp; x-rays showed plaques of calcification in the scalp, right flank, shoulder, and dorsum of the left foot; serum calcium and phosphorus were normal. When seen by us (at 33 months) he had a history of polydipsia, bed-wetting, polyphagia, screaming attacks, and increased subcutaneous calcifications. His height was 88.2 cm, which placed him on the 3rd centile; his weight was 15.4 kg, falling between the 75th and 90th centiles. Multiple subcutaneous calcified lesions on the right shoulder, right occiput, and back of legs were noted. No central nervous system abnormality was noted other than mild mental retardation and hypotonia. His hands were short and chubby but there was no evidence of shortened metacarpals. Gesell assessment placed him at behavioural level of about 2 years. The serum calcium level was 7.6 mg/100 ml, serum phosphorus 6.4 mg/100 ml, and serum magnesium 2.0 mg/100 ml.

Case 2. A 9-year-old Caucasian female was admitted to hospital for reassessment of pseudohypoparathyroidism and behavioural problems. Subcutaneous calcifications had been present since birth; the diagnosis of pseudohypoparathyroidism had been made on the basis of low serum calcium (7.1 mg/100 ml) and raised serum phosphorus (7.5 mg/100 ml) as well as shortened metacarpals. When examined by us (at age 9 years) she exhibited emotional instability and had learning problems. Her height was 128.5 cm (25th centile) and her weight 40.9 kg (97th centile). The significant clinical findings included multiple subcutaneous calcifications and shortening of the 3rd, 4th, and 5th metacarpals bilaterally. Serum calcium was 10.4 mg/100 ml and phosphorus 5 mg/100 ml while she was on a dosage of 50 000 units of vitamin D daily. The metyrapone test for assessment of pituitary-adrenal axis was normal.

Control subject. The control subject was an 8-year-old male sib of Case 1. The significant features in this boy are small physical stature and short metacarpals. Since it has been known that pseudohypoparathyroidism is transmitted by an autosomal recessive mode, and that the transition from normocalcaemia to hypocalcaemia has been noted in patients with pseudohypoparathyroidism as is seen in the affected sib, parathyroid hormone infusion was carried out in this case to rule out the disease.

Parathyroid hormone (PTH) infusion

Infusion of PTH (Eli Lilly, (L) 5EY84C) was performed after overnight fasting at 10, 25, 50, and 100 mU/kg per min, changing at 45-minute intervals as described by Kaminsky *et al.* (1970). The patients and a control were hydrated by drinking water, and urine specimens were collected every 15 minutes through an indwelling catheter. Calcium, phosphate, creatinine, and cyclic AMP concentrations were determined in each sample. Cyclic AMP was determined by the protein binding method of Gilman (1970), creatinine by the Jaffé reaction. Serum calcium, phosphorus, and magnesium levels were measured before and at the completion of the test procedures. In the control patient (7-year-old brother of Case 1) urinary cyclic AMP levels rose in a dose-dependent manner in response to PTH infusion (Fig.). In sharp contrast, urinary cyclic AMP levels in Cases 1 and 2 remained unchanged throughout the entire infusion sequence (Fig.). After the infusion, cyclic AMP excretion was measured in the patients for a period of 3 days. All values remained at the characteristically low levels. Urinary phosphorus excretion levels are presented in

TABLE I

Urinary phosphorus excretion during PTH infusion

	Urinary P excretion (mg/h)		
	Case 1	Case 2	Control
PTH infusion (mU/kg per min)			
10	9.32	16.8	22.56
25	7.65	21.0	24.01
50	19.45	28.4	9.56
100	16.48	32.3	15.08
Baseline control	8.40	15.0	13.50

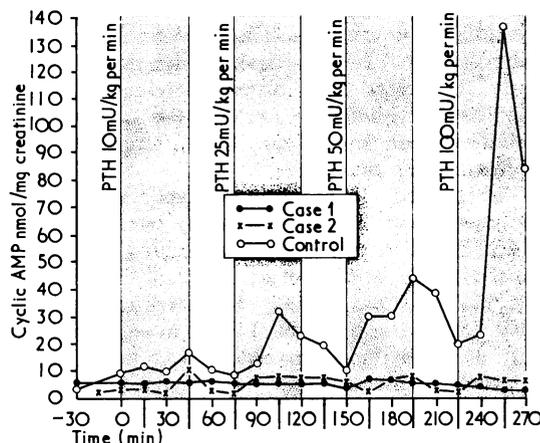


FIG.—Urinary cyclic adenosine monophosphate (AMP) response to parathyroid hormone (PTH) infusion in Cases 1 and 2 and control subject.

Table I. No significant increased excretion of urinary phosphorus was observed after infusion of an initial small dose of PTH, while significant phosphorus diuresis was observed in the control subject. A twofold increase in urinary phosphorus was shown after an increase in dosage of PTH from 10 mU/kg per min to 50 mU/kg per min. Serum calcium, phosphorus, and magnesium levels before and after completion of the infusion are shown in Table II. There was a rise in calcium and fall in phosphorus concentration in the control. There was a fall in both phosphorus and calcium concentrations in the serum of Case 1, while no change was observed in Case 2.

Discussion

Features of pseudohypoparathyroidism include hypocalcaemia, hyperphosphataemia, tetany, convulsions, short stature, short metacarpals, round face, dental aplasia, mental retardation, cataracts, and subcutaneous calcifications. Although Albright (*Albright et al.*, 1942) used the term pseudohypoparathyroidism to distinguish a case in which serum calcium and phosphorus values were normal, the possibility of transition from normo-

TABLE II

Serum calcium, phosphorus, and magnesium levels in PTH infusion study

	Calcium (mg/100 ml)		Phosphorus (mg/100 ml)		Magnesium (mg/100 ml)	
	Pre	Post	Pre	Post	Pre	Post
Case 1	7.7	7.3	7.3	5.9	2.3	2.0
Case 2	9.6	9.6	4.6	4.6	2.1	1.9
Control	9.3	9.9	4.7	4.1	2.3	2.1

Pre, before PTH infusion; Post, after PTH infusion.

calcaemia to hypocalcaemia in pseudohypoparathyroidism is now well established (Mann, Alterman, and Hills, 1962) and was again shown in one of our cases. It seems that normocalcaemia alone is insufficient evidence to exclude the diagnosis of pseudohypoparathyroidism when appropriate clinical features are present.

The concept of the role of cyclic AMP as a 'messenger' for several hormones has now been accepted and there has been increasing interest in the clinical application of this concept (Murad and Pak, 1972; Murad, 1973). Defective excretion of cyclic AMP after infusion of PTH in adult patients with pseudohypoparathyroidism has been shown by various investigators (Chase *et al.*, 1969; Kaminsky *et al.*, 1970; Greenberg *et al.*, 1972). The 2 children studied here likewise failed to respond to the hormone. The usefulness of phosphaturic response to PTH in the diagnosis of pseudohypoparathyroidism has frequently been challenged (MacGregor and Whitehead, 1954). In our patients an increase in urinary phosphate was observed when an increased dose of PTH was infused. The failure of urinary cyclic AMP to rise in response to increasing dosage of PTH, in contrast to the sharp rise in normal subjects, may be pathognomonic of pseudohypoparathyroidism. Our results support the possibility that measurement of urinary cyclic AMP after PTH infusion may be superior to measurement of urinary phosphate as a diagnostic method in this disease.

Summary

Measurement of urinary cyclic AMP (adenosine 3'5'-cyclic phosphate) and examination of calcium and phosphorus metabolism was carried out in two children with pseudohypoparathyroidism. In both patients infusion of parathyroid hormone failed to elicit any change in urinary cyclic AMP, while a dose-dependent increase in urinary cyclic AMP occurred in a normal control. The findings agree with the concept of unresponsiveness of renal cortical tissue to parathyroid hormone in pseudohypoparathyroidism and provide further evidence that measurement of urinary cyclic AMP during parathyroid hormone infusion may be the method of choice in the diagnosis of this disease.

The authors are indebted to Drs. F. H. A. Gaudin and K. P. Fellenz for permission to include their patients in the study and to Dr. D. Hardwick for technical assistance.

REFERENCES

- Albright, F., Burnett, C. H., Smith, P. H., and Parson, W. (1942). Pseudohypoparathyroidism—an example of Seabright-Bantam syndrome. *Endocrinology*, **30**, 922.

- Chase, L. R., Melson, G. L., and Aurbach, G. D. (1969). Pseudohypoparathyroidism: defective excretion of 3'5'-AMP in response to parathyroid hormone. *Journal of Clinical Investigation*, **48**, 1832.
- Gilman, A. G. (1970). A protein binding assay for adenosine 3'5'-cyclic monophosphate. *Proceedings of the National Academy of Sciences of the U.S.A.*, **67**, 305.
- Greenberg, S. R., Karabell, S., and Saade, G. A. (1972). Pseudohypoparathyroidism: a disease of the 'second messenger'. *Archives of Internal Medicine*, **129**, 633.
- Kaminsky, N. I., Broadus, A. E., Hardman, J. G., Jones, D. J., Jr., Ball, J. H., Sutherland, E. W., and Liddle, G. W. (1970). Effects of parathyroid hormone on plasma and urinary adenosine 3'5'-monophosphate in man. *Journal of Clinical Investigation*, **49**, 2387.
- MacGregor, M. E., and Whitehead, T. P. (1954). Pseudohypoparathyroidism. *Archives of Disease in Childhood*, **29**, 398.
- Mann, J. B., Alterman, S., and Hills, A. G. (1962). Albright's hereditary osteodystrophy comprising pseudohypoparathyroidism and pseudopseudohypoparathyroidism. *Annals of Internal Medicine*, **56**, 315.
- Murad, F. (1973). Clinical studies and applications of cyclic nucleotides. *Advances in Cyclic Nucleotide Research*, **3**, 355.
- Murad, F., and Pak, C. Y. C. (1972). Urinary excretion of adenosine 3'5'-monophosphate and guanosine 3'5'-monophosphate. *New England Journal of Medicine*, **286**, 1382.

WAH JUN TZE*, JOHN SAUNDERS†, and GEORGE IAN DRUMMOND‡
 Department of Paediatrics and Pharmacology, University of British Columbia, and Children's Hospital, Vancouver, B.C.

*Correspondence to Dr. W. J. Tze, Children's Hospital, 250 West 59th Avenue, Vancouver, Canada V5X 1X2.

Present addresses: †St. Thomas's Hospital, London, S.E.1.
 ‡Department of Pharmacology, University of Calgary, Calgary, Alberta, Canada.

Lupus-scleroderma syndrome induced by ethosuximide

Systemic lupus erythematosus (SLE) induced by anticonvulsant drugs is well known to many clinicians, though Alarcón-Segovia (1969) in his excellent review article was able to find only 60 published cases. Various anticonvulsant drugs, like diphenylhydantoin, troxidone, and primidone, have this potential despite differences in chemical structure. Recently another anticonvulsant, ethosuximide, has also been implicated in inducing the lupus syndrome (Livingston *et al.*, 1968). However, scleroderma has never been reported to be induced by drugs. Winkelmann (1971) in his comprehensive review, mentioned no drugs in the pathogenesis of scleroderma.

This paper describes a young Chinese girl who developed SLE and scleroderma while on treatment with ethosuximide for epilepsy.

Case report

A 16-year-old Chinese girl had suffered from grand mal epilepsy since the age of 2 and was controlled with