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Familial pseudohypoparathyroidism without somatic anomalies

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A family is described in which affected individuals showed pseudohypoparathyroidism, with hypocalcemia, hyperphosphatemia and increased serum levels of parathyroid hormone, but none of the somatic anomalies frequently associated with this disorder. The untreated individuals showed radiologic evidence of osteitis fibrosa. The administration of parathyroid hormone evoked only a slight increase in the excretion of cyclic adenosine monophosphate but no change in the renal tubular reabsorption of phosphate and no rise in the serum calcium level. The infusion of ethylenediamine tetra-acetic acid caused an appropriate increase in the serum level of parathyroid hormone, but again there was no apparent renal or skeletal response to the hormone. There were no associated abnormalities in calcitonin, thyrotropin or prolactin levels and no thyroid dysfunction. Therapy with vitamin D corrected the hypocalcemia but did not improve the renal and skeletal responsiveness to parathyroid hormone. The inheritance of the disorder in this family was compatible with an autosomal dominant mode with variable penetrance, but other modes could not be excluded.

On décrit une famille dont les individus atteints manifestaient une pseudohypoparathyroïdie, avec hypocalcémie, hyperphosphatémie et une augmentation des taux sériques d'hormone parathyroïdienne, sans présenter les anomalies somatiques souvent reliées à cette maladie. Les individus non traités ont montré des signes radiologiques d'ostéite fibreuse. L'administration d'hormone parathyroïdienne n'a entraîné qu'une légère augmentation de l'excrétion de l'adénosine monophosphate cyclique sans qu'il n'y ait changement de la réabsorption tubulaire rénale des phosphates, ni augmentation de la calcémie. La perfusion d'acide éthylènediamine tétra-acétique a causé une augmentation appropriée des taux sériques d'hormone parathyroïdienne, mais, là encore, on n'a constaté aucune réaction rénale ou squelettique apparente à l'hormone. Il n'y avait ni anomalie des taux de calcitonine, de thyrotropine ou de prolactine, ni dérèglement thyroïdien. Un traitement à la vitamine D a corrigé l'hypocalcémie mais n'a pas amélioré la réactivité rénale ou squelettique à l'hormone parathyroïdienne. La transmission génétique de la maladie dans cette famille est compatible avec un mode autosomique dominant avec pénétrance variable, mais d'autres modes ne peuvent être exclus.

Patients with pseudohypoparathyroidism have hypocalcemia and hyperphosphatemia, the features usually associated with a deficiency of parathyroid hormone, but in this condition the abnormalities result from a defect in the receptor complex sensitive to this hormone on the target cells of the kidney or skeleton or both.[1,2] As originally described, this condition is associated with short stature, a round face, obesity, short metacarpals and metatarsals, soft tissue calcification, dental anomalies and mental retardation.[3] The somatic abnormalities also occur in individuals who have normal serum calcium levels with or without subnormal responsiveness to parathyroid hormone, in a variant termed pseudopseudohypoparathyroidism or Albright's hereditary osteodystrophy. Conversely, individuals with pseudohypoparathyroidism but none of the dysmorphic features have been described.[4-6] This report describes a family with isolated pseudohypoparathyroidism.

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The family (Fig. 1)

Clinical features

The proband (III-27) presented at age 14 years with a major seizure. He had had three febrile seizures in the first year of life but none since. His height and weight had always been at the 50th percentile, his physical appearance was normal, the metacarpals were of normal length and there was no evidence of subcutaneous calcification, cataracts or moniliasis. Trousseau's sign (spasm of muscles provoked by pressure on the nerves supplying them) was elicited. Serum levels were as follows: calcium 6.5 mg/dl (1.6 mmol/l), ionized calcium less than 2.0 mg/dl (0.5 mmol/l), phosphate 8.1 mg/dl (2.6 mmol/l), magnesium 1.3 mEq/l (0.7 mmol/l), total protein 7.3 g/dl and alkaline phosphatase 161 IU/l (normal range 16 to 60 IU/l); the levels of serum electrolytes, blood gases, blood urea nitrogen and blood glucose were normal. The endogenous creatinine clearance was 146 ml/min per 1.73 m^2; the 24-hour urinary excretion of calcium was 22 mg (0.5 mmol) and of phosphate 590 mg (19 mmol). Skeletal roentgenograms showed changes of osteitis fibrosa, with resorption of the distal ends of the clavicles (Fig. 2), subperiosteal resorption of the phalanges and demineralization of the lamina dura. There was no intracranial calcification. Adrenal function (assessed from serum cortisol levels before and after administration of adrenocorticotropin) and thyroid function (assessed from serum levels of thyroxine, triiodothyronine and thyroid-stimulating hormone before and after administration of thyrotropin-releasing hormone) were normal. The serum prolactin concentration was 11.5 ng/ml and rose normally to 31 ng/ml when thyrotropin-releasing hormone was given. Psychologic testing showed normal intelligence. He was treated with vitamin D, 50 000 IU/d, and within a few months the radiologic changes of osteitis fibrosa disappeared; his serum calcium level has remained normal for 7 years.

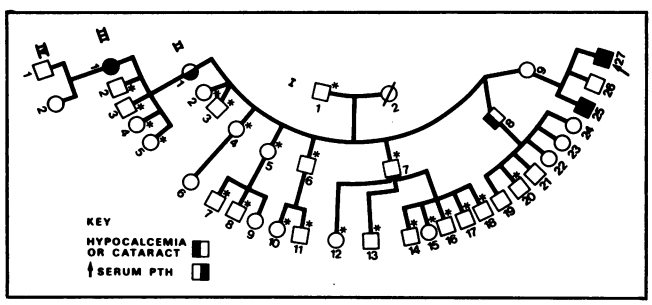

FIG. 1—Pedigree of family with isolated pseudohypoparathyroidism. All members were tested for serum calcium and phosphate levels and were examined for somatic abnormalities. Assays for serum parathyroid hormone (PTH) were not carried out in individuals marked with asterisk.

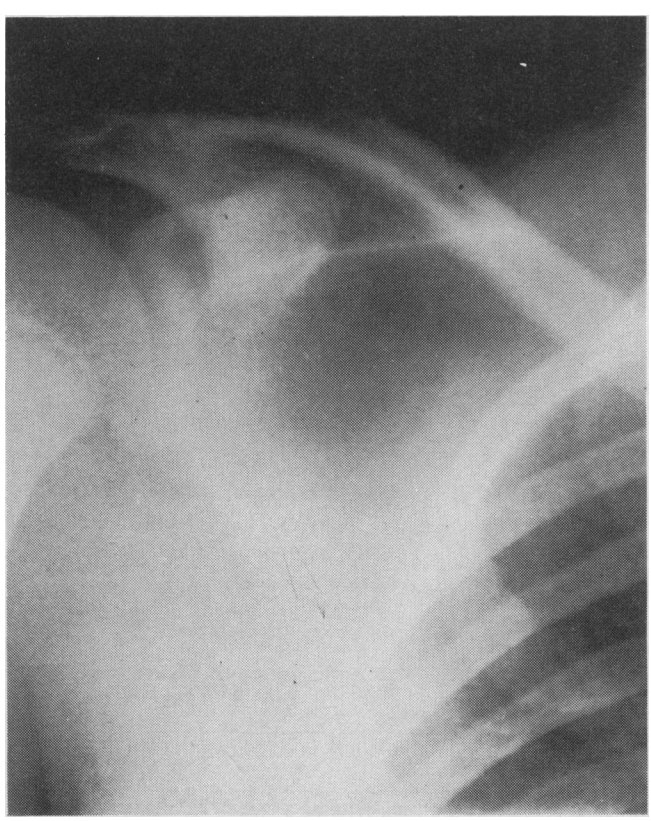

FIG. 2—Changes of osteitis fibrosa in proband, with decalcification of distal end of clavicle.

In the proband's asymptomatic brother (III-25) Chvostek's sign (spasm of the facial muscles provoked by tapping of the muscles or branches of the facial nerve) and Trousseau's sign were elicited. Serum levels were as follows: calcium 2.1 mg/dl (0.5 mmol/l), phosphate 6.1 mg/dl (2.0 mmol/l), magnesium 1.3 mEq/l (0.6 mmol/l), total protein 7.1 g/dl and alkaline phosphatase 53 IU/l. He was of normal height and intelligence, had none of the somatic features of Albright's hereditary osteodystrophy and showed no evidence of cataracts, moniliasis, steatorrhea, alkalosis or renal insufficiency. His 24-hour urinary excretion of calcium was 11 mg (0.3 mmol) and of phosphate 685 mg (22 mmol). Skeletal roentgenograms showed demineralization of the skull and lamina dura but no subperiosteal resorption or intracranial calcification. Adrenal and thyroid function (assessed as in the proband) was normal. The serum prolactin concentration was 14 ng/ml and rose to 21 ng/dl when thyrotropin-releasing hormone was given. He was treated with vitamin D, 50 000 IU/d, and the radiologic abnormalities disappeared; his serum calcium level has remained normal.

A 31-year-old female cousin (III-1) had experienced paresthesia and carpopedal spasms since the age of 12 years. Bilateral cataracts were removed at age 28, at which time her serum calcium level was 4.5 mg/dl (1.1 mmol/l) and her serum phosphate level 7.0 mg/dl (2.3 mmol/l). She showed none of the somatic abnormalities of Albright's hereditary osteodystrophy. She was treated irregularly with vitamin D, 50 000 IU/d. At the time of the present studies the following serum levels were recorded: calcium 8.4 mg/dl (2.1 mmol/l), ionized calcium 3.2 mg/dl (0.8 mmol/l), phosphate 3.9 mg/dl (1.2 mmol/l), magnesium 1.6 mEq/l (0.8 mmol/l), total protein 7.5 g/dl and alkaline phosphatase 15 IU/l. Radiologic examination disclosed punctate intracranial calcification in the region of the basal

ganglia but no evidence of osteitis fibrosa.

All living members of the family underwent determination of their serum calcium, phosphate and alkaline phosphatase levels and physical examination by their own physicians. Serum was obtained from some of them for measurement of the parathyroid hormone concentration. One uncle of the proband (II-3) was found to have a low serum calcium level (7.8 mg/dl [1.9 mmol/l]) in association with cirrhosis and hypoproteinemia, but his records showed that the calcium levels had previously been normal. Another uncle (II-8) had cataracts but normal serum levels of calcium, phosphate and alkaline phosphatase.

Special investigations

Methods: The serum concentrations of parathyroid hormone,[7] calcitonin[8] and 25-hydroxycholecalciferol[9] were measured in the laboratory of Dr. Sara Arnaud at the Mayo Clinic, Rochester, Minnesota. Levels of cyclic adenosine monophosphate (AMP) in serum and urine were measured by radioimmunoassay.[10]

To test the renal response to parathyroid hormone we obtained serum and urine specimens hourly for 3 hours before and after the intravenous administration of 200 U of bovine parathyroid hormone of demonstrated effectiveness (Lilly, lot 8CG48A); the specimens were stored at −20°C until assayed for calcium, phosphate, creatinine and cyclic AMP. The acute phosphaturic response was calculated in terms of both the percentage of phosphate reabsorbed by the tubules and the maximum amount reabsorbed per 100 ml of glomerular filtrate.[11] The skeletal response to this hormone was assessed from the effect on the serum calcium level of the intramuscular administration of 200 U of bovine parathyroid hormone every 12 hours for 12 doses.

The effect of hypocalcemia on the serum level of parathyroid hormone and on the serum and urine levels of calcium, phosphate, creatinine and cyclic AMP was observed during a 2-hour intravenous infusion of disodium ethylenediamine tetra-acetic acid (EDTA), 70 mg/kg. Serum samples were obtained at 15-minute intervals during the infusion and at 30-minute intervals for 5 hours thereafter; hourly urine collections were obtained for 2 hours before, during and for 4 hours after the infusion. The urine calcium concentration was measured by atomic absorption spectrometry.

Results: The mean serum levels of calcium, immunoreactive parathyroid hormone, calcitonin and 25-hydroxycholecalciferol in the affected individuals and some of their relatives are shown in Table I. All three patients showed high levels of parathyroid hormone while hypocalcemic; when vitamin D therapy restored the calcium level to normal there was an appropriate decline in the level of parathyroid hormone. All of their relatives with normal serum calcium levels who could be tested showed normal levels of parathyroid hormone except one elderly woman (II-1), who initially appeared to have an increased level (190 μlEq/ml); however, the levels in serial dilutions of her serum did not parallel the radioimmunoassay dose–response of the hyperparathyroid standard serum. All the values for 25-hydroxycholecalciferol were within normal limits except that of the female patient (III-1), who was receiving vitamin D therapy.

Table I—Mean serum levels of calcium, parathyroid hormone, calcitonin and 25-hydroxycholecalciferol in three patients with pseudohypoparathyroidism and healthy relatives

Subjects (by pedigree no.)	Serum levels			
	Calcium, mg/dl (mmol/l)	Parathyroid hormone, μlEq/ml	Calcitonin, ng/ml	25-hydroxycholecalciferol, ng/ml
Patients				
Before therapy				
III-27	6.5 (1.6)	150	< 0.03	37.9
III-25	7.0 (1.7)	54	0.04	49.5
During vitamin D therapy				
III-27	9.7 (2.4)	27	—	—
III-25	9.7 (2.4)	37	—	—
III-1	8.4 (2.1)	97	—	126.0
Relatives				
Proband's father	10.5 (2.6)	28	—	44.6
II-1	10.3 (2.6)	?*	—	27.5
II-8	9.4 (2.3)	17	—	—
II-9	10.1 (2.5)	14	—	48.9
III-6	9.8 (2.4)	19	—	—
III-9	10.0 (2.5)	24	—	—
III-19	9.9 (2.5)	13	—	—
III-21	9.6 (2.4)	19	—	—
III-22	9.6 (2.4)	23	—	—
III-23	10.1 (2.5)	15	—	—
III-24	9.7 (2.4)	26	—	—
III-26	10.8 (2.7)	26	—	31.5
Normal range	9.0–10.8 (2.2–2.7)	< 40	< 0.21	10–50

*The level in this individual appeared to be increased, but in several determinations her serum demonstrated a lack of parallelism with the standard serum.

The short-term effects of intravenously administered parathyroid hormone on phosphate and cyclic AMP excretion are summarized in Table II. All three patients showed high basal values for the percentage of phosphate reabsorbed by the renal tubules and for the maximum amount of phosphate reabsorbed per 100 ml of glomerular filtrate, and demonstrated resistance to the renal actions of the hormone, which normally causes a decrease in phosphate reabsorption. Their urinary excretion of cyclic AMP was increased by the hormone, but not to the degree observed in the healthy relatives. Studies in the two male patients after 4 months of vitamin D therapy and normal serum calcium levels did not suggest an improvement in their renal response to parathyroid hormone. The other brother of the proband (III-26), who had a normal serum calcium level, was found to have a high basal level of tubular phosphate reabsorption and a subnormal renal response to intravenously administered parathyroid hormone; however, his basal urinary excretion of cyclic AMP and the response to administration of the hormone were normal.

The repeated intramuscular administration of bovine parathyroid hormone for 6 days to the two male patients had no effect on their serum calcium levels, although there was a slight fall in their serum phosphate levels. When this test was repeated after 2 years of vitamin D therapy no change was found in the serum calcium or phosphate levels, the plasma or urinary cyclic AMP levels or the maximum tubular reabsorption of phosphate.

The responses of these two patients to hypocalcemia induced by EDTA infusion are shown in Fig. 3. Although the hypocalcemia caused an appropriate rise in the serum levels of parathyroid hormone, in neither patient did this elicit the normal increase in the urinary excretion of cyclic AMP or reduction in the renal tubular reabsorption of phosphate. In addition, the bone response to endogenous parathyroid hormone ap-

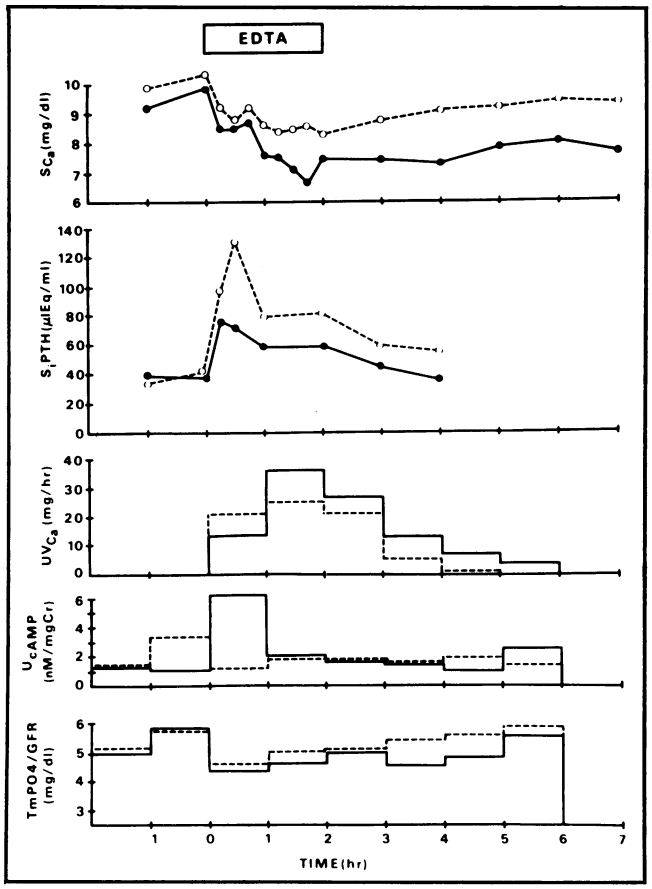

FIG. 3—Effect of intravenous infusion of 70 mg/kg of disodium ethylenediamine tetra-acetic acid (EDTA) over 2 hours in two patients (III-27, white circles; III-25, black circles) with isolated pseudohypoparathyroidism receiving vitamin D therapy. Responses assessed in terms of changes in serum levels of calcium and immunoreactive parathyroid hormone, in urinary excretion of calcium and cyclic adenosine monophosphate and in maximum tubular reabsorption of phosphate adjusted to glomerular filtration rate according to Bijvoet.[11]

Table II—Short-term renal effects of intravenously administered parathyroid hormone in the three patients and relatives

Subject (by pedigree no.)	Renal tubular reabsorption of phosphate*: % Basal	% After test	Maximum amount, mg/dl Basal	Maximum amount, mg/dl After test	Excretion of cyclic AMP, nmol/mg creatinine* Basal	Excretion of cyclic AMP, nmol/mg creatinine* After test
Patients						
Before therapy						
III-27	97.1	95.9	10.7	9.9	1.9	3.5
III-25	95.4	95.3	7.7	7.3	2.6	6.3
During vitamin D therapy						
III-27	95.1	94.9	5.7	6.0	1.7	4.9
III-25	97.5	94.4	7.0	6.5	1.5	4.1
III-1	95.4	91.7	4.7	3.9	1.8	7.7
Relatives						
Father of proband	87.5	72.1	3.9	2.3	3.3	10.4
II-1	87.0	80.0	3.5	2.6	2.7	31.5
II-9	91.1	74.9	3.2	2.0	2.7	8.5
III-26	94.6	89.8	5.1	4.5	3.6	9.4
Normal range[11–13]	81–95	63–88	2.5–4.2	1.7–2.9	2.4–5.4	9–31

*Each basal value is the mean of three hourly determinations, while each "after-test" value represents the maximum response (the lowest percentage or amount of phosphate reabsorbed and the greatest excretion of cyclic adenosine monophosphate) evident from three hourly collections after the intravenous administration of 200 U of bovine parathyroid hormone.

peared to be impaired, since the serum calcium levels did not return to basal levels in the first 5 hours after infusion.

Discussion

The combination of hypocalcemia, hyperphosphatemia and elevated serum levels of parathyroid hormone without evidence of an underlying systemic disorder suggests pseudohypoparathyroidism. The associated somatic abnormalities of Albright's hereditary osteodystrophy need not be present.[5] Patients with this disorder have increased levels of parathyroid hormone and defective end-organ responses to administration of the hormone, in contrast to patients with idiopathic hypoparathyroidism, who simply lack parathyroid hormone. In healthy individuals exogenous parathyroid hormone elicits a maximum decrease in the renal tubular reabsorption of phosphate of about 13.7 ± 6.4%,[12] whereas in our three patients the mean maximum decrease was 1.7%. The specific renal effect of parathyroid hormone is to decrease the maximum tubular reabsorption of phosphate,[14] but since this varies with the glomerular filtration rate it must be adjusted for that rate, as described by Bijvoet,[11] before comparisons are made. In our patients parathyroid hormone induced a mean decrease in the maximum amount of phosphate reabsorbed of 0.44 mg/dl, similar to that reported in pseudohypoparathyroidism, while in the healthy relatives of our patients the decreases were within the normal range of 0.95 ± 0.33 mg/dl.[12]

There is considerable evidence that cyclic AMP mediates the effects of parathyroid hormone and that the excretion of cyclic AMP reflects the response of renal tubular cells to the hormone.[13] In our patients both the administration of parathyroid hormone and the EDTA-induced increase in the endogenous hormone caused a rise of only two- to threefold in the urinary excretion of cyclic AMP; this minimal response has been observed in patients with so-called type I pseudohypoparathyroidism,[6] in whom the defect appears to be an inability of the hormone to evoke an appropriate increase in the intracellular production of cyclic AMP. In so-called type II pseudohypoparathyroidism, in contrast, the urinary excretion of cyclic AMP and the response to parathyroid hormone are normal; here the defect is presumed to be an inability to respond to the signal of intracellular cyclic AMP.[12]

Repeated intramuscular injections of parathyroid hormone did not raise the serum calcium levels in our patients, and the return of their serum calcium levels to baseline following an EDTA-induced decrease was delayed; these observations suggest that there was also resistance to the skeletal calcium-mobilizing action of parathyroid hormone. It was therefore surprising to observe the typical radiologic changes of osteitis fibrosa, which are usually characteristic of hyperparathyroidism. This finding and an increase in the serum alkaline phosphatase level are not uncommon in pseudohypoparathyroidism[4,15,16] and presumably indicate that at some stage of the disease skeletal responsiveness to parathyroid hormone is relatively intact. This earlier stage might account for the descriptions of children with radiologic evidence of osteitis fibrosa and documented renal unresponsiveness to parathyroid hormone who appear either to have normal serum calcium levels[17] or to be able to raise their serum calcium level following the administration of large amounts of parathyroid hormone.[18] A similar transition period could account for the often delayed appearance of hypocalcemia in individuals with Albright's hereditary osteodystrophy.

The calcium-mobilizing action of parathyroid hormone requires the presence of 1α,25-dihydroxycholecalciferol (1,25-DHCC); the final step in the synthesis of this material from vitamin D occurs in the kidney in response to stimuli such as hypophosphatemia and parathyroid hormone.[19] In pseudohypoparathyroidism the combination of hyperphosphatemia and reduced renal responsiveness to parathyroid hormone leads to a deficiency of 1,25-DHCC, which exacerbates the skeletal unresponsiveness to parathyroid hormone and results in hypocalcemia.[20] The observation that the hypocalcemia of pseudohypoparathyroidism can be corrected by small amounts of 1,25-DHCC, in contrast to the large doses of vitamin D required, may be further evidence for secondary impairment of vitamin D metabolism in this disorder.[21]

Several patients with pseudohypoparathyroidism have been described in whom target cell responsiveness was improved by either calcium infusion[22] or vitamin D therapy.[23,24] However, in our three patients months of vitamin D therapy had no apparent effect on either renal or skeletal responsiveness to parathyroid hormone, even though the serum calcium levels were normal and the serum phosphate levels either normal or only slightly increased during that period.

The variable clinical expression of pseudohypoparathyroidism most likely reflects genetic heterogeneity, although subtle differences in the interplay of secondary changes in the metabolism of calcium, phosphate, vitamin D or parathyroid hormone may contribute. It has been reported that the thyroidal content of calcitonin is increased in this syndrome;[25] however, the serum levels of calcitonin were appropriate in our patients, and there is no evidence that changes in calcitonin levels influence the clinical presentation. Other endocrine abnormalities that have been reported in pseudohypoparathyroidism, such as thyroid dysfunction[26,27] and deficiency of thyrotropin or prolactin,[28,29] were not present in our patients.

In classic pseudohypoparathyroidism the mode of inheritance has been thought to be X-linked dominant,[30] although some studies have suggested that autosomal dominant inheritance, possibly with more severe expression in females and therefore a bias of ascertainment, is more likely.[31] Unfortunately, in this first report of familial pseudohypoparathyroidism without somatic anomalies the pedigree does not serve to differentiate between these two modes of inheritance, presumably because of variable penetrance of the genetic defect. Repeated study of the mother of the proband (II-9) showed no abnormalities, although one would expect her to be affected. Similarly, two infant

children (IV-1 and IV-2) of one of the affected patients are known to have normal serum levels of calcium and phosphate, although assays of serum parathyroid hormone and tests of responsiveness to this hormone have not been carried out. Indeed, it is possible that peripheral unresponsiveness to parathyroid hormone is not the primary defect in pseudohypoparathyroidism but appears only after a variable period as a result of some as yet unrecognized genetic defect.

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