True Idiopathic Hypoparathyroidism as a Sex-Linked Recessive Trait

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TRUE IDIOPATHIC HYPOPARATHYROIDISM (THP) is a relatively rare disease, as evidenced by the fact that only 58 acceptable cases had been reported in the literature up to 1960 (Bronsky, 1958; Bergstrand, 1958; Buchs, 1955, 1957; Axelrod, 1950; Naef, 1959; Soper, 1957; Symon, 1959). Familial occurrence of THP is so uncommon that this disease is not usually thought of as being hereditary. Cases of THP presenting with hypocalcemic convulsions during the neonatal period or at ages less than one year are particularly unusual.

It is the purpose of this paper to present two cases of neonatal THP occurring in siblings, together with evidence suggesting that there may be more than one type of THP, and that one type is transmitted as a sex-linked recessive trait.

The requirements for acceptance of a case as THP were first set forth by Drake (1939) for idiopathic hypoparathyroidism and subsequently were modified by Bronsky (1958) to exclude pseudohypoparathyroidism. The criteria are:

1) low serum calcium
2) high serum phosphorus
3) chronic tetany or convulsions
4) absence of roentgenologic signs of rickets or osteomalacia
5) absence of renal insufficiency, steatorrhea, chronic diarrhea, and alkalosis
6) absence of physical characteristics of pseudohypoparathyroidism, such as brachydactyly, dwarfing, or subcutaneous calcium deposition.

Excluded from the category of THP were cases showing failure to respond to parathormone by increased urinary phosphorus excretion, and cases with meager or questionable clinical findings having demonstrable parathyroid glands on biopsy or post-mortem examination. However, in cases with clear-cut clinical findings it was not required for inclusion as THP that response to parathormone be tested, or that biopsy or post-mortem examination be made. Some cases which may well have been THP had to be excluded because the information given in the reports was insufficient to permit distinction between THP and pseudohypoparathyroidism.

CASE REPORTS

Case No. 1. C.B., a white male, was first seen at the age of 7 weeks because of recurrent generalized convulsions during the previous 24 hours. Birth history

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was normal, with no trauma, cyanosis or jaundice, and the patient had been on breast feedings since birth. The child was afebrile, and the physical examination was negative except for convulsive state. A lumbar puncture revealed normal spinal fluid, and subdural taps were negative. Serum calcium was 3.0 mEq./L. (normal: 4.5 to 5.5 mEq./L.), and serum phosphorus was 3.7 mEq./L. (normal: 2.5 to 3.5 mEq./L.). Oral calcium and anticonvulsants were started. Serum Ca rose to 3.8 mEq./L., and major seizures subsided, but the child continued to have intermittent twitchings of the face and the extremities. Excessive mucus was noted to drool continuously from the mouth. On one occasion difficult respirations with inspiratory stridor were noted.

Against advice, the child was signed out of the hospital by his parents, but was returned at the age of 2½ months because twitchings and major seizures continued to occur. On this second admission serum Ca was consistently low (2.8 to 3.3 mEq./L.), and serum P consistently high (4.1 to 6.1 mEq./L.). The Sulkowitch test on the urine was repeatedly negative. On several occasions the convulsions responded temporarily to intravenous calcium, but recurred after a few hours. The child was treated for one week with large daily doses of Vitamin D, oral calcium, and aluminum hydroxide gel, after which the convulsions and twitchings subsided, although serum Ca and P failed to return to normal.

The patient was discharged from the hospital at the age of 3½ months and returned for re-admission at the age of 4½ months because of an upper respiratory infection. Bilateral cataracts were noted at this time. The child had had no further convulsions, although he was receiving no medication other than added calcium. Serum Ca on admission was 4.8 mEq./L., P was 4.7 mEq./L. During hospitalization, the serum Ca again dropped to low levels (3.2–3.3 mEq./L.), the serum P rose (6.5–7.0 mEq./L.), and convulsions recurred. Vitamin D was restarted, Ca and P returned to more nearly normal levels, and the convulsions ceased.

During the subsequent 2½ years this child had eight additional hospital admissions, usually for convulsions. Chvostek and Trousseau signs were always negative, even when the serum Ca was low. X-rays of skull, long bones, and hands were normal. Intravenous pyelograms were negative on two occasions. Repeated urinalyses, BUN determinations, and two urea clearance tests were normal. Blood sugars, serum electrolytes (Na, Cl, K, and CO_2), alkaline phosphatase, and serum proteins were consistently within normal limits. Two Ellsworth-Howard tests, run with simultaneous normal controls of similar age and weight, showed a definite increase in urine phosphate in response to parathormone. There was no chronic diarrhea or steatorrhea, and the child had no monilial infections.

Oral Vitamin D and calcium have been continued up to the present. The daily dose of Vitamin D required to maintain serum Ca and P at relatively normal levels has fluctuated, without apparent reason, between 50,000 and 250,000 units. On therapy, serum Ca has ranged between 3.2–5.8 mEq./L., with

most of the values falling between 4.4–5.4 mEq./L. Serum P has ranged between 2.5–7.0 mEq./L. The patient had one episode of hypercalcemia (Ca 8.3 mEq./L., P 1.1 mEq./L., with 4+ urine Sulkowitch), which responded to decrease in dosage of Vitamin D. He is at present maintained on 50,000 units daily, with added oral calcium, aluminum hydroxide gel, and a high Ca/P ratio milk. The most recent serum Ca was 3.9 mEq./L., and serum P 3.4 mEq./L.

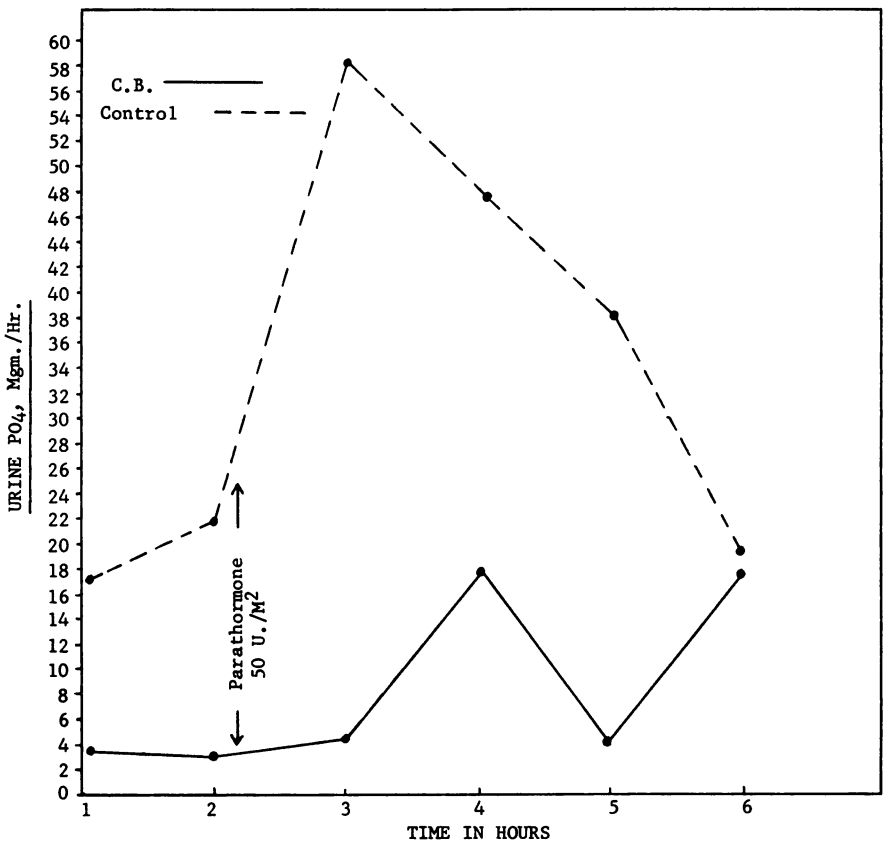
This patient is now 3 years old and is grossly retarded both mentally and physically. His extremities are spastic; he has no head control and does not speak. The EEG shows diffuse disorganization with no clearcut focal abnormality.

Case No. 2. D.B., a younger male sibling of Case 1, was hospitalized at the age of 5 days because of generalized convulsions beginning 2 hours prior to admission. There was no history of cerebral birth injury, cyanosis, or jaundice, and the child was afebrile. He had been receiving an evaporated milk formula (1:2 dilution). Physical examination was negative except for generalized convulsions and intermittent twitchings of face and extremities. Serum calcium was 2.1 mEq./L., with a phosphorus of 8.1 mEq./L. Urine Sulkowitch was negative. Lumbar puncture revealed normal spinal fluid. Blood sugar, serum electrolytes (Na, K, Cl, and CO_2), BUN, serum proteins and alkaline phosphatase were within normal limits. EEG showed a paroxysmal dysrhythmia. X-rays of skull, long bones and hands were normal. An Ellsworth-Howard test done on the tenth day of life showed an increase in urine phosphate in response to parathormone.

Convulsions and twitchings continued throughout the first 10 days of hospitalization, responding only for a few hours to intravenous injections of calcium. Oral calcium, aluminum hydroxide gel, and phenobarbital were started, and the patient was placed on a high Ca/P ratio milk. Convulsions gradually subsided as serum Ca rose to 4.5 mEq./L. and P dropped to 6.2 mEq./L. The urine Sulkowitch became positive. After 2 seizure-free weeks, for no apparent reason, the Sulkowitch again became negative, serum Ca dropped to 3.2 mEq./L., P rose to 7.3 mEq./L. and convulsions began again. These were controlled by increasing the amount of oral calcium given. Serum Ca rose to 4.0 mEq./L., and the urine Sulkowitch again became intermittently positive.

The patient was discharged from the hospital at the age of 9 weeks, on the above medications. He had no difficulty, except that the mother noted inspiratory stridor associated with feedings. He had no further convulsions during the next 9 months, although his serum Ca ranged between 3.6–4.1 mEq./L., and the P between 3.4–8.7 mEq./L.

At the age of 11 months, he developed a febrile illness and again began to have convulsions. During this hospital admission, the serum Ca ranged from 2.8 to 3.1 mEq./L., P from 6.0 to 7.0 mEq./L. Convulsions subsided after the first 3 days, when the patient became afebrile. However, because of persistently low Ca and high P, Vitamin D was started. Dosage has ranged from 50,000 to 200,000 units daily. The child is now 2 years old and has had no further con-

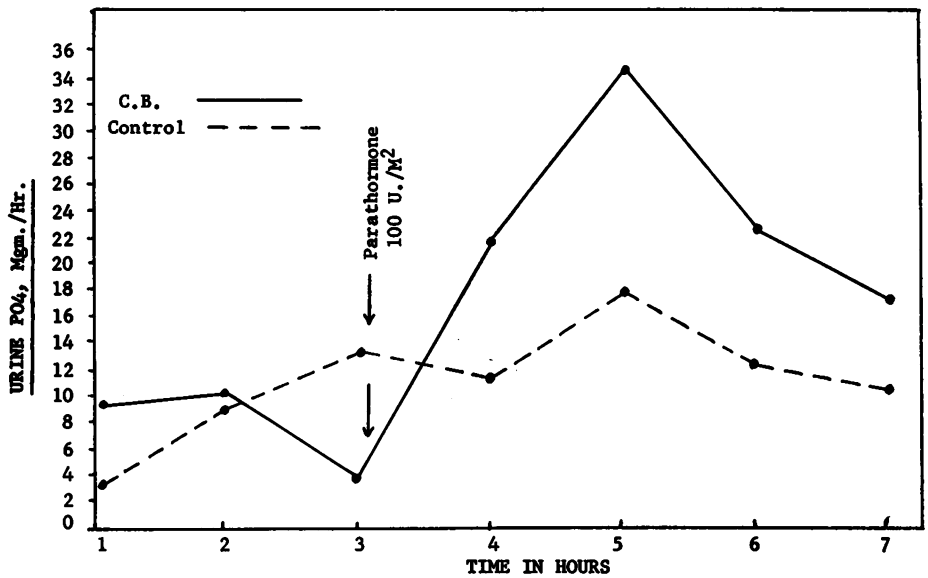


C.B., age 4½ months.
Receiving low P milk with added Ca; No Vitamin D.

FIG. 1

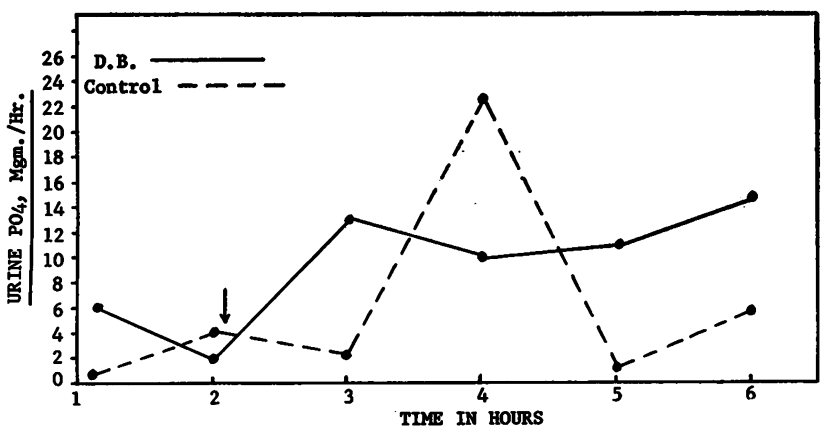
vulsions, although serum Ca and P remain slightly abnormal despite therapy. He is mentally normal and now has a normal EEG. He has no cataracts and has never had a monilial infection. Except for one brief episode of mild pyuria which readily responded to treatment, urinalyses have been consistently negative and the BUN remains normal.

The results of Ellsworth-Howard tests performed on Case 1 and Case 2 are shown in Figures 1, 2, and 3. Both patients, as compared with their controls, showed an adequate phosphate diuresis in response to parathormone. While a discussion of the intricacies of application and interpretation of the Ellsworth-Howard test is beyond the scope of this paper, it should be mentioned that this test, per se, is of little value in establishing a diagnosis of THP, and that even its use in distinguishing between THP and pseudohypoparathyrodism is open to some question (McGregor and Whitehead, 1954). However, the results presented here are compatible with the commonly described findings in THP as opposed to pseudohypoparathyroidism.



C.B., age 3 years.
Receiving Vitamin D 75,000 U./d., low P milk, added Ca.
(Vitamin D omitted on day of test).

FIG. 2



D.B., age 10 days.
No medication.

FIG. 3

THE PEDIGREE

The results of investigation of the family background of these cases are shown in Fig. 4. This information was obtained from the mother (IV-48) and maternal grandmother (III-24) of the two probands, and was independently corroborated by III-2. The hospital records of IV-8 and V-3 were examined, and V-3's physicians were consulted.

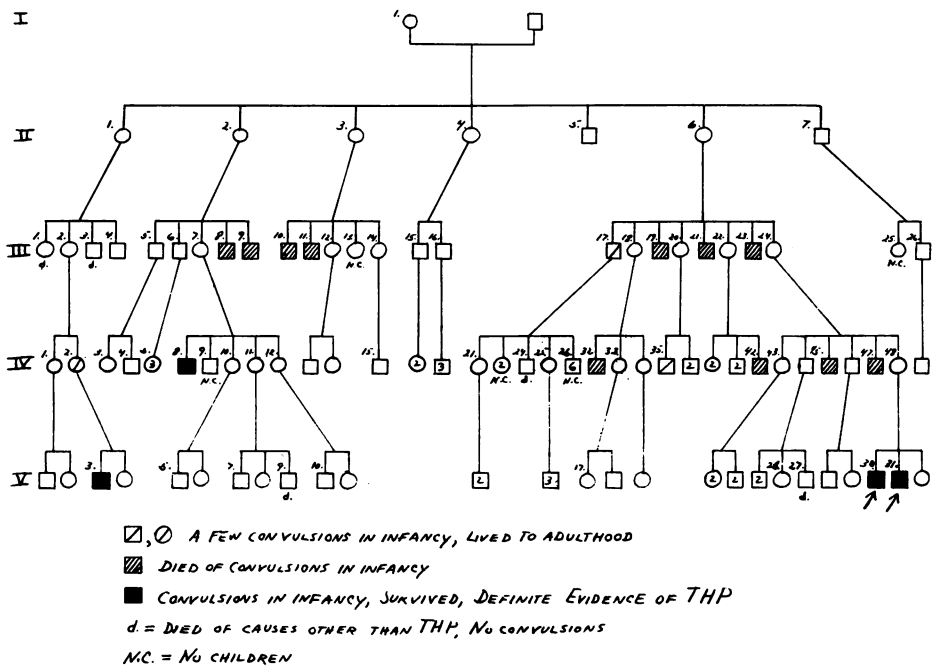


FIG. 4

In each of the 11 males who died of convulsions in infancy, the convulsions began before one year of age and were said to be afebrile. In seven of these the convulsions began between 2 and 8 weeks of age, and in the other four convulsions began at about 5 to 6 months. Seven of these babies died within a few weeks after the onset of convulsions, but four of them lived to the ages of 1½ to 4 years, having intermittent periods of convulsions throughout this time.

Two males had a few convulsions in infancy but lived to adulthood. One of these, III-17, has had no further convulsions and is said to be in good general health. He has 11 children, seven boys and four girls, none of whom have had convulsions. No information is at present available concerning the present status of IV-35, the second of these males.

One female, IV-2, had "quivering spells", lasting one or two minutes up to the age of about 18 months, and what was probably a generalized convulsion at the age of 5 years. Since then she has had no seizures and is said to be in good general health.

Males other than the probands, for whom there is known clinical evidence of THP:

IV-8 had convulsions at least as early as 9 months of age, associated with carpopedal spasm and laryngeal stridor. He was admitted to various hospitals in this city four times during his first two years of life, each time with typical tetany and convulsions which responded to calcium and Vitamin D. He is now

25 years old, somewhat mentally retarded, still has convulsions, and takes medication for "low calcium".

V-3 was diagnosed as probable THP at another local hospital, where he was admitted at the age of two weeks with convulsions, positive Chvostek and Trousseau signs, a low serum calcium and high phosphorus. These conditions persisted until about 2½ months of age, but finally responded to large doses of calcium and Vitamin D. This patient is now 3 years old, and is still under treatment. He has some degree of mental retardation and moderate spasticity of the extremities.

DISCUSSION

Examination of the pedigree of the two cases reported here indicates a probability that THP, at least in this family, is inherited as a sex-linked recessive trait. It is of interest that the maternal grandmother of the two probands, in a letter concerning her family history, rather neatly characterizes this mode of inheritance when she states: "I want to point out that no girls have had spasms. Only the girls' boys, and not all of them. No boys' children have had any spasms".

That the male relatives who died of convulsions in infancy suffered from THP cannot be proven, but seems likely. If this probability is accepted, then the pedigree fulfills the criteria of sex-linked recessive inheritance to the extent that only males are affected, the females being carriers and unaffected. None of the males related to a female carrier by a male parent or grandparent were affected.

Unfortunately, there is at present no clinical method of detecting the carrier state. Serum calcium and phosphorus were normal in both parents of the probands, and were also normal in the mothers of four other reported cases of neonatal THP (Buchs, 1955 and 1957; Rhyne, 1956), so these determinations are of no aid in detecting carriers.

To test the validity of the assumption that this pedigree represents sex-linked inheritance, computation was made of the expected incidence of affected and normal males on the maternal side of the probands' ancestry. There is no direct information concerning I-1. However, if this is sex-linked inheritance, then the mother (I-1) of the carrier women in Generation II must have carried the gene. With this assumption, calculations were made according to the method recommended by Steinberg (1959). This method is based on the theory that in a female known to carry the gene, the probability that she would pass it on to any particular son or daughter is 1/2, and the probability that this daughter, if she has the gene, would transmit it to any one son is again 1/2. So the probability that the first known carrier (I-1) would transmit the gene to any particular grandson or grand-daughter would be $1/2 \times 1/2$, or 1/4. To carry this a generation further, the probability of any particular great-grandson or great-granddaughter of I-1 receiving the gene is $1/2 \times 1/2 \times 1/2$, or 1/8. The probabilities are somewhat different for females having a direct blood relationship to the index

cases, as these women are known to carry the gene. Hence, for II-6, III-24, and IV-48, the probability of their transmitting the gene reverts to 1/2.

Results of computation made by this method are shown in table one. The deviation of observed from expected ratios is statistically not significant ($\chi_1^2 = .687$, P = .50–.30). The results, then, are consistent with the hypothesis that in this family THP is inherited as a sex-linked recessive trait.

The criterion of the inability of affected males to transmit the trait to or through their sons cannot be demonstrated, because the affected males who would now be old enough to have children died and did not reproduce. For the same reason, the invariable transmission of the carrier state to daughters of affected males cannot be shown.

The one possibly affected male (III-17) who survived and did reproduce did not transmit overt disease to any of his children or grandchildren. It is highly doubtful that III-17 actually had THP, as he is now in his fifties and is said to be in good health.

The possibility that this pedigree represents sex-limited inheritance of an autosomal gene, rather than sex-linked inheritance, cannot be excluded, as neither ability nor inability of affected males to transmit the gene to their sons can be demonstrated. However, to quote Roberts (1959), "Sex linkage in man is so common, and complete sex limitation almost certainly so rare, that

TABLE 1. EXPECTED AND OBSERVED NUMBERS OF AFFECTED AND NORMAL SONS OF I-1 AND OF EACH OF FEMALES RELATED TO I-1 VIA FEMALES

Females	Sons			
	Affected		Normal	
	Expected	Observed	Expected	Observed
I-1	1.00	0.0	1.00	2.0
II-1	.50	0.0	1.50	2.0
II-2	1.00	2.0	3.00	2.0
II-3	.50	2.0	1.50	0.0
II-4	.50	0.0	1.50	2.0
II-6	2.00	3.0	2.00	1.0
III-7	.25	1.0	1.75	1.0
III-12	.125	0.0	.875	1.0
III-14	.125	0.0	.875	1.0
III-18	.25	1.0	.75	0.0
III-20	.75	0.0	2.25	3.0
III-22	.75	1.0	2.25	2.0
III-24	2.00	2.0	2.00	2.0
IV-1	.063	0.0	.937	1.0
IV-2	.063	1.0	.937	0.0
IV-10	.063	0.0	.937	1.0
IV-11	.063	0.0	.937	1.0
IV-12	.063	0.0	.937	1.0
IV-33	.125	0.0	.875	1.0
IV-43	.50	0.0	1.50	2.0
Totals	10.69	13.0	28.31	26.0

Omitted: 2 Index cases (V-30 & V-31), and V-9 (died of unknown cause a few hours after birth).

the alternative explanation, while it cannot be disproved, must be considered somewhat fanciful".

On careful examination of the information furnished in available case reports of THP, it becomes apparent that there is more than one type of THP. The observed differences in clinical characteristics and genetic aspects suggest the following classification of types of THP:

I. Early-onset
   A. Sex-linked
   B. Non-sex-linked (congenital absence of parathyroid glands, associated with multiple congenital anomalies)

II. Late-onset
   A. Familial
      1. Addison's associated
      2. Non-Addison's associated
   B. Non-familial
      1. Addison's associated
      2. Non-Addison's associated.

Considering first the cases of early-onset THP, it should be noted that these constitute a minority of the total number of THP cases. Hypocalcemic convulsions due to idiopathic THP do not usually occur during the first year of life, most cases going several years before convulsions develop, and some cases never manifesting convulsions (Emmerson, 1941; Goldman, 1952). Table 2 lists the eight reported cases of idiopathic THP with convulsions beginning during the first year of life, plus the two cases reported here for the first time. Harrison (1956) mentions two other cases of neonatal THP, not included in the table, which apparently have not been formally reported. The sex of these two infants is not stated.

The predominance of males in this group is rather striking, in view of the fact that in Bronsky's review (1958) of 50 reported cases of all types of THP, 24

TABLE 2. REPORTED CASES OF TRUE IDIOPATHIC HYPOPARATHYROIDISM WITH CONVULSIONS BEGINNING DURING FIRST YEAR OF LIFE

Reference	Sex	Age at Onset Convulsions	Congenital Anomalies
Soper (1957)	M	Tetany in newborn period. Convulsions a 9 months.	None recorded
Bergstrand (1958)	M	"A few months less than 1 year"	None recorded
Buchs (1955)	M	7 days	None recorded
Buchs (1955)	M	7 days	None recorded
Buchs (1957)	M	3 weeks	None recorded
Forbes (1956)	M	5 days	None recorded
Rhyne (1956)	F	7 days	Bilateral congenital glaucoma
Symon (1959)	M	"A few weeks"	None recorded
This paper	M	5 days	None recorded
This paper	M	7 weeks	None recorded

Total Cases – 10; M – 9, F – 1

were male and 26 were female. If one were to include in table 2 the two cases of probable THP noted in the present pedigree (IV-8 and V-3), the total would be 12 cases, all but one of which occurred in males.

Of the cases in table 2, only those of Buchs and those from this hospital are recorded as being familial. Buchs' cases occurred in three male siblings, but he gives no family history except that the parents and a female sibling were normal. No extensive investigation of family history is mentioned in the other case reports, so the possibility that they were also familial, and perhaps sex-linked, cannot be excluded.

From the pedigree of the two patients reported in this paper, and from the marked predominance of males in the early-onset group of THP cases, the suggestion may be drawn that early-onset cases of THP represent a distinct and different type of the disease, inherited in a sex-linked manner. However, it does not necessarily follow that all cases of early-onset THP are of this type. Other types of THP might show an occasional case presenting convulsions earlier than is characteristic of those particular types.

Proof or disproof of the implication that early-onset THP is inherited in a sex-linked pattern would require, of course, a much more extensive investigation of the pedigrees of patients in this group. It would require, also, an explanation of the occurrence of neonatal THP in a female, as in the well-documented case reported by Rhyne (1956). This case was unusual also in that the child had congenital bilateral glaucoma. No family history was given in this report, other than the statement that the parents were normal and there were no siblings.

Rhyne's case, besides being the only female in the early-onset THP group, is also the only one of these cases in which any associated congenital anomaly is recorded. This case may perhaps belong to the small group described by Lobdell (1959), in which congenital absence of the parathyroid glands was associated with multiple other congenital anomalies. Lobdell reported a case of hypoparathyroidism in a male infant with hypocalcemic symptoms beginning during the first few days of life and death occurring at the age of 55 days despite therapy. At autopsy a careful search of the entire neck block revealed no parathyroid tissue, but the child was found to have a double aortic arch with a patent ductus arteriosus, absence of the thymus, and agenesis of the thyroid isthmus. Lobdell cites four similar cases, from the foreign literature, in which congenital absence of the parathyroids was associated with a variety of congenital anomalies such as acrania, microcephaly, aniridia, hypoplasia of the thymus, and partial thyroidal agenesis (Rössle, 1932 and 1938; Blaim and Lewicki, 1955). Two of these cases occurred in males, one in a female, and the sex of the fourth case is not recorded.

Another case similar to Lobdell's has recently been reported in the American literature by Farber and Vawter (1960). This was a female infant in whom findings of hypoparathyroidism were present from the age of 6 days, with death occurring at 12 days. At autopsy the only parathyroid tissue which could be found consisted of one very small group of cells, located high in the submucosa

of the posterior pharynx. There were multiple congenital anomalies, including absence of the gall bladder, a hypoplastic and ectopic thymus, hypoplasia of the jaw, hypoplasia of the lungs and tetralogy of Fallot.

It is possible that in addition to Rhyne's case, some of the other cases of early-onset THP recorded in table 2 also properly belong to this group, having congenital anomalies which were not apparent on external examination.

Another possible explanation for the appearance of neonatal THP in a female would be the expression of a sex-linked recessive trait in an individual who is only phenotypically a normal female.

Returning to the suggested classification of THP according to type, the late-onset type, which includes the majority of all cases, remains to be considered. This type may be tentatively divided into a familial variety, and a variety which is not apparently familial.

Familial cases of THP are unusual, there being recorded only 8 such cases in 3 families (table 3), excluding the three males in one family reported by Buchs and previously discussed as belonging to the early-onset group. In none of these three families was there any history of THP in previous generations. Of the eight familial cases of late-onset THP, six were of the type which is associated with Addision's disease, either in the patient or in other members of the family, and which is frequently also associated with monilial infections. The remaining two familial cases were not apparently associated with Addison's disease, and no moniliasis is described. It is entirely conceivable, however, that these last two cases might eventually belong to the Addison's-associated group, since in most instances of Addison's-associated THP the hypoparathyroidism precedes the Addison's, occasionally by several years.

The apparently non-familial group of late-onset THP cases, like the familial group, includes both Addison's-associated and non-Addison's-associated types. The nine reported cases of non-familial, Addison's-associated THP are shown in table 3. The remainder of the non-familial, late-onset group did not show signs of Addison's disease at the time of reporting, although some of them did manifest moniliasis. Some of these cases without Addison's disease, had they been followed long enough, might very likely have developed the disease. For example, the case of isolated THP originally reported by McQuarrie (1941) (table 3) was later mentioned by Papadatos (1954), in a report of another case, as having developed Addison's disease.

None of the early-onset cases of THP (table 2), familial or non-familial, had either Addison's disease or moniliasis at the time of reporting. It is possible, of course, that these conditions might later appear in any of them.

The mechanisms responsible for a deficiency of parathyroid hormone in any type of THP are unknown. A search of the literature for autopsied cases of THP reveals only seven such cases (table 4), aside from those previously mentioned as being associated with multiple congenital anomalies. All of these seven cases were of the late-onset, non-familial type, and five of them were associated with Addison's disease. In six cases no parathyroid tissue was found, but in one case parathyroid remnants were discovered. In view of the relatively late

TABLE 3. FAMILIAL, LATE-ONSET THP AND ADDISON'S-ASSOCIATED THP

Reference	Sex	Familial	Addison's	Monili-asis	Age at Onset THP
Sutphin (1943)	M	+	+	+	10 yrs.
	F	+ One Family	+	+	6 yrs.
	F	+	+	+	12 yrs.
Goldman (1952)	M	+	+ (Family history)	−	10 yrs.
	M	+ One Family	+ (Family history)	−	12 yrs.
	M	+	+ (Family history)	−	12 yrs.
Forbes (1956)	M	+ One Family	−	−	3½ yrs.
	F	+	−	−	2½ yrs.
McQuarrie (1941)	M	−	+	−	?5½ yrs.
Whitaker (1956)	M	−	+	+	15½ yrs.
Malloy (1958)	M	−	+	+	?6 yrs.
Forbes (1956)	F	−	+	−	?3 yrs.
Forbes (1956)	F	−	+	−	4½ yrs.
Perlmutter (1956)	F	−	+	−	10 yrs.
Leifer (1953)	M	−	+	−	?3 yrs.
Leonard (1946)	F	−	+	−	?3 yrs.
Papadatos (1954)	M	−	+	−	?10 yrs.

TABLE 4. AUTOPSIED CASES OF THP

Reference	Sex	Age at Onset THP	Addison's	Familial	Parathyroid Glands
Perlmutter (1956)	F	10 yrs.	+	−	None found
Whitaker (1956)	M	15½ yrs.	+	−	None found
Leonard (1946)	F	?3 yrs.	+	−	None found
Forbes (1956)	F	?3 yrs.	+	−	None found
Papadatos* (1954)	M	?5½ yrs.	+	−	None found
Cantarow (1939)	F	3½ yrs.	−	−	None found
Drake (1939)	M	4 yrs.	−	−	Parenchyma replaced by fat cells in all 4 glands.

* Papadotos refers to the follow-up on a case previously reported by McQuarrie (1941)

onset of hypocalcemic symptoms, it is difficult to imagine how the parathyroid glands could have been absent from birth in these cases. It would seem more likely that the development of THP was the result of later damage to the glands, either by exogenous or endogenous factors.

In the cases of early-onset THP (table 2) it might be postulated that the

parathyroid glands are congenitally absent. Another theory might be that of an inborn enzymatic defect interfering with the normal metabolism of parathyroid hormone (or hormones), similar to the enzymatic blocks described in congenital adrenal hyperplasia (Bongiovanni, 1958; Eberlein, 1958) and in goitrous cretinism (Stanbury, 1957).

No information is available regarding post-mortem findings in the early-onset, sex-linked type of THP. Theoretically, however, an enzymatic defect such as postulated could result either in damage to the glands with subsequent atrophy, or in hypertrophy due to an attempt at compensation for inadequate function. Or, compensatory hypertrophy might precede ultimate atrophy. Pursuing the theory of an enzymatic block still further, differences in degree of block might account for some of the differences in age at onset of symptoms and length of survival exhibited by cases of early-onset THP.

It is hoped that the report presented here will arouse interest in more extensive investigation of pedigreees of patients with THP. It is hoped, also, that the classification of THP presented here, although it is obviously tentative, will stimulate authors of new case reports to evaluate their findings in relation to other information in the literature, rather than simply as individual cases. From this approach may come some clarification of the present vast confusion concerning this disease.

SUMMARY

Two cases of neonatal true idiopathic hypoparathyroidism ocuring in male siblings are reported. A pedigree is presented which indicates sex-linked inheritance of THP in this family, and the suggestion is made that the majority of cases of early-onset THP may be inherited in this same pattern.

A distinction is drawn between this sex-linked, early-onset type of THP, and a non-sex-linked type of later-onset. The latter type is divided, on the basis of clinical observations, into familial and apparently non-familial varieties, each of which is further subdivided into those associated with Addison's disease and those which are not apparently Addison's-associated. What portion of the non-sex-linked, late-onset group is genetically determined is at present uncertain.

More thorough investigation of the ancestry of cases of THP reported in the future will serve to clarify what is now merely an implied division of THP into these different types.

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