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Albright's Hereditary Poly-Osteochondrodystrophy

(Pseudo-pseudo-hypoparathyroidism with diabetes hypertension, arteritis and polyarthrosis)

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Introduction

Hypoparathyroidism is a relatively common complication of thyroid surgery. The prevalence of tetany in this series has been variously reported from 0.2% to 5.8%.

Partial parathyroid insufficiency might commonly persist and give rise to long term symptoms even when plasma calcium levels are in a normal range.

Idiopathic hypoparathyroidism (IHP) is however a rare disease. Approximately 100 cases have been reported in the literature, although many more remained unreported. Reviews of the literature on IHP have been given by Drake et al. (1939), Lachmann (1941), Steinberg (1952), and Bronsky et al. (1958). IHP can be hereditary and is possibly incompletely dominant (Béthenod et al. 1964).

In 1942 Albright et al. described a syndrome with biological and clinical findings characteristic of hypoparathyroidism but refractory to parathyroid extract as ascertained by a negative Ellsworth-Howard test. The syndrome was labelled pseudo-hypoparathyroidism (PHP) because the target-organ (renal tubuli) fails to respond adequately to parathyroid hormone. Parathyroid biopsy obtained from some rare cases discloses a nearly normal or slight hyperplastic parathyroid histology (Albright et al., 1942; Elrick et al., 1950; Mann et al., 1962) Bell et al. (1963). The patients affected by this syndrome show a typical morphological syndrome, with various dyschondroplastic anomalies, tissue calcifications and ossifications, exostoses and trophic disturbancies (teeth, eye-lens, skin).

The most prominent clinical features are: short stature (between 145 and 160 cms.), generally less than 60 inches or 152 cms., relative obesity, round face, brachymetacarpy (mainly I, IV and V), brachymetatarsy (mainly IV) and slight mental retardation.

Up to 1962, 69 cases were reported in the literature, the first familial cases being published in 1950 (Elrick et al., 1950). Some cases of PHP are accompanied by

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A.Ge.Me.Ge. – Vol. XIV – N. 3 (1965)

hypertension, diabetes and hypothyroidism. Some cases of PHP seem to have been described under other denominations before the publication of Albright in 1942 (Pende, 1920; Kirklin and Childrey, 1936; Piaggio-Blanco et al., 1936; Martin and Bourdillon, 1940; Himsworth and Maizels, 1940; Lachmann (3 cases, 1941).

Extensive reviews of the literature on PHP have been given by Klotz and Kahn, 1957; Bergstrand et al., 1958; Bronsky et al., 1958; Royer et al., 1959; Nagant de Deuxchaisnes et al., 1960, and Forbes, 1962.

In 1952 Albright, Forbes and Henneman described a syndrome without symptoms or biological findings of tetany, but with the same somatic features as PHP and named it pseudo-pseudo-hypoparathyroidism (PPHP).

Histological examination of the parathyroidis in PPHP does not seem to have been performed up to 1964.

About 100 cases of PPHP have been described up to now. No more than 7 cases were known before 1960. The first familial cases were reported in 1956 (Seringe and Tomkiewicz). It is still in doubt wether the case of McGavack and Reinstein (1941) may be accepted as PPHP (see further). The mother of the patient with PPHP described by Browne (quoted by Elrick et al., 1950) also may have had PPHP. The case 3 and 4 from Gorman et al. (1962) can hardly be accepted as two cases of PPHP. Critical reviews of the literature of PPHP have been given by Mann et al., 1962; Cruz and Barnett, 1962 and Minozzi et al., 1963. An extensive review on PPHP and related problems has not yet been given as far as we known.

Personal observations

We have studied a family with:

1. 1 case of PPHP, diabetes, hypertension, polyarthrosis and arteritis;
2. 1 case of PPHP with polyarthrosis and hypertension;
3. 1 case of PPHP with hypertension;
4. At least 8 other cases of PPHP and at least 2 PPHP " formes frustes ".

This is the second observation in Belgium after the 3 cases described by Nagant de Deuxchaisnes and Hoet in 1960 (Fig. 1).

Another observation of a child of 12 years with PPHP is being studied at present (Dr. O. Steeno, Leuven, Personal communication).

We believe that our pedigree is the first in the medical literature where more than 10 cases of PPHP are found in 4 successive generations (Goeminne, 1963).

When our pedigree study was completed in 1963 a still more extensive pedigree of 125 members (43 were incompletely studied and 22 cases with PPHP discovered) was published recently in 1964 by Hermans, Gorman and Martin from the Mayo Clinic.

III, 15. Proband. R. E., female, 53 years of age, living in Wetteren (Belgium).

Weight at birth, high but unknown.

Diabetes detected at 38 years. She receives daily 60 U of Insuline. Menopause at 47 years. Hypertension noted at 48 years. At present she complains of

polyarticular pains at the ankles, knees, hips and elbows. At the same time she noted asthenia, paresthesia and muscular cramps in the legs, both at rest and with effort.

The *clinical examination* does not reveal any peculiarity. Arterial blood pressure: between 200/100 and 220/120 mm. Hg. The spinal column is slightly painful at percussion. The motility of the joints is normal. The peripheral arteries are palpable. Normal tendineous reflexes. No periferal trophic lesions. The Chvostek and Trousseau reflex is negative. We are puzzled by her bizarre dysmorphic habitus (Fig. 2). She is short stocky build (height: 148 cms.) with a relative obesity (60 kgs.). We note a round face, with a broad nose, a short neck (Figs. 5 and 6). The hair is normal. The fingers are short stubbed, especially the fourth, and there is a typical dimple sign, when the hands are made to a wrist (Fig. 8). The fourth finger is bilaterally shorter than normal (Fig. 10). The nails are broad and short. The toes are also short, especially the fourth. She has a dental prothesis from the age of 47. The skin is dry. The breasts are normal. These somatic features suggest the syndrome named by Albright (1952): Pseudo-pseudo-hypoparathyroidism. The patient told us that other members in the family have analogous anomalies with brachydactyly and short stature.

Somatic features: 1. Height: 150 cms., 2. Weight: 60 kgs., 3. Span: 147 cms., 4. Vertex to pubis: 80 cms., 5. Pubis to sole 70 cms., 6. Head circumference: 56 cms., 7. Neck circumference: 36 cms. 8. Bitrochanteric circumference: 95 cms.

Laboratory examinations

Urine: negative, density 1031. Basal calciuria: 200 mgs. Basal phosphaturia: 600-1000 mgs. Basal natriuria: 120-172 mEq. Basal potassiuria: 42-60 mEq. Sedimentation rate 5/19. Peripheral blood: normal. Uremia: 0.5 g./l. Uricemia: 2.2 mgs.%. Cholesterolemia: 312 mgs.%. lipoprotein 295 U (normal value for the Burstein reaction: 210 U). Alkaline phosphatases, floculation tests and electrophoresis: normal. C.R.P., R.A., L.E. test negative. Antistreptolysine titre: 12 U. B.W. negative. Natriemia: 152 mEq./l. Serum potassium 3.3 to 4.4 mEq./l. Serum calcium: 10.3 - 8.7 - 8.5 - 8.4 - 9.2 - 9.0 mgs.%. Serum phosphate: 2.1 - 2.9 - 2.8 - 4 mgs.%. Phenolsulfophtalein excretion test: 36%, after 15 minutes and 56% after 70 minutes (total urinary excretion). Maximum urea clearance: 50 ml./min. Urinary dilution test: normal. Urinary 17 keto-steroids: 5.44 mgs./24h. Urinary 17-OH-steroids: 8.73 mgs./24h. Urinary adrenalin and nor-adrenalin: normal values. IV calcium loading test after Nordin (15 mgs./kg.: 900 mgs. calcium): after 6 hours 117 mgs. are excreted in the urine. That means that after 6h., 13% of the calcium loading is excreted, which is a normal value. An Ellsworth-Howard test was not performed.

Other examinations

The electrocardiogram is normal, with a long QT interval: 0.42 sec., heart rate: 80 (QT-c = 0.35 sec.).

Oscillometric examination of the legs: low values at the femoral arteries, but

normal at the ankles. Basal metabolic rate: +17%. I.V. Regitine test: negative. Renal radioactive Hippurantest: normal. Ophthalmologic examination: hypertensive retinopathy (stade II-III). No lenticular opacities, no blue sclerae. O.R.L. examination: slight bilateral perception surdity. No otosclerosis.

Radiographic examinations

(Prof. Dr. Van de Velde - Radiologic Dept.).

Hands: bilateral brachymetacarpy IV. Slight brachy-mesophalangy. V-Shaped chondrodystrophic lesions in the middle phalanx of the second finger. Subcutaneous calcifications (Fig. 22).

Arms: slight bilateral radius curvus with typical shortening of the distal epiphyseal part of the ulna (cubitus brevis) (Fig. 30).

Elbows: osteo-chondrodystrophic lesions on the two elbows (Fig. 31).

Shoulders: dyschondroplastic anomalies of the humeral and acromio-clavicular articulations (Fig. 32).

Feet: brachymetatarsy IV of the left foot and global brachyphalangy (Fig. 26).

Legs: calcifications in the femoral arteries. One exostosis on the proximal part of the right fibula (Fig. 35).

Skull: no basal ganglia calcifications. Two unerupted third molar teeth (Fig. 34).

Thorax: slight global heart hypertrophy.

Cervical spine: arthrotic lesions in C6 and C7.

Lumbar spine and pelvis: no abnormalities. No aortic calcifications, but calcification of the femoral arteries (Fig. 36).

I.V. pyelography: normal.

E.E.G. examination

Slow basal rhythm, with paroxysmal spontaneous discharges of thêta activities. Presence of waves of 8 c/sec. of 20 to 30 microvolts, with many very rapid waves of 16 to 18 c/sec. of 10 to 20 microvolts. Hyperventilation improves the synchronisation and the waves of 8 c/sec. and 7 c/sec. appear more clearly. Spontaneous appearance of series of waves of 6 c/sec. and 5 c/sec. with an aplitude of 50 microvolts, generalised in the two cerebral hemipheres.

Bio-electric anomalies, analogous with those seen in hypoparathyroidism (Dr. R. Matthys - Neurologic Dept.; Dir. Prof. Dr. De Busscher).

Other family members

I. 1 and 3: *Volck. X. Y.*: probably normal. Nothing else is known about these persons.
I. 2: *Volck. G.*: very probably short stature and short stubby hands.
I. 4: *Volck. P.* (born in Bambrugge-Belgium): was living in Oordegem. Died when 10 years old. Short stature (about 155 cms.). Was well known by the family to have brachydactyly.

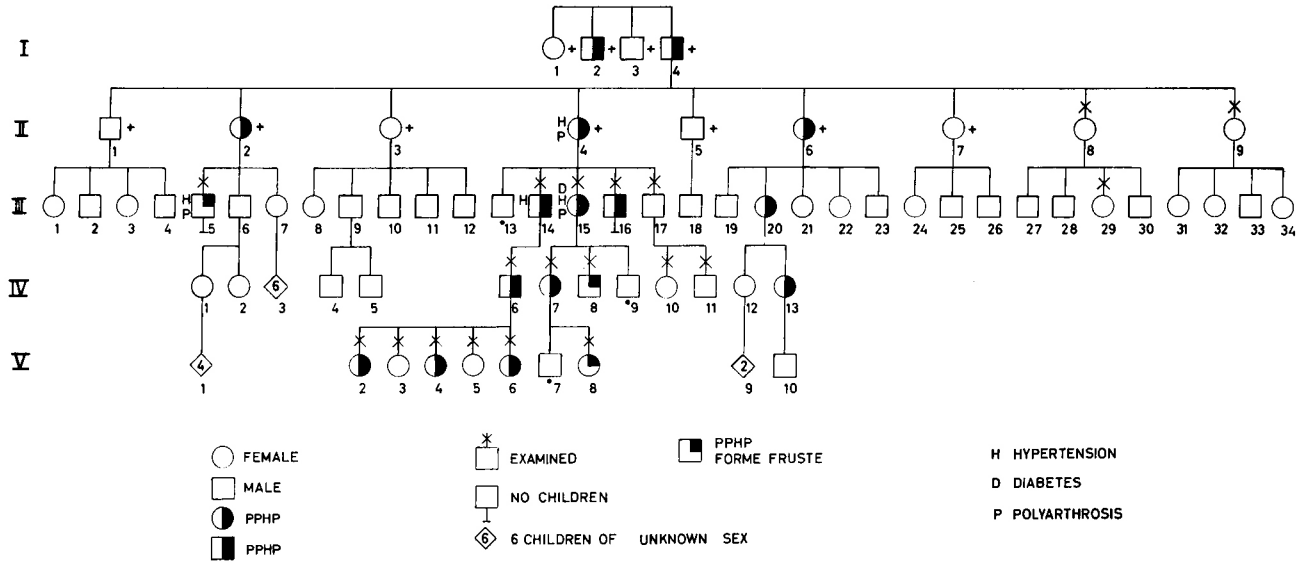

Fig. 1. Albright's hereditary polyosteochondrodystrophy: pseudo-pseudo-hypoparathyroidism with hypertension, diabetes, arteritis and polyarthrosis (personal observation, 1962 and 1963)

Fig. 2. Case III, 15. Short stature, relative obesity, broad face, short extremities

Fig. 3. Case III, 14. Short stocky build in PPHP

Fig. 4. Case III, 16. Short stocky build in PPHP

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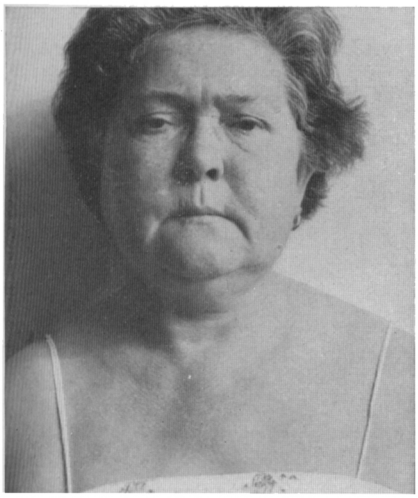

Fig. 5. Case III, 15. Short neck and broad face in PPHP

Fig. 6. Case III, 15. Slight retrognathism in PPHP

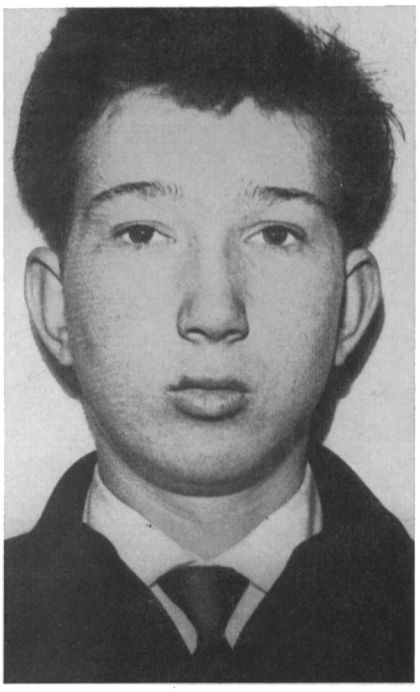

Fig. 7. Case IV, 8. Round face in a case "fruste" of PPHP

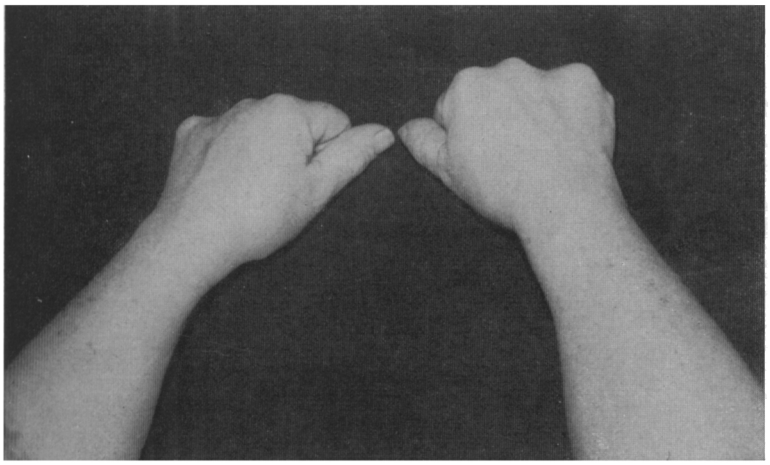

Fig. 8. Case III, 15. Typical "dimple sign" due to a bilateral brachymetacarpy

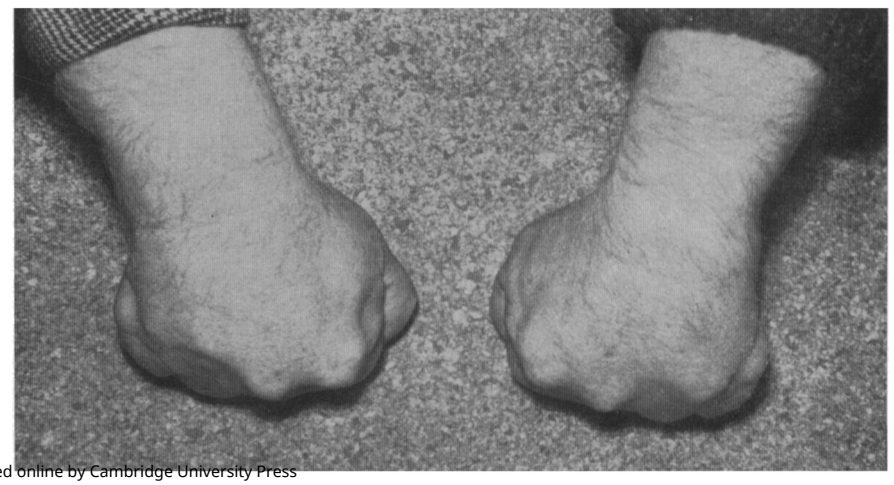

Fig. 9. Case III, 16. Bilateral brachydactyly IV and V (large dimple sign)

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II. 1: *Volck. Aug.*: known to have had normal stature (about 170 cms.) without brachydactyly. Died when 70 years old. 4 normal children without PPHP (III, 1, 2, 3, 4).

II. 2: *Volck. Ros.* (Oordegem): was known to have had a short stature (about 160 cms.) with a relative obesity and round face. She had bilaterally short fingers and short toes. Died when 60 years old from cardiac failure. She had 3 children III, 5, 6, 7.

II. 3: *Volck. M.*: probably no PPHP. Hypertension at 60 years. Obesity. Normal stature (about 170 cms.). No brachydactyly. Died at 73 years. She had 5 children without PPHP (III, 8, 10, 11, 12).

II. 4: *Volck. Palm.*: PPHP. Was said to have had a short stature (about 155 cms.), obesity, a round face and brachydactyly of the hands and feet. Polyarthrosis and hypertension at 70 years. Also (senile?) cataract. Died at 78 years from a cancer of the stomach. She had 5 children: three with PPHP (III, 14, 15, 16).

II. 5: *Volck. Vit.*: normal. Stature about 180 cms. Died at 70. Had one normal son (III, 18).

II. 6: *Volck. Colar.* (Wetteren): was known to have had a short stature (about 160 cms.), a round face, with a stocky build with obesity, and brachydactyly of the hands and feet. No hypertension. She had 5 children. Only one daughter (III, 20) had PPHP. The others (III, 19, 21, 22, 23) are all normal.

II. 7: *Volck. Louise*: is said to have been normal. There was no short stature, no brachydactyly, no hypertension, and no obesity. She died at 50 years from a cancer of the stomach. Her 3 children are said to be normal (III, 24, 25, 26).

II. 8: *Volck. Leontine* (Wetteren): 76 years old when seen by us in 1962. Stature: 170 cms. No hypertension, no obesity and no brachydactyly. Her children (III, 27, 28, 30) are said to be normal. Her daughter (III, 29) is definitely normal.

II. 9: *Volck. Margr.* (Wetteren): 72 years old when seen by us in 1962. No brachydactyly, no hypertension, no obesity and no polyarthrosis.
Somatic features: Height: 160 cms., weight: 60 kgs., span 159 cms., Vertex to pubis: 81 cms., pubis to sole: 78 cms., head circumference: 55 cms.
Glycemia: 1.08 g.‰, uremia: 0.46 g.‰, kreatininemia: 1.0 mg.%, cholesterolemia: 320 mg.%.
Her four children are known to be normal (III, 31, 32, 33, 34).

III. 5: *V. Kerck. A.* (Borsbeke), 66 years old when seen in Nov. 1963. Hypertension (19/10) known for years. Polyarthrosis complaints for about 5 years. No diabetes. Somatic features: height: 165 cms., weight: 70 kgs., span: 160 cms., vertex to pubis: 81 cms., pubis to sole: 84 cms., no brachydactyly of hands and feet on clinical examination. A slight brachymetatarsy could no be confirmed, because X-ray examinations were not available. He has no children.

III. 6 and 7: Normal person, with normal stature (170 cms.). The children of III 6 and III 7, IV, 1, 2 and IV 3 are all normal.

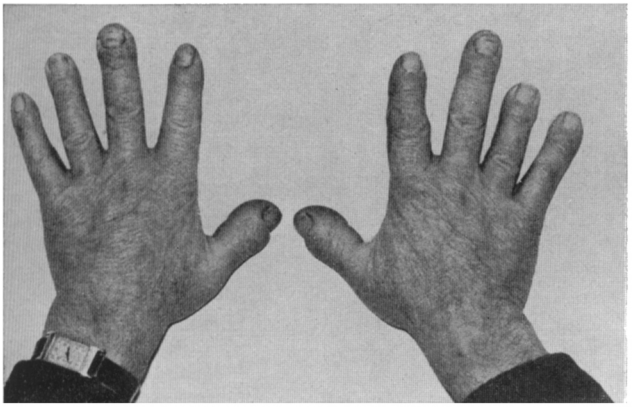

Fig. 10. Case III, 15. Bilateral brachydactyly I and V of the hands

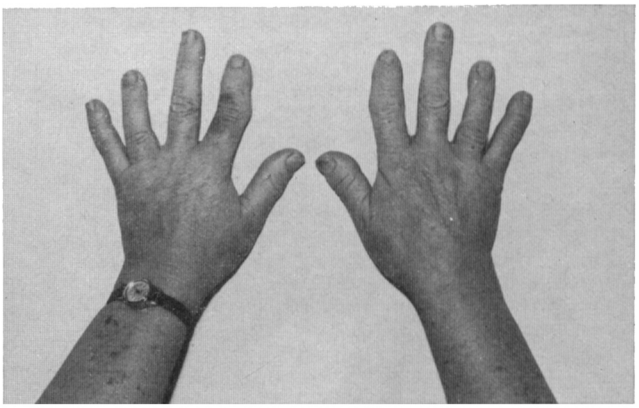

Fig. 11. Case III, 14. Short stubby hands. Brachydactyly mainly I and IV

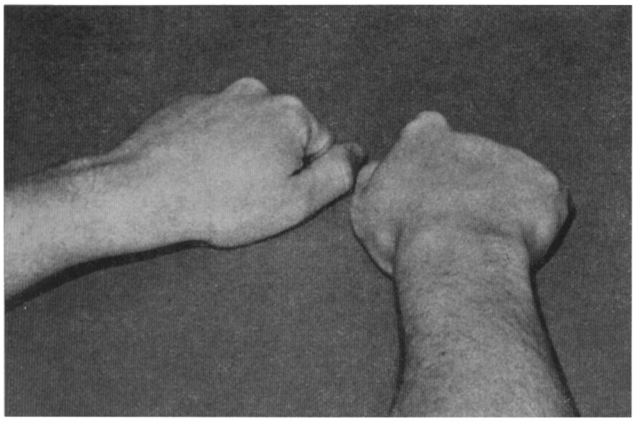

Fig. 12. Case III, 16. Short stubby hands in PPHP, with brachydactyly mainly I, IV and V

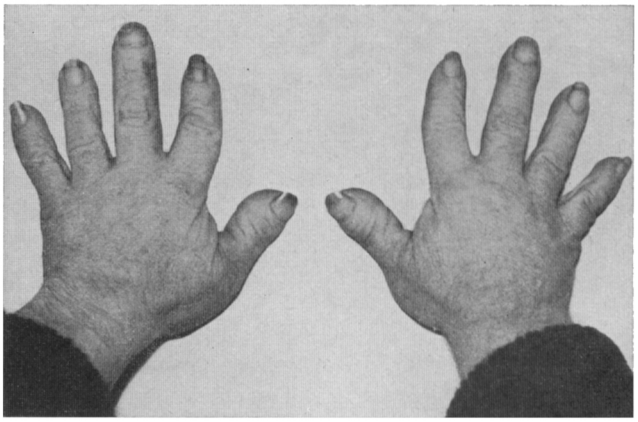

Fig. 13. Case IV, 6. Brachydactyly IV and V on the left hand and III, IV and V on the right hand

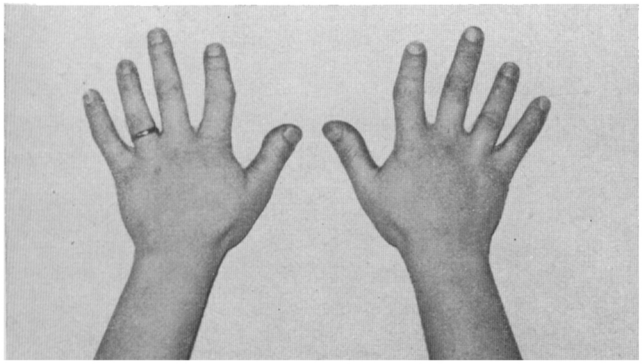

Fig. 14. Case IV, 7. Bilateral brachydactyly IV of the hands with a typical distal deformity of the indexfinger

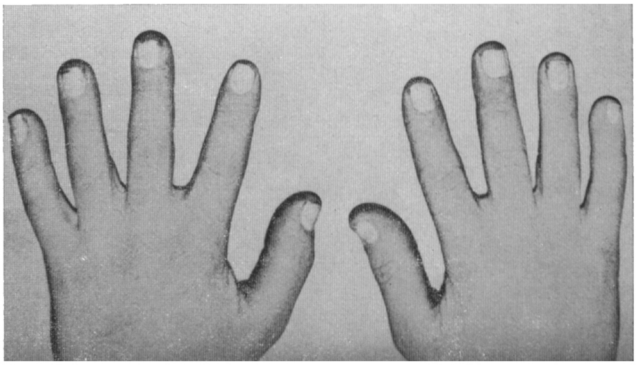

Fig. 15. Case IV, 8. Very slight bilateral brachydactyly IV (confirmation by radiographic examination)

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III. 9: *Danck. P.*: no PPHP. Suffered from a mental disease (psychosis). Nothing else is known about this patient.

III. 13: died at 6 months from convulsions. Nothing else is known about this child.

III. 14: *Rls. Henr.* (Wetteren): 60 years old when seen by us in 1963 (Fig. 3). Extensive dental caries when 20 years old. Stomach ulcer when 52 years old. Hypertension (20/10) when 55 years old.
Somatic features: height: 160 cms., weight: 55 kgs., span 161 cms., vertex to pubis: 80 cms., pubis to sole: 80 cms., head circumference: 57 cms. bilateral brachymetacarpy I and IV (Figs. 11 and 23) and brachymetatarsy IV bilaterally (Figs. 17 and 27). Radius curvus and short ulna. Chondrodystrophic lesions on the elbows (Fig. 29). No diabetes. Unerupted molar teeth (Fig. 33). Bad vision. No mental retardation. Eczema on both hands.
Urine: albumin: neg.; sugar: neg.; specific density 1022.; cholesterol: 310 mgs.%.

III. 16: *Rls. Alf.* (Wetteren): 49 years old when examined by us in 1962. Good health. Sound teeth. Normal dry skin. No diabetes, no hypertension, no polyarthrosis. Somatic features: round face and very stocky build (Fig. 4). Height: 159 cms., weight: 67 kgs., span 149 cms., vertex to pubis 80 cms., pubis to sole: 79 cms., head circumference: 57 cms. Bilateral brachymetacarpy IV and V (Figs. 9 and 12).
Short toes and severe hallux valgus (Fig. 18). Short broad nails (thumbnail 16 × 12 mms.). Bad vision. He has no children. Urine: alb.: neg.; sugar: neg., density 1022; cholesterol: 265 mgs.%.

III. 17: *Rls. Kam.* (Beveren Waas): 45 years old when seen by us in 1963. Normal, no features of PPHP. No brachymetacarpy, no diabetes, no hypertension and no polyarthrosis.
Height: 172 cms., weight: 72 kgs., urine: alb neg.; sugar: neg. density 1017. Cholesterol: 260 mgs.%. He has two normal children (IV, 10, 11).

III. 20: *Sch. L.* (Brussels): about 60 years old. She has 2 daughters, one with PPHP (IV, 13). The other daughter is normal and also her two children (V9) are thought to be normal.

IV. 6: *Rls. Rob.* (Melsele-Waas): 33 years old when seen in 1962. PPHP. Sound teeth. No round face. Normal skin. No diabetes, no hypertension.
Somatic features: height: 156 cms., weight: 61 kgs., vertex to pubis: 83 cms., pubis to sole: 75 cms., span: 152 cms., head circumference 58 cms. Brachymetacarpy: left side IV, right side III, IV, V. (Fig. 13). Brachymetatarsy: left: IV, right III and IV (Fig. 19). He has 5 female children of whom three have PPHP (V, 2, 4, 6). Two are normal (V, 3, 5).

IV. 7: *V. d. W. Paula* (Heusden): 30 years old. PPHP. No complaints. Sound teeth. Slight retrognathism. Bilateral brachymetacarpy IV (Figs. 14 and 24). Short toes (Fig. 20). No diabetes, hypertension or polyarthrosis. Had undergone myomectomia. Had exzema when primigravida. Normal menstruations. Somatic features: height: 153 cms., weight: 53 kgs., span: 145 cms., vertex to pubis: 81 cms., pubis to sole: 72 cms., head circumference: 56 cms. Short broad

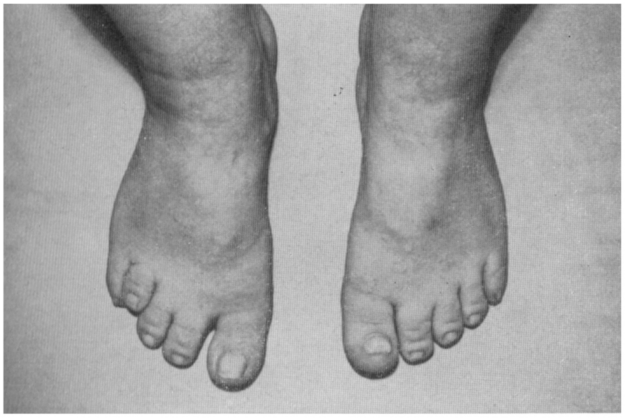

Fig. 16. Case III, 15. Brachydactyly IV on the right foot and global short toes

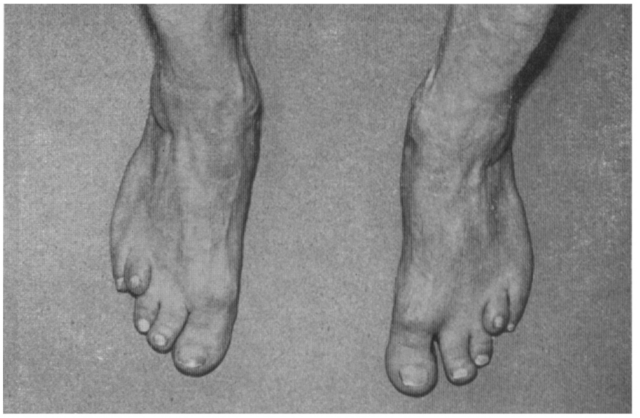

Fig. 17. Case III, 14. Bilateral brachydactyly IV of the feet. Bilateral partial subcutaneous syndactylism II and III

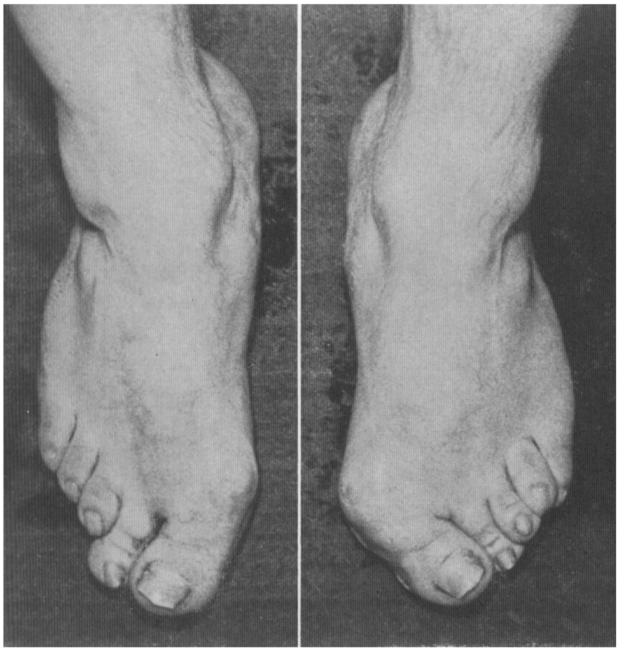

Fig. 18. Case III, 16. Short toes and severe hallux valgus in PPHP

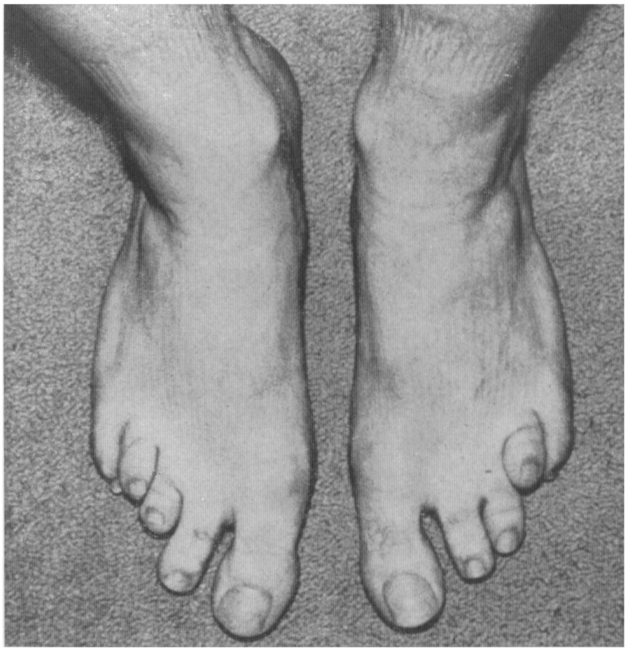

Fig. 19. Case IV, 6. Brachydactyly IV on the left foot and III and IV on the right foot

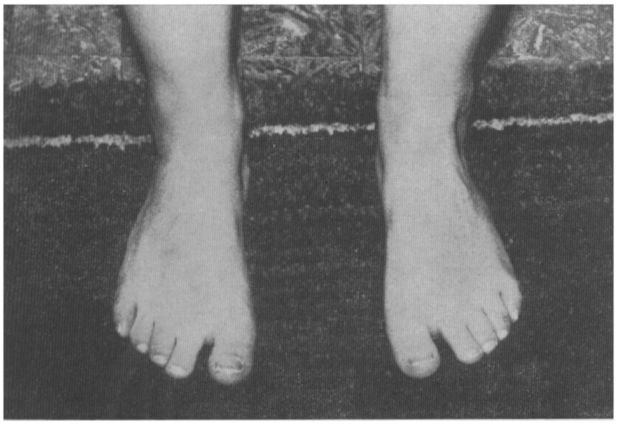

Fig. 20. Case IV, 7. Short toes in PPHP

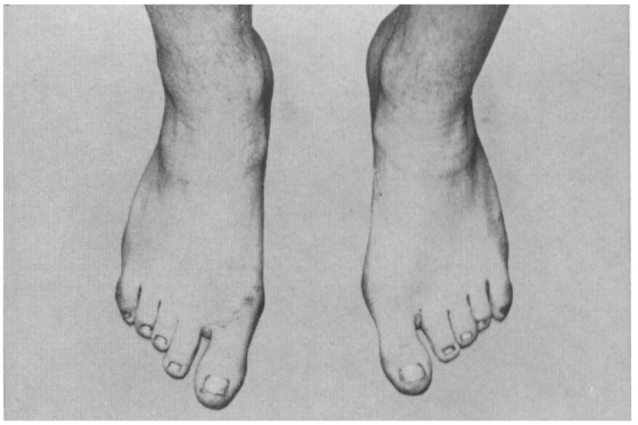

Fig. 21. Case IV, 8. Short toes in PPHP (Global brachyphalangy as confirmed by radiographic examination)

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nails: 12 × 10 mms. Her first child (V, 7) died when 3 weeks old from pneumonia (?). A second living child has possibly PPHP, with brachymetacarpy (V, 8).

IV. 8: *V. d. W. W.* (Wetteren): 17 years old when seen in 1962 (Fig. 7). Somatic features: stature 167 cms., span 163 cms., vertex to pubis 84 cms., pubis to sole: 83 cms. Slight bilateral brachydactyly IV (Figs. 15 and 25). Short toes (Figs. 21 and 28).
Cholesterol: 305 mgs.%. "Forme fruste" of PPHP with slight brachymetacarpy and normal stature.

IV. 9: Died when 3 years old, probably from diphtheria. Nothing else is known about this child.

IV. 10: *Rls. M.*: 15 years old. Normal. No brachydactyly. Height: 162 cms., weight: 54 kgs.

IV. 11: *Rls. P.*: 14 years old. Normal. No brachydactyly. Height: 172 cms., weight 62 kgs.

IV. 13: she has probably PPHP (short stature, stocky build and brachydactyly. Her child (V, 10) 2 years old is said to be normal.

IV. 12: normal person, with two normal children (V, 9).

V. 1: the 4 children of IV, 1 are all normal.

V. 2: *Rls. Bea*: 8 years old when seen in Dec. 1963.
PPHP. No complaints. Somatic features: round face, slight stocky build. Height at 7 years: 116 cms. At 8 years: 120 cms. Span at 8 years: 107 cms. Bilateral brachymetacarpy I and IV. Bilateral brachymetatarsy IV. No laboratory or X-ray studies available.

V. 3: *Rls. Jo*: 6 years old, when seen in Dec. 1963. Normal. No complaints. Somatic features: proportionate build. Height: at 5 years: 116 cms., at 6 years: 120 cms. Span at 6 years: 118 cms. No laboratory or X-ray studies available.

V. 4: *Rls. A. M.*: 5 years old when seen in Dec. 1963. PPHP. No complaints. Somatic features: slight round face and stocky build. Height at 4 years, 110 cms.; at 5 years, 115 cms. Span at 5 years, 103 cms. Bilateral brachymetacarpy I and IV. Short toes with brachymetatarsy IV on the right side. No laboratory or X-ray studies available.

V. 5: *Rls. G.*: 4 years old when seen in Dec. 1963. Normal. No complaints. Proportionate build. Somatic features: height at 4 years: 104 cms., span at 4 years: 95 cms., no laboratory or X-ray studies available.

V. 6: *Rls. Lut.*: 3 years old when seen in Dec. 1963. Very probably PPHP. No complaints. Somatic features: height at 3 years, 96 cms., span at 3 years, 85 cms. Bilateral brachymetacarpy IV, short stubby toes. No laboratory or X-ray studies available.

V. 7: Died early in childhood. Nothing else in known about this child.

V. 8: *Pl. Car.* (Heusden): 10 months old when seen in 1962. Normal birth-weight. Height, 71 cms. Possibly PPHP.

V. 9: Two normal children.

V. 10: Normal child.

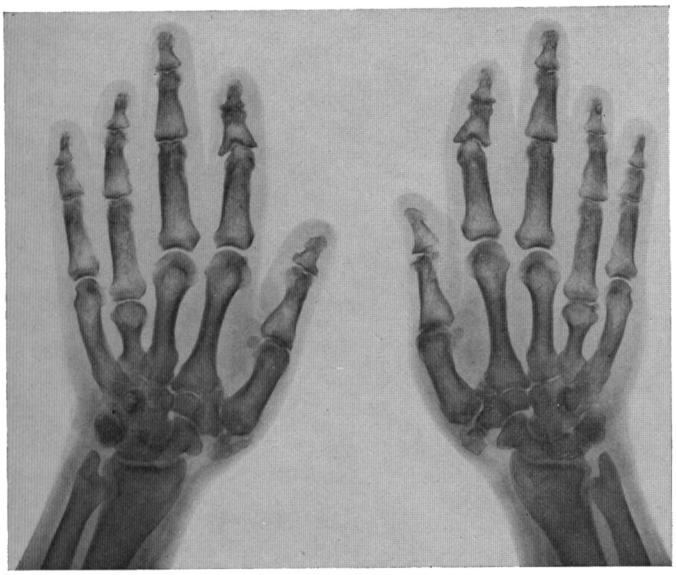

Fig. 22. Case III, 15. Bilateral brachymetacarpy IV. Typical V-shaped dyschondroplastic anomalies on the proximal ends of the middle phalanx of the 2nd finger. Partial synostosis of this middle phalanx with the distal phalanx. Subcutaneous ossifications on the wrist

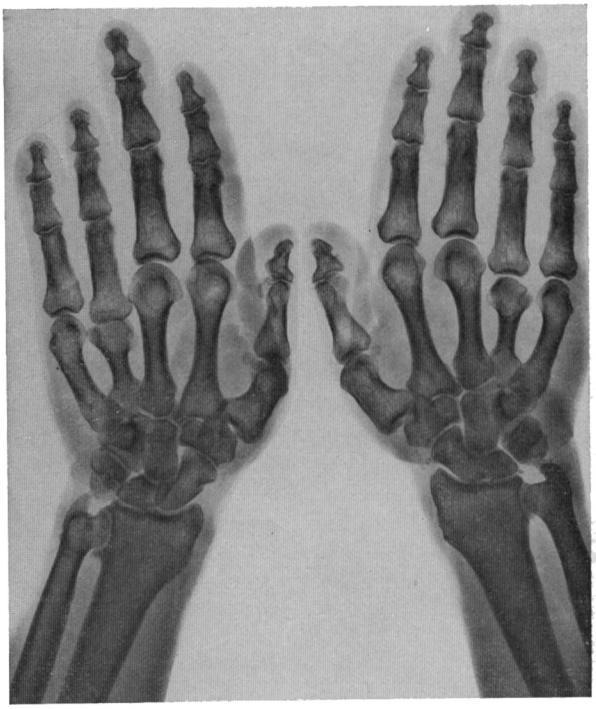

Fig. 23. Case III, 14. Bilateral brachymetacarpy I and IV

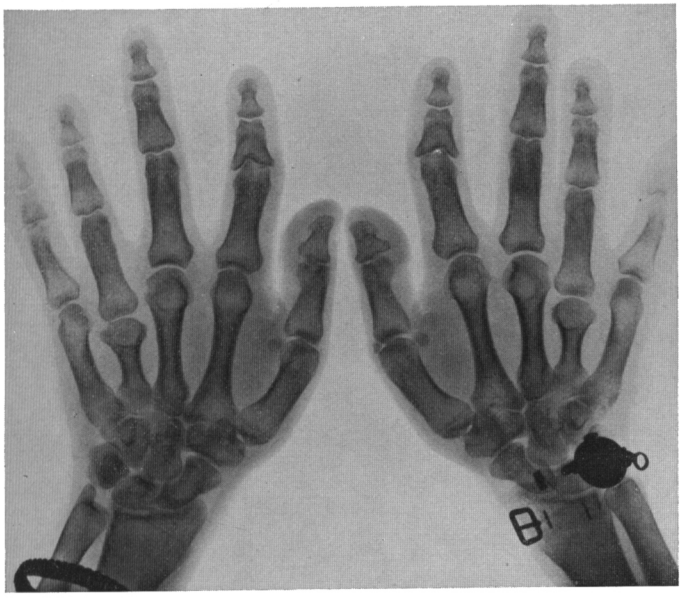

Fig. 24. Case IV, 7. Bilateral brachymetacarpy IV. Typical V-shaped dyschondroplastic anomalies on the proximal end of the middle phalanx of the 2nd finger

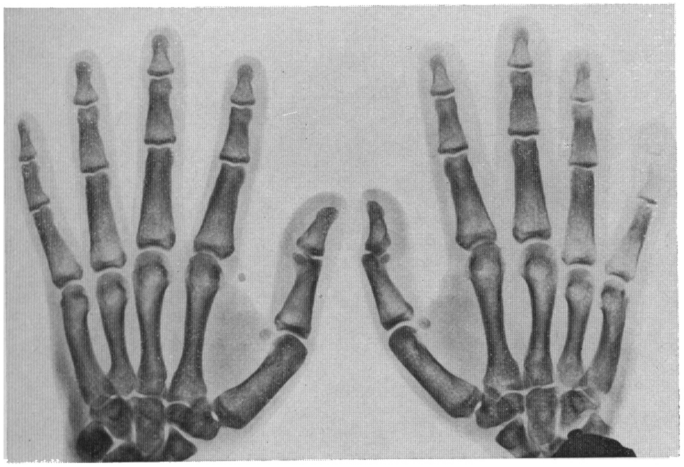

Fig. 25. Case IV, 8. Very slight bilateral brachymetacarpy IV in a "forme fruste" of PPHP. Positive "metacarpal sign"

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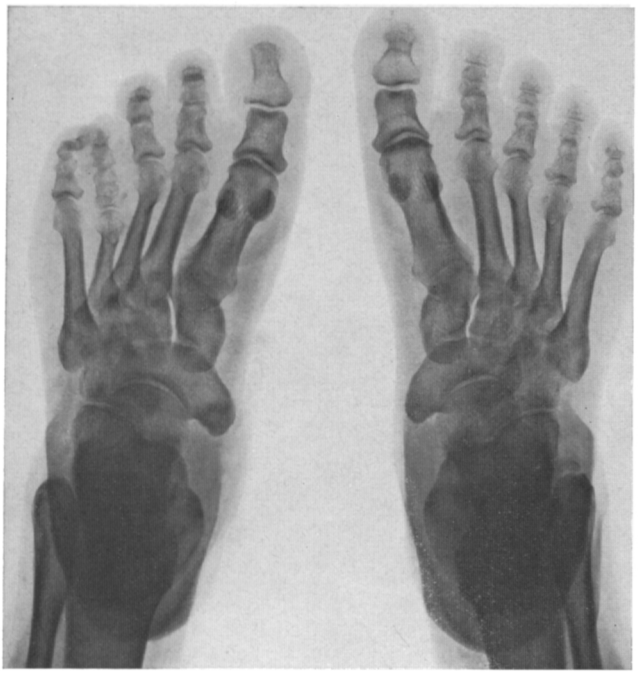

Fig. 26. Case III, 15. Brachymetatarsy IV of the left foot. Global brachymesophalangy

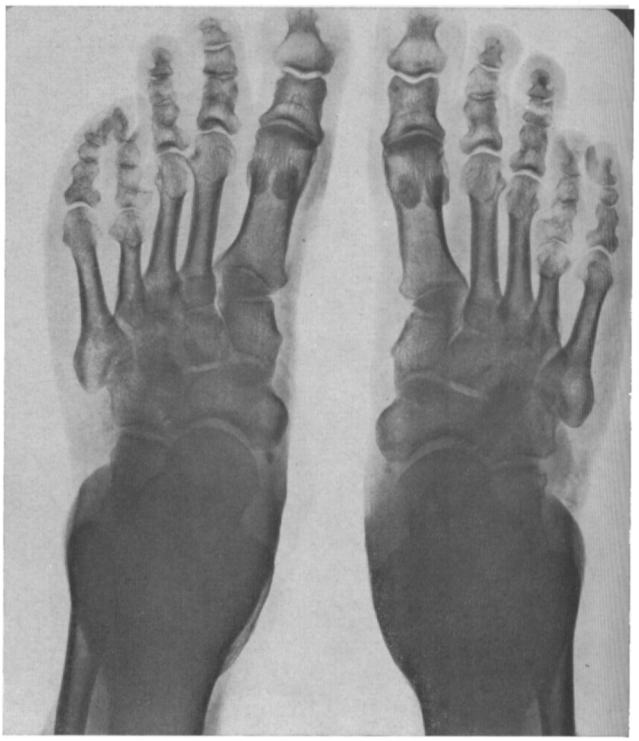

Fig. 27. Case III, 14. Bilateral brachymetatarsy IV and global brachymesophalangy

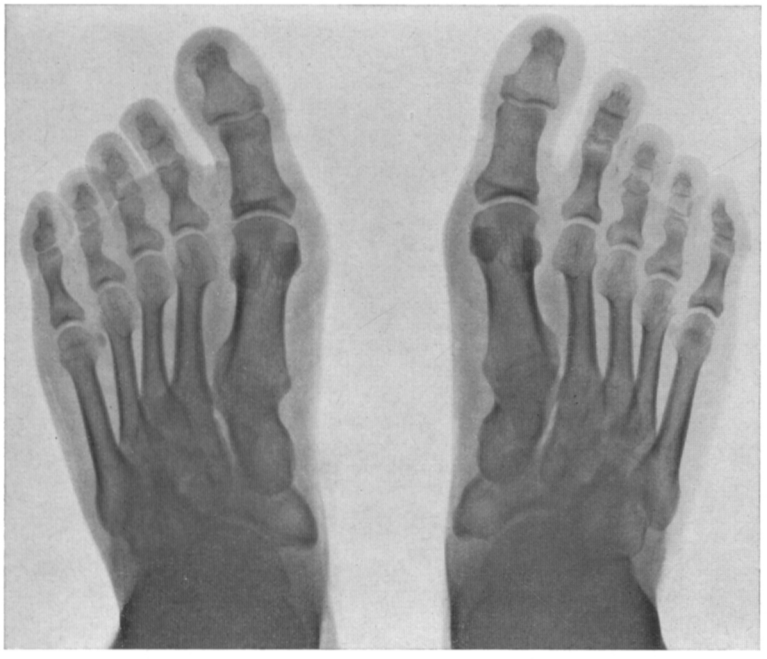

Fig. 28. Case IV, 8. Global brachyphalangy of the toes in a " forme fruste " of PPHP

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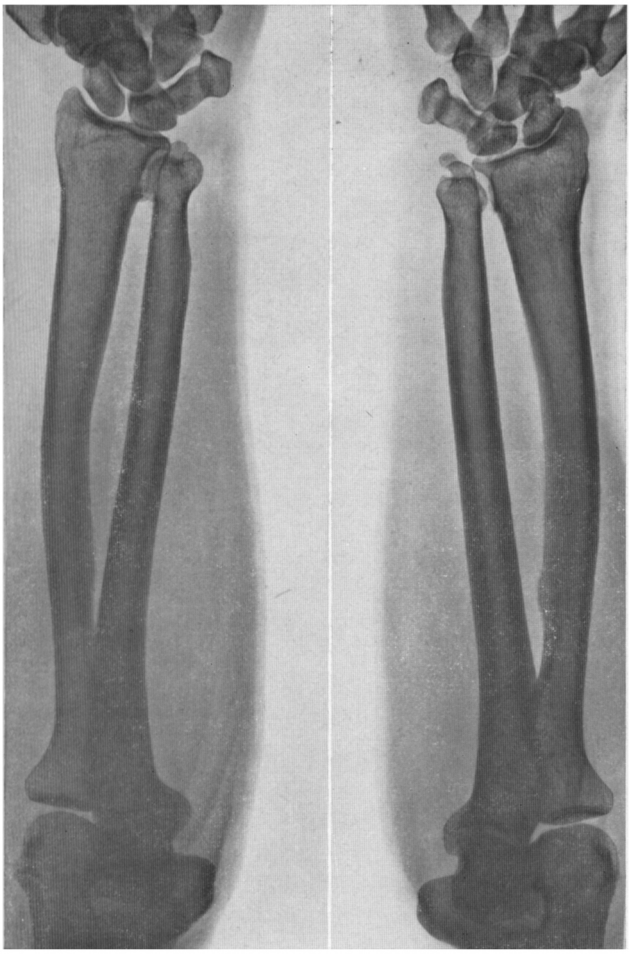

Fig. 29. Case III, 14. Ulna brevis and slight radius curvus

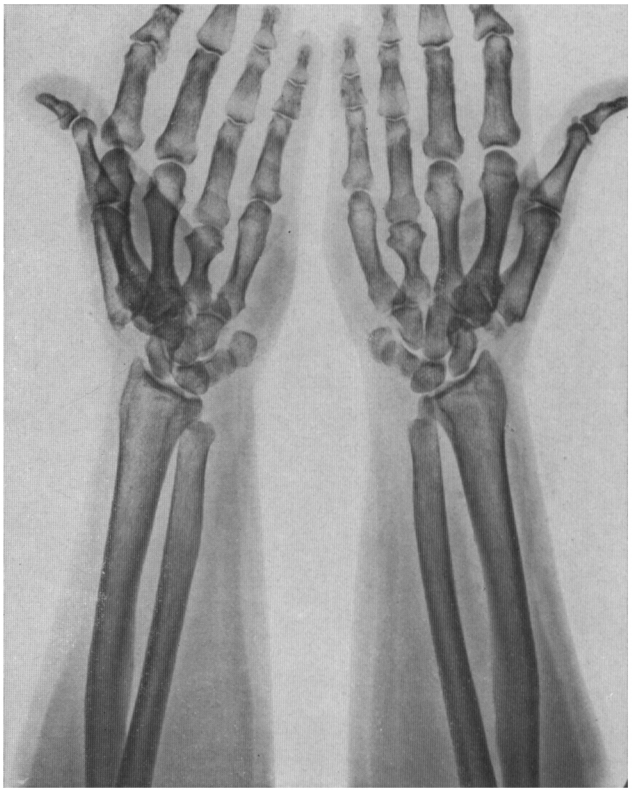

Fig. 30. Case III, 15. Ulna brevis and slight radius curvus

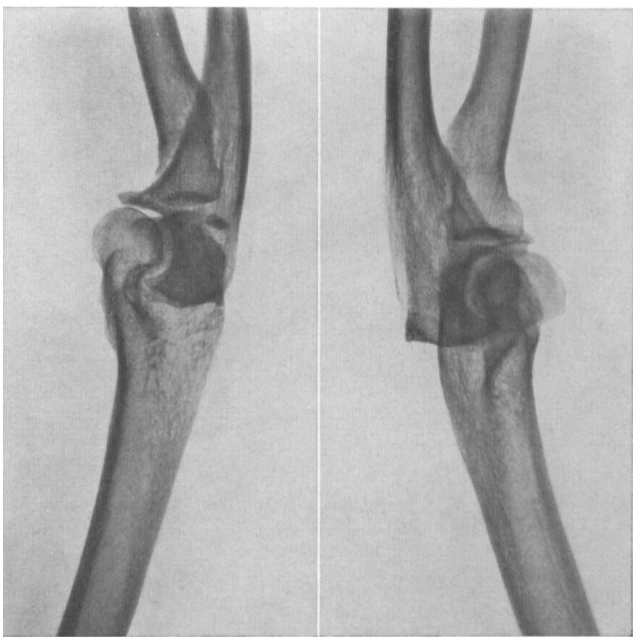

Fig. 31. Case III, 15. Dyschondroplastic anomalies on the elbows and abnormal bone density

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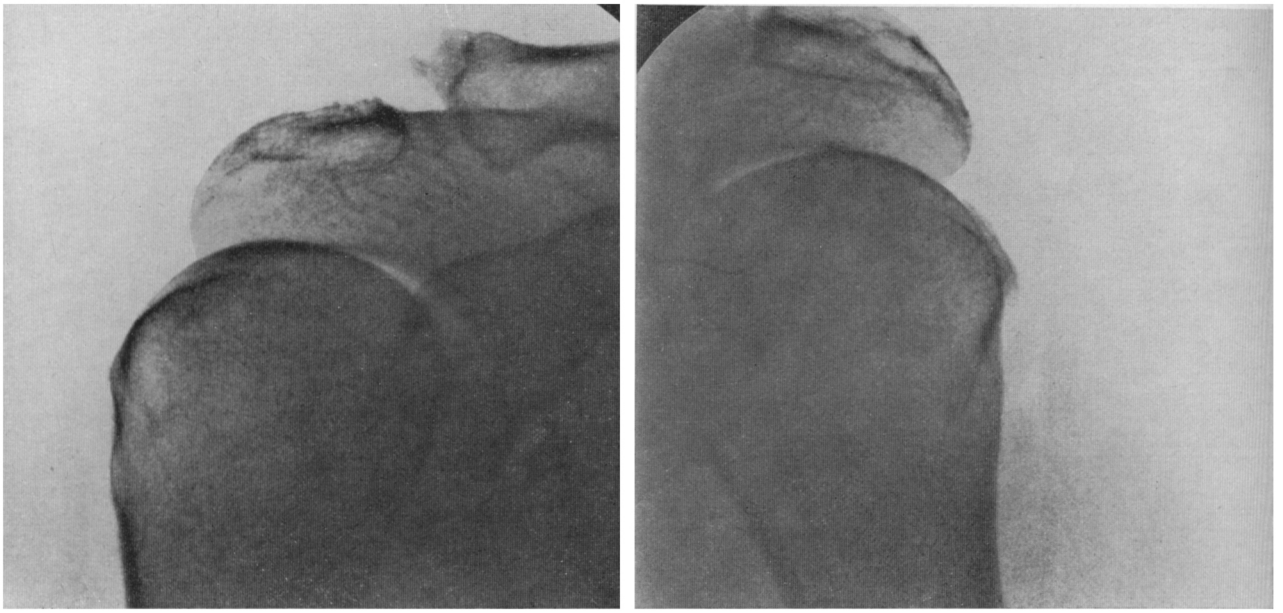
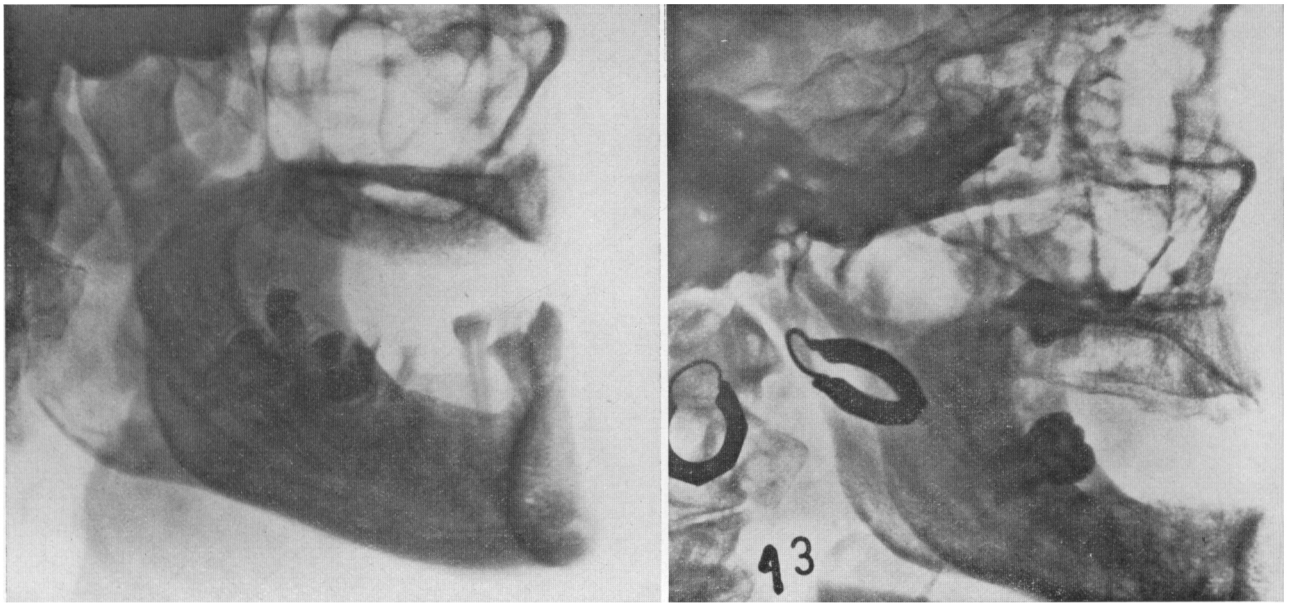


Fig. 32. Case III, 15. Dyschondroplastic anomalies of the humeral and acromioclavicular articulations



Figs. 33 and 34. Case III, 14 and III, 15. Unerupted molar teeth

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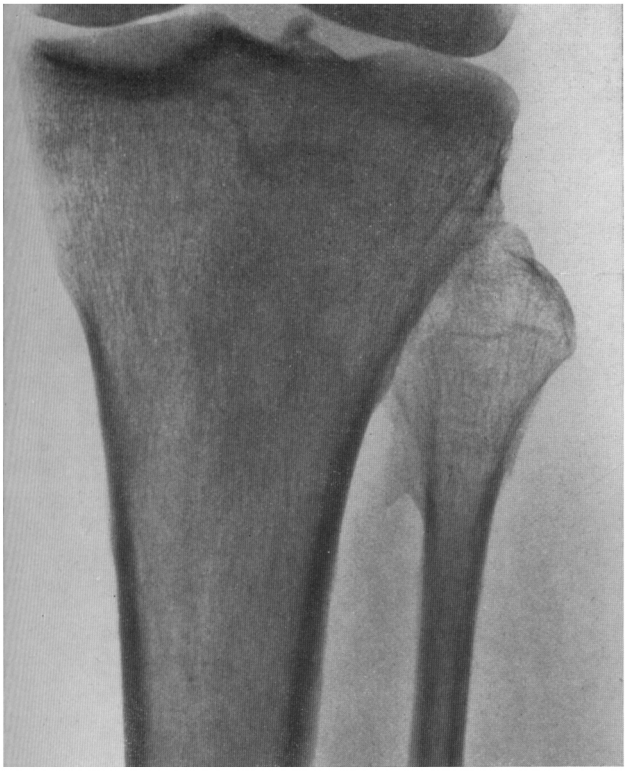

Fig. 35. Case III, 15. An exostosis on the proximal fibula end

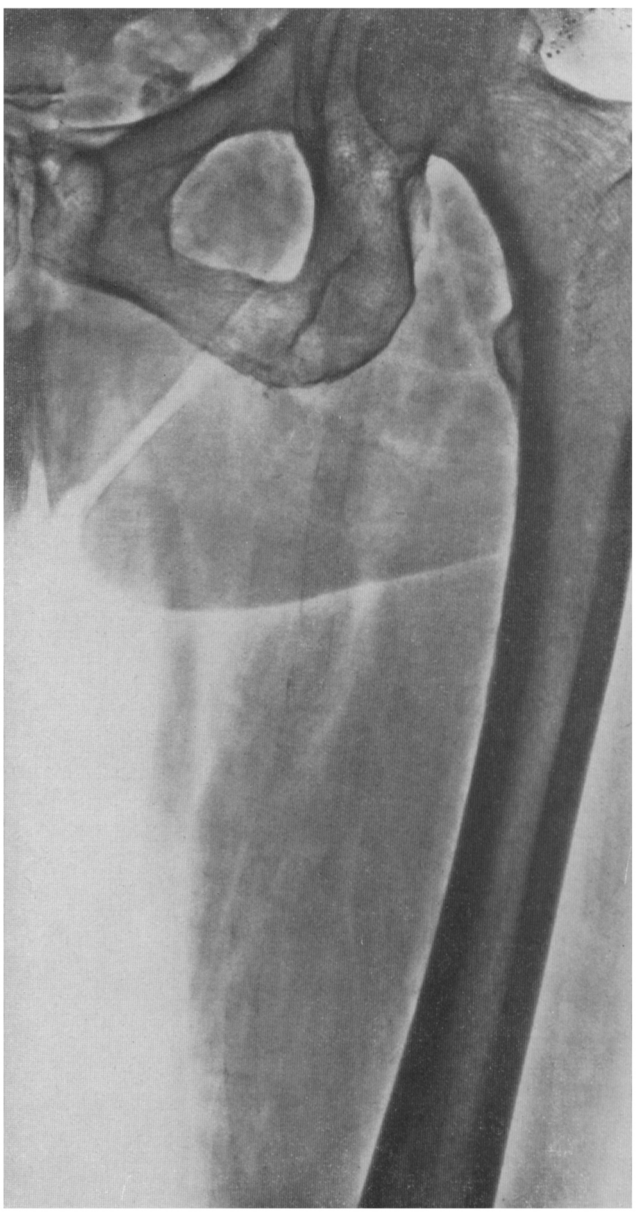

Fig. 36. Case III, 15. Calcification of the femoral arteries in PPHP

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Biological syndrome

Nearly all the cases of PPHP display a normal serum calcium and phosphate (Tab. 1.)

Some rare cases disclose a slight hypo-calcemia and a slightly elevated serum phosphate (see further).

Only in a few cases the blood magnesium is recorded; 2.5 mgs.% in the case of Ray and Gardner (1959).

Nearly all cases show normal serum alkaline phosphatase values, although a tendency to low values is to be noted. Slight hypercholesterolemia may occur without hypothyroïdism (Miles and Elrick, 1955; Tanz, 1960; Ahmed 1961).

Urine analyses and renal function are usually normal.

The basal 24 hour calciuria is normal (100-250 mgs.) in PPHP (Tanz, 1960; Schwarz, 1961; Adrian et al., 1963; personal observation, 1963).

The basal 24 hour phosphaturia is normal (600 to 700 mgs.) in PPHP (Hortling et al., 1960; Gorpe et al., 1961).

A decreased calciuria in PPHP is however noted by Seringe and Tomkiewicz, 1956; Mc Neely et al., 1959; Royer et al., 1959 (2nd, 3rd and 4th case); Tanz, 1960 (2nd case); Vartio and Meronen, 1961; de Sèze et al., 1961. A low phosphaturia is noted by Adrian et al. (1963).

In some rare cases of PPHP both the calciuria and phosphaturia are decreased in children (Miles and Elrick, 1955; de Meulemeester, 1961).

PPHP shows a normal excretion either from aminoacids or phenolic acids (Sutton, 1962; Jancar, 1965).

Ellsworth-Howard test (E-H test)

Administration of parathormone produces an increase of phosphaturia (renal response) and an increase of calcemia (skeletal response) in such cases where these two target organs are normal.

The response in patients with PPHP to injected parathormone has not been consistent and has ranged from no response; Smulyan and Raïsz (1959), passing by a slight response; (Miles and Elrick, 1955; Roche, 1955; Wallach et al., 1956; Nagant de Deuxchaisnes et al., 1960; Schwarz, 1961; to a normal response (Laligant, 1957; Stecker, 1961; Benedek and Danowski, 1962; Minozzi et al., 1963).

In other instances no responses were obtained, due to inactive extracts (Albright et al., 1952; Mc Neely et al., 1956; Gilgore et al., 1962), where the same lot of parathormone failed to give a response in normal control subjects.

In still other cases the tests were reported as negative but no control study was done (Ray and Gardner, 1959, Barr et al. (1960) Tanz (1960) Hortling et al. (1960); Schöngut and Cserhati, 1963). Contradictory results may arise on reiterated tests (Nagant de Deuxchaisnes et al., 1960). The spontaneous morning-rise in phosphate excretion was not always taken into account in still other cases, and was probably interpreted as induced phosphaturia (Danowski, 1962).

Tab. 1

Biological syndrome in PPHP

Serum calcium	normal
Serum phosphate	*normal or very slight increase*
Calciuria	normal or very slight decrease
Phosphaturia	normal or very slight decrease
Alkaline phosphatases	normal
Ellsworth-Howard test	slight response

Clinical syndrome in PPHP

Tetany	: absent
Chvostek sign	: occasionally present
Paresthesias	: occasionally present

Morphological syndrome of PPHP

Short stature	85%
Round face	80%
Relative obesity	90%
Relative short extremities	90%
Brachymetacarpy	95%
Brachymetatarsy	35%
Slight brachyphalangy	10%
Partial cutaneous syndactylism	10%
Short broad nails	70%

Osseous and trophical syndrome in PPHP

Ectopic calcifications and exostoses	60%
Basal ganglia calcifications	14%
Hyperostosis frontalis interna	10%
Arterial calcifications	5%
Skin dystrophy	20%
Dental dystrophy	30%
Nail dystrophy	10%
Lenticular opacities	15%
Blue sclerae	8%
Radius curvus	10%
Cubitus brevis	10%
Coxa vara	5%

Clinical conditions and endocrinopathies associated with PPHP

Hypertension	25%
Diabetes	25%
Polyarthrosis	15%
Hypothyroidism	25%
Periphereal arteritis	25%
Slight mental retardation	65%

Tab. 2. Increase of phosphaturia in response to administration of parathyroid extract. Ellsworth-Howard test

	Increase of phosphaturia
Normal persons	3-4
Idiopathic hypoparathyroidism	10
Pseudo-hypoparathyroidism	0
Pseudo-pseudo-hypoparathyroidism	2-3

It seems that no great diagnostic significance can be attached to the E-H test in view of the multiplicity and variability of factors involved in the interpretation of its results (Mac Gregor and Whitehead, 1954; Mann et al., 1962).

Grounds for lack of confidence in this procedure are summarized by Mann et al., 1962.

This Ellsworth-Howard test is no longer considered as a reliable procedure for diagnosis or classification, nor as a valid clinical proof of hormone resistance. However, average responses are seen in Tab. 2, were it is seen that PPHP possibly represents an intermediate state between normal and pseudo-hypoparathyroidism concerning renal-end organ responsiveness (see also Fig. 39).

Calcium infusion test of Howard

An elevation of the serum calcium level in normal persons will decrease the production of the parathyroid glands, causing a rise in the serum inorganic phosphate concentration with a marked reduction in the urinary phosphate excretion. A decrease of the phosphate clearance is also observed.

A calcium infusion test according to Howard in cases with PPHP disclosed a nearly normal response with a clear decrease (—30%) of the phosphaturia (Mc Neely et al., 1956; Gorpe et al., 1961; Schwarz, 1961). By adjunction of 1,000 U of Parathormone, this decrease of phosphaturia persisted (Schwarz, 1961).

However, Smulyan and Raïsz (1959) found only a slight decrease of the phosphate: kreatinine clearance from 0.2 to 0.1 after an intravenous calcium loading, in a patient with PPHP. Low responses were also obtained by Wallach et al., 1956.

Hortling et al. (1960) and Adrian et al., 1963 found only a very slight or insignificant decrease (—4%) of the phosphaturia after IV calcium loading in PPHP. The Nordin test in these cases of PPHP indicates also that no more than 10 to 20% of the calcium loading is excreted in the urine in the first 24 hours. This is also seen in osteomalacia. The reason for this is not yet clear (abnormal bone avidity for calcium?).

A two- or three-fold increase of the calciuria after calcium loading is however seen by Tanz (1960), Hortling et al. (1960) and Schwarz (1961).

Further studies with the Ellsworth-Howard test and the Calcium loading are necessary in this syndrome.

Changes in TRP% values, rather than in average urinary phosphate values per hour, before and after parathyroid injection may seem to give more valuable results in the future.

Calcium balance studies, Edetic acid infusion tests and sodiumphytate tests, to our knowledge, have not yet been performed in patients with PPHP.

These tests will perhaps reveal some slight relative hypoparathyroid state in such cases.

Clinical symptoms

PPHP is generally a symptomless disease. Overt tetany does not occur in PPHP. Only some cases have been described by French authors to display a positive Chvostek sign despite a normo-calcemic state. Seringe and Tomkiewicz (1956), Royer et al. (1959), Klotz et al. (1962) noted in 14 cases, 12 patients with positive Chvostek sign after hyperpnoe. The Erb and Trousseau sign are always negative. But paresthesia, tingling and numbness in the legs may occur. Vague abdominal discomfort is noted in some instances. The general health and longevity are normal.

The diagnosis is most often made only in the third and fourth decade of life.

Electromyographic pattern in PPHP

Electromyographic examination (chronaxy, rheobases) were performed only in a few patients and were found normal by Nagant de Deuxchaisnes et al. (1960).

However, repetitive activity with " multiplets ", as seen in tetany, is noted in normocalcemic PPHP patients by Royer et al. (1959).

Also in 11 cases with PPHP, Klotz et al (1962) noted EMG abnormalities suggesting latent tetany in 9 patients.

More investigations are clearly needed in this field and would be very promising. We were unfortunatly not able to perform such an investigation in our patients.

Electrocardiographic anomalies

Long QT intervals are seen in IHP with hypocalcemia.

The QT interval in PPHP is normal (Seringe and Tomkiewicz, 1956). In certain cases of PPHP the QT interval seems to be of a high normal value. Miles noted a QT interval of 0.37 seconds for a rate of 72/min. (QTc = 0.36). In our proband the ECG was practically normal, however with a long QT interval of 0.42 seconds for a rate of 80/min. (QTc = 0.35 seconds). Further observations on PHP and PPHP are needed in this field.

Electroencephalographic pattern in PPHP

Electroencephalographic abnormalities are common in PPHP, as stated by Miles and Elrick (1955), Roche (1955), Mc Neely et al. (1956), Seringe and Tomkiewicz (1956), Casey et al. (1959), Barr et al. (1960), Tanz (1960), Papadatos and Alivisatos (1960), Nagant de Deuxchaisnes et al. (1960), Dickson et al. (1960), de Sèze et al. (1961), Cruz and Barnett (1962), personal case, 1963).

Abnormalities consist of a diffuse abnormal pattern, with paroxysmal spiking and sharp irregular slow activity. In some cases this pattern arises only after hyperventilation (Ray and Gardner, 1959). Miles and Elrick (1955) considered these changes as genetic in origin.

They resemble however changes seen in true hypoparathyroidism.

Morphological syndrome in PPHP

Dysmorfic habitus (Tab. 1)

Nearly all the patients with PPHP display characteristic changes in the habitus, including a round face, a prominent forehead, a broad nose, a thick-set or slight webbed neck, a short stature with a relative obesity, short extremities, short broad hands and feet, with brachydactyly (mainly I, III and IV) due to a brachymetapody. The skin is dry, hair-coarse and a dull sensorium. Not all the patients consistently show identical clinical or somatic features, variability being considerable in both syndromes of PHP and PPHP. The congenital anomalies are so diversified that no single one can be considered to be pathognomic or constant (constellation syndrome).

Little is known about the anthropometric features of the syndrome in patients below 20 years of age.

Short stature (near the 3th percentile) is essential in the diagnosis. The retardation start at the age of 4 years as stated by our cases and a patient quoted by Nagant de Deuxchaisnes et al. (1960). The height at birth is still unknown in PPHP.

A female child with PPHP measured 62 cms. (instead of 71 cms.) when 10 months old (Royer et al. 1959).

The age-height correlation in children is represented in fig. 37 from 28 cases of the literature and 3 personal cases.

The mean adult height is 158.8 cms. (n = 20), for men; and 151.8 cms. (n = 43) for women. Nearly 15% of the cases have however a normal height. There is no real " nanosomia " nor " dwarfism ", where Martin (1956) is quoted to admit only the name " dwarfism " under 130 cms. of height in man and 121 cms. in women (Tab. 3).

Relative short extremities in comparison with the stature are another typical feature in PPHP. The upper segment, lower segment ratio (US-LS) measured by the vertex to pubis and pubis to sole distance is roughly 0.93 in the normal white adult, having been higher (1.05) in the prepuberal period.

Only in certain instances of PPHP this value has been measured, and found gen-

Tab. 3. Anthropometric features of PPHP

Patient's sex and age	Height cms.	Weight kgs.	Armspan cms.	Span to height ratio S/H	Vertex to the pubis (US) cms.	Pubis to the floor (LS) cms.	US to LS ratio	Author
♀ 24	157							Albright et al. 1952
♀ 24	145	88						Miles and Elrick 1955
♂ 40	154	55						Roche 1955
♂ 24	155	58						Mc Neely et al. 1956
♂ 24	165							Wallach et al. 1956
♀ 16	147				79	68	1,16	Seringe and Tomkiewicz 1956
♀ ?	142							Cusmano et al. 1956
♀ 17	149	60			74	75	0,98	Laligant 1957
♂ 10	122	30						Moureau et al. 1958
♀ 7	128	41						Ray and Gardner 1959
♀ 61	147	113						Casey et al. 1959
♀ 26	158							Nagant de Deuxchaisnes 1959
♀ 40	155	59						Rubenstein and Cody 1959
♀ 65	142							Smulyan and Raïsz 1959
♀ 4	90	13						Royer et al. 1959
♀ 9	124	27						Royer et al. 1959
♀ 10m	62							Royer et al. 1959
♀ 6	116	23						Royer et al. 1959
♀ 6	97	16						Royer et al. 1959
♀ 16	144	54						Hortling et al. 1960
♀ 26	158							Nagant de Deuxchaisnes et al. 1960
♀ 35	157		138		78	79		Barr et al. 1960
♀ 33	149	69	145	0,97	74,5	74,5	1,00	Tanz 1960
♂ 36	150	79	142	0,94	74	76	0,98	Tanz 1960
♀ 57	147	59	150	0,98	72	75	0,96	Tanz 1960
♀ 16	150	59						Papadatos and Alivisatos 1960
♀ 13	132	53						Papadatos and Alivisatos 1960
♀ 79	145							Dickson et al. 1960
♀ 48	153	81						Todd et al. 1960

Tab. 3 *(cont.)*

Patient's sex and age	Height cms.	Weight kgs.	Armspan cms.	Span to height ratio S/H	Vertex to the pubis (US) cms.	Pubis to the floor (LS) cms.	US to LS ratio	Author
♂ 18	163	62						Todd et al. 1960
♀ 49	138	60						de Sèze et al. 1961
♀ 7	110	24	100	0,90	64	46	1,39	de Meulemeester 1961
♂ 20	172	71	150	0,87				Uhr and Bezahler 1961
♀ 43	157	45	135	0,85				Uhr and Bezahler 1961
♀ 60	149	80			77	76	1,01	Gorpe et al. 1961
♀ 50	143	72						Ahmed 1961
♀ 40	152	68						Ahmed 1961
♂ 26	157	70						Stecker 1961
♀ 30	156	55						Vartio and Meronen 1961
♀ 48	150	66						Vartio and Meronen 1961
♀ 59	152	61						Nagant de Deuxchaisnes et al. 1960
♂ 25	159	81						Nagant de Deuxchaisnes et al. 1960
♀ 12	126	27						Nagant de Deuxchaisnes et al. 1960
♂ 23	145	54	137	0,94	72,5	72,5	1,00	Schwarz 1961
♂ 38	167	106						Gilgore et al. 1962
♂ 35	164	119						Mann et al. 1962
♂ 17	160	61	153	0,95				Gorman et al. 1962
♀ 31	155	60						Gorman et al. 1962
♀ 23	140	53	125	0,89	73	67	1,08	Cruz and Barnett 1962
♀ 18	150	37			70	80	0,87	Cruz and Barnett 1962
♀ 19	158	69						Klotz et al. 1962
♀ 18	141	48						Klotz et al. 1962
♀ 16	143	54						Klotz et al. 1962
♂ 12	134	38						Klotz et al. 1962
♀ 17	116	33						Klotz et al. 1962
♀ 58	158	70						Klotz et al. 1962
♀ 37	133	42						Klotz et al. 1962
♀ 28	158	73						Klotz et al. 1962
♀ 15	145	56						Klotz et al. 1962
♀ 32	145	65						Klotz et al. 1962
♀ 18	155	63						Klotz et al. 1962

Tab. 3 *(cont.)*

Patient's sex and age	Height cms.	Weight kgs.	Armspan cms.	Span to height ratio S/H	Vertex to the pubis (US) cms.	Pubis to the floor (LS) cms.	US to LS ratio	Author
♀ 12	123	35						Klotz et al. 1962
♀ 39	151							Schöngut and Scerháti 1963
♂ 60	145	65						Minozzi et al. 1963
♀ 66	140	65						Minozzi et al. 1963
♂ 30	145	50						Minozzi et al. 1963
♀ 72	142	42						Minozzi et al. 1963
♂ 39	160	75						Minozzi et al. 1963
♂ 27	160	60						Minozzi et al. 1963
♂ 60	160	55	161	1,00	80	80	1,00	Our cases 1962 and '63
♀ 53	150	60	147	0,98	80	70	1,14	Our cases 1962 and '63
♂ 49	159	67	149	0,94	80	79	1,01	Our cases 1962 and '63
♂ 33	156	61	152	0,97	84	73	1,15	Our cases 1962 and '63
♀ 30	153	53	145	0,95	81	72	1,12	Our cases 1962 and '63
♀ 7	116							Our cases 1962 and '63
♀ 8	120		107	0,89				Our cases 1962 and '63
♀ 4	110							Our cases 1962 and '63
♀ 5	115		103	0,90				Our cases 1962 and '63
♀ 3	96		85	0,89				Our cases 1962 and '63
♀ 42	137							Adrian et al. 1963
♀ 82	150							Hermans et al. 1964
♀ 75	161		152	0,94				Hermans et al. 1964
♂ 48	165		160	0,97				Hermans et al. 1964
♀ 31	159		156	0,98				Hermans et al. 1964
♀ 4	96		86	0,90				Hermans et al. 1964
♀ 67	152		150	0,99				Hermans et al. 1964
♀ 71	171		164	0,96				Hermans et al. 1964
♀ 45	174		163	0,94				Hermans et al. 1964
♀ 43	170		168	0,99				Hermans et al. 1964
♀ 10	160		162	1,01				Hermans et al. 1964
♂ 65	175		165	0,94				Hermans et al. 1964
♀ 32	152		138	0,91				Hermans et al. 1964
♀ 12	152		132	0,87				Hermans et al. 1964
♂ 10	130		147	1,13				Hermans et al. 1964
♀ 6	110		104	0,95				Hermans et al. 1964

erally higher in adults with PPHP. From 15 cases with PPHP from the literature and our series, we found a mean value of 1.06 (range: 1.00 to 1.15).

The arm-span height ratio is generally below 1. From 31 patients we found a mean value of 0.94 (range: 0.85 to 0.98). Only in 2 persons of 15 cases seen by Hermans et al. (1964) did the arm-span exceed the height and both were children aged 10.

A relative obesity is another very important feature in PPHP; nevertheless it may be absent in some cases; Roche (1955), Mc Neeley et al. (1956), Nagant de Deuxchaisnes et al. (1960).

Birth weight is still un known in PPHP The weight-age is normal in boys until 20. In girls the weight-age seems to be augmented only after the age of 15.

The weight: height ratio (ponderal index after Livi) range from 23.8 to 29.9 (average 25.9) in men (n = 20), and from 22.2 to 32.8 (average 26.4) in women (n = 41). Mean normal values for this index range from 22 to 24. Relative obesity occurs with values over 25. (Formula for this index: $1000 \times \frac{\sqrt[3]{\text{weigth in kgs.}}}{\text{height in cms.}}$

In PPHP this index increases slightly with advancing age (from 24.7 at 20 years, to 26.5 at 50 years in males, and from 25.8 at 20 years, to 26.7 at 50 years in females).

The weight in adults with PPHP ranges from 50 to 119 kgs. with an average of 66.9 kgs. in men (n = 17) and from 40 to 113 kgs. with an average of 63.4 kgs. in women (n = 18).

Brachydactyly

Brachydactyly is mainly caused by a brachymetapody (brachymetacarpy and or brachymetatarsy) and secondary to a relative brachyphalangy. Short metacarpals are essential and nearly always present in PPHP.

Brachymetacarpy causes a " knuckle dimple " over the metacarpophalangeal joint, called " Albright's sign ".

Metacarpals IV and V are involved in more than 50%, metacarpal I and III in less than 50%, metacarpal II only rarely (cfr. Tab. 4). Brachymetacarpy II is seldom seen in PPHP (less than 10%). Brachymetacarpy I alone with short thumbs is noted only by Wallach et al. (1956). The type of brachymetacarpy is not the same in different members of the same family (Seringe and Tomkiewicz, 1956), personal observations (1963).

Tab. 4. Frequency of brachymetacarpy and brachymetatarsy in PPHP

Order of appearance of the conjugation cartilage in the metacarpals	II	III	IV	V	I
Frequency of shortness of the metacarpals	10%	40%	75%	65%	40%
Frequency of shortness of the metatarsals	5%	15%	25%	15%	10%

Evaluation after data from Nagant de Deuxchaisnes et al., 1960; (24 hands of 12 patients); Minozzi et al., 1963 (36 hands of 18 patients) and Herman et al., 1964 (22 hands of 11 patients).

An analogous pattern is found in the metatarsals, except for metatarsal V.

Metatarsal IV is involved in less than 50%, the other metatarsals only rarely. There is a greater incidence of shortened metacarpals (92% of cases) than of shortened metatarsals (50% of cases) (Cruz and Barnett, 1962).

Mann et al. (1962) concluded that the metacarpals are involved three times more frequently than the metatarsals.

In no instance is there metatarsal involvement without involvement of some metacarpals (Goeminne, 1963).

X-ray investigations may reveal a slight type of brachymetapody not supposed by clinical examination (Nagant de Deuxchaisnes, 1960; personal observations, 1963).

Brachymetacarpy IV and V may occur in normal persons (Cusmano et al., 1956). Isolated brachymetatarsy IV, with normal stature may also occur in normal persons of some families (personal observations, 1963).

The " metacarpal sign " of Archibald et al. (1959) is not a reliable procedure in PPHP, in view of the frequent shortening also of the third metacarpal bone. This sign is considered positive if a line drawn tangentially through the circumference of the distal heads of the fourth and fifth metacarpals runs through the distal end of the third metacarpal.

The shortness of the metacarpals occurs through two mechanisms: shortening of the metacarpal diaphyses together with an early closure of the epiphyseal lines in the metacarpal bones, as seen in a case of Nagant de Deuxchaisnes et al. (1960).

Shortening of the metacarpal diaphyseal bone occurs through the shortening of the diaphyseal ossification centers during development (Cusmano et al., 1956).

The reduction in the growth rate at the center of the epiphyseal cartilage may predispose to early union with the diaphysis.

It would appear if this is correct, that growth did not stop because of early union, but that early union took place because growth stopped (Elrick et al., 1950).

Pseudo-epiphyseal lines constitute a transitory state to early fusion of the epiphyseal and diaphyseal parts of the metacarpal at his proximal end (Nagant de Deuxchaisnes et al., 1960).

At the age of three years the metacarpal epiphysis is already engulfed or invaginated by the diaphysis.

The complete closure of the epiphyseal lines in the metacarpal bone occurs at the age of six to seven, as observed by de Meulemeester (1961). The normal age of union is about 14 years.

In children, there may be an advanced skeletal maturation of all the bones in the hands (Seringe and Tomkiewicz, 1956; Ray and Gardner, 1959). But more data on other bones in other cases are lacking thus far.

Brachytelephalangy

Some patients show marked shortening of the distal phalanx of one or more fingers or toes. Wallach et al. (1956), Ray and Gardner (1958) Nagant de Deuxchaisnes (1959), Gorman et al. (1962), Schöngut and Cserhati (1963), Minozzi et al. (1963).

Rubenstein and Cody (1959), believe that stubby terminal phalanges should be regarded as one of the important features of the syndrome.

Malformed terminal phalanges of the big toes may occur (Tanz, 1960).

Brachymesophalangy

In the patient of Barr et al. (1960) there was a shortening of the middle phalanges of the fingers with a typical deformity of the proximal portions. Brachymesophalangy of the fingers with clinodactyly is noted by Royer et al. (1959).

Brachymesotelephalangy of the toes is noted by Minozzi et al. (1963).

Fusion of several phalanges does generally not occur in PPHP.

We observed a partial fusion of a middle and distal phalanx of the second finger in two patients.

Brachyphalangy is caused by early closure of the epiphyseal lines due to the chondrodystrophic lesion of the proximal epiphyseal nucleus. A good example of the early tendency of the conically shaped epiphyses to invaginate the diaphyses, is the middle phalanx, where a very typical inversed V-shaped dyschondroplastic groove has first been noted by Elrick et al. (1950), Miles and Elrick (1955) and Ahmed (1961).

It is in doubt wether the case described by Mc Gavack and Reinstein (1941) represents an example of PPHP. Indeed, brachyhyperphalangy and brachyhypophalangy does not occur in PPHP, although hypophalangy is noted in a grand mother and a mother of a female patient with PPHP (Papadatos and Alivasatos, 1960).

Extra toes are noted in a member of a family with PPHP (Cruz and Barnett, 1963).

Partial cutaneous syndactyly

Partial cutaneous syndactyly is occasionally seen in PPHP (Nagant de Deuxchaisnes et al., 1960; personal observations, 1962). Syndactyly in family members of patients with PPHP is noted by Papadatos and Alivisatos (1960).

Bilateral campodactyly in PPHP is noted by Gorpe et al. (1961).

Other chondrodystrophic articular lesions and bone deformities

Chondrodystrophic lesions with premature closure of the epiphyses may also frequently occur in other articulations and in the vertebral columm. All these anomalies give raise to typical bone deformities, which may also be partially due to a disturbed enchondral bone formation.

Radius curvus

A bilateral moderate radius curvus in PPHP is noted by: Roche (1955), Engel et al. (1956), Seringe and Tomkiewicz (1957), Nagant de Deuxchaisnes et al. (1959, 1960), Royer et al. (1959), Barr et al. (1960), Tanz (1960), Cruz and Barnett (1962), Goeminne (1963).

Ulna brevis

A short ulna is seen in the X-ray illustration provided by Roche (1955). This author however paid no attention to this feature. A short ulna is further noted in patients with PPHP (Uhr and Bezahler, 1961), and in some family members of patients with PPHP (Todd et al., 1961). The distal epiphysis of the ulna can be hypoplastic or binucleated and presents a noticeable retardation as seen in a boy of 12 years with PPHP (Nagant de Deuxchaisnes et al., 1960).

The radius curvus associated with a ulna brevis gives rise to a slight expression of the Madelung deformity. Subluxations of the hand, however, have never been noted in PPHP. A ulna valgus is noted by Seringe and Tomkiewicz (1956, 1957).

Carpal angle

Minozzi et al. (1964) calculated the carpal angles in 25 cases of PPHP (6 personal cases and 19 reported in the literature). They found a mean value of 121°, which is smaller than in normal subjects (131°). The carpal sign of Kosowicz (1962) is thus frequently present.

A positive carpal sign is also found in gonadal dysgenesis (50 to 60% of the cases), in hypogonadism (15%), in pubertas praecox (12%), in achondroplasia (17%) and in some normal subjects (5%).

Elbow

A cubitus valgus is common in this condition. (Personal case (1963), Adrian et al. (1963). We noted extensive chondrodystrophic lesions on the elbow in one of our patients with PPHP. Bilateral (congenital?) dislocation of the elbows has been described by Gorpe et al. (1961). Deformed elbows occurred also in the case of Casey et al. (1959).

Vertebral anomalies

These are no constant features in this syndrome. Spondylarthrose complaints are however frequently noted (see further). Some vertebral anomalies are occasionally described. Spina bifida occulta, platyspondyly and Schmorl nodules is noted once by Nagant de Deuxchaisnes et al. (1960).

Occipitalisation of the first cervical vertrebra is described in one case (Gorman et al., 1962).

A cervical rib is noted by Seringe and Tomkiewicz (1956) and Laligant (1957).

Vertebral osteochondritis with kyphoscoliosis and vertebral epiphysitis is noted by Nagant de Deuxchaisnes (1959 and 1960). Vertebral osteoarthritis with demineralisation is noted by Dickson et al. (1960). Hyperostitic spondylarthrosis is noted by Nagant de Deuxchaisnes et al. (1960). However neither osteoporosis nor osteosclerosis is usually seen in PPHP (see further).

Hip lesions

Osteochondritic lesions of the ischiopubis arc may occur (Nagant de Deuxchaisnes et al., 1960).

A child of 7 years with PPHP had also a congenital luxation of the hip (de Meulemeester, 1961). No other such association has been reported. Minozzi et al. (1963) however noted 2 such cases of congenital luxation of the hip in members of families with PPHP.

Coxa vara in PPHP has been described by Miles and Elrick (1955), Roche (1955), Mc Neeley et al. (1956) and Nagant de Deuxchaisnes et al. (1960). Coxa valga is mentioned by Royer et al. (1959). Dyschondroplastic lesions of the hips with Coxarthrosis is noted by Tanz (2 cases, 1960) and Nagant de Deuxchaisnes et al. (1960).

Genu valgum is mentioned only by Roche (1955). Genu varum is seen by Engel et al. (1956).

Tibia curvus is seen in a female of 50 years with gonadal dysgenesis with brachymetacarpy by Engel et al. (1956).

Severe *hallux valgus* was observed in this condition in some of our patients.

Spontaneous bone fractures before puberty is rare in PPHP but is noted by Gorman (1962) in a female with PPHP.

Fourteen of the 43 subjects from the large PPHP kindred examined by Hermans et al. (1964) gave also a history of fractures: seven of these were among 15 cases of PPHP. In some cases there appeared to be a discrepancy between the degree of trauma and its effects.

The relation of bone fractures to PPHP is unknown. They may represent chance occurrences.

We may note that skeletal decalcification does generally not occur in PPHP.

Subcutaneous calcifications and ossifications

They are frequently seen in PPHP but are rarely extensive. They do not appear as frequent as in PHP.

Subcutaneous calcification and/or *ossifications* have been seen by Albright et al. (1952), Wallach et al. (1956), Mc Neely et al. (1956), Casey et al. (1959), Ray and Gardner (1959), Smulyan and Raïsz (1959), Tanz (1950), Stecker (1961), Todd et al. (1961), de Meulemeester (1961), Schöngut and Cserhati (1963), personal observations (1963).

They may be observed at the head, neck, abdominal wall and most frequently at the distal parts of the legs. However, they may be absent in the majority of cases before 25 years of age (Nagant de Deuxchaisnes, 1960).

Exostoses

Exostoses have been described by: Roche (1955), Wallach et al. (1956), Mc Neeley et al. (1956), Engel et al. (1956), Fabbrini et al. (1958), Casey et al. (1959), Tanz (1960), Uhr and Bezahler (1961), Cruz and Barnett (1962). Nagant de Deuxchaisnes et al. (1959), and Minozzi et al. (1963) observed clavicular exostoses while Rubenstein and Cody (1959) observed pubic arch exostoses.

In general, exostoses are seen at the tibiae, fibulae, humerus claviculae, hips, metacarpals and phalanges.

Calcification and ossification of the auricular cartilage is unusual but is mentioned in PPHP by Smulyan and Raïsz (1959) and Dickson et al. (1960).

Scapulo-humeral periarthritic calcifications are noted by Nagant de Deuxchaisnes et al. (1960).

Intracranial calcifications

Basal ganglia calcification is uncommun in PPHP (7 times in 51 cases, or 14%, after the review of Cruz and Barnett, 1962). It is mentioned by Tanz (1960) and Dickson et al. (1960).

A meningeal calcification is noted by Gorman et al. (1962). Calcium deposits have been seen in the falx cerebri of one patient (Casey et al. 1959).

Other cranial anomalies

Profound and pronounced *impressiones digitiformes* are noted by Nagant de Deuxchaisnes et al. (1960) and Laligant (1957). A thickening of the diploë with hyperostosis frontalis interna may occur (Cusmano, 1956; Ray and Gardner, 1959; Ahmed, 1961; Gorman et al., 1962).

Hyperostosis frontalis interna alone was also seen in four females and one male (5 times in 51 cases, or nearly 10%: Albright et al., 1952; Engel et al., 1956; Nagant de Deuxchaisnes et al., 1960; Cruz and Barnett, 1962).

Prognathism is seen by Schwarz and Bahner (1961).

A slight hypoplasia of the mandible with retrognathism is noted by Royer et al. (1959), Nagant de Deuxchaisnes et al. (1960), Hermans et al. (1964). This feature is also present in our proband.

A very high arched palate is seen by Cruz and Barnett (1962).

A cleft palate is noted by Royer et al. (1959).

The examination of the head in incomplete in all published case histories. It is impossible to decide whether the " round face " is due to a brachycephalic skull and a europrosopic face or simply to thick soft tissues.

It would be interesting to know more about the anatomy of the skull in PPHP as obviously something went wrong in the formation of the long bones. As the formation of the skull bones is of another type, except for the mandible, it might be interesting to know wether the PPHP affrects one or the other type of bone formation.

Skin dystrophy

Dryness of the skin, with thin coarse hair is very common in PPHP. Cutaneous moniliasis (as seen in IHP) is only cited by Royer et al. (1959).

Naevi pigmentosi in the face and back have been described by de Meulemeester (1961).

Cutaneous hemangiomas in the neck and lumbar region are seen by Nagant de Deuxchaisnes et al. (1960).

Lichen planus was seen by Nagant de Deuxchaisnes et al. (1960).

Eczema may occur in some cases (Royer et al. 1959). One of our patients had also eczema of the hands.

Nail dystrophy

Broad nails, mainly of the thumbs, in PPHP is mentioned by Albright et al. (1952), Ray and Gardner (1959), Barr et al. (1960), Papadatos and Alivisatos (1960), Cruz and Barnett (1962), Gorman et al. (1962), Hermans et al. (1964).

The broad-length ratio may be higher than 2.5 (normal values in children 1.0-1.5).

This feature may however be absent and seems not essential in the diagnosis (Royer et al., 1959, Ahmed 1961). Brittleness of the nails is cited by Laligant (1957).

Dental dystrophy

Dental dystrophic lesions are noted by Laligant (1957). Malocclusion and poor enamel development are seen by Cruz and Barnett (1962). It could be useful to know which teeth and which level of the teeth are affected, as, if the dental enamel hypoplasia is a part of the PPHP syndrome, this might give a clue on the time of onset of the disease. Early and extensive caries of the teeth may occur. Unerupted molar teeth are mentioned by Nagant de Deuxchaisnes (1960) and Hermans et al. (1964). We also noted unerupted molar teeth in two of our patients where radiographic examination of the teeth was performed. Four patients of 15 with PPHP in the family studied by Hermans et al. (1964) had abnormal dentition (retained babyteeth, early dental caries, unerupted wisdom teeth).

We consider that this features may represent a sign of early frust hypoparathyroidism.

Ocular anomalies

Lenticular opacities are seldom seen in PPHP. In these cases, where they are present, they are small and peripheral. They are only mentioned in PPHP by Miles and Elrick (1955), Roche (1955), Engel et al. (1956), Smulyan and Raïsz (1959),

Casey et al. (1959), Papadatos and Alivisatos (1960), Dickson et al. (1960). Cataract is present in less than 10% of the cases of PPHP.

Blue sclerae in PPHP were noted by Roche (1955) and in two sisters with PPHP by Seringe and Tomkiewicz (1956, 1957), also by Wallach et al. (1956) and by Cruz and Barnett (1962).

Internal strabismus in PPHP is noted by Royer et al. (1959), Ray and Gardner (1959) and in a family member again by Cruz and Barnett (1962). Congenital (?) tortuosity of the vessels and pseudo-papilledema were found by Stecker et al. (1961).

Bilateral congenital megalocornea is noted by Royer et al. (1959). Heterochromia of the iris is mentioned in one patient by Hermans et al. (1964).

Mental symptoms

Anxiety, tension, depression and irritability are seldom seen in PPHP. Rare cases present some type of epileptoid seizures which are hard to classify (de Sèze et al., 1961; Cruz and Barnett, 1962; Adrian et al., 1963). Overt tetany by definition never occurs in PPHP.

The presence of an essential type of tremor is noted by Hermans et al. (1964) in two patients with PPHP.

A certain degree of mental retardation is commonly noted. Miles and Elrick (1955), Mc Neely et al. (1956), Seringe and Tomkiewicz (1956), Ray and Gardner (1959), Casey et al. (1959), Papadatos and Alivisatos (1960), Rubenstein and Cody (1959), Nagant de Deuxchaisnes (1960), Ahmed (1961), Schwarz (1961), de Sèze et al. (1961), Gilgore et al. (1962), Crzu and Barnett (1962), Rördam (1964).

True oligophreny is rare.

Many patients have a normal intelligence as stated by Roche (1955), Wallach et al (1956), Tanz (1960). Our patients presented no mental retardation.

There is no clear relation between the occurrence of convulsions and the hypocalcemia in PHP (Wise and Hart, 1952). It is possible that in both PHP and PPHP there exists a real genodystrophy of the central nervous system, which can partially explain the mental retardation and other related mental symptoms (Klotz et al., 1962).

Deafness

In a female of 16 years with PPHP there was a slight mixt deafness. This was also noted in a patient by Laligant (1957), Seringe and Tomkiewicz (1956). Our propositus presented also a slight perceptive deafness. This association seems to be fortuitous.

Hypogenitalism in PPHP

Unilateral cryptorchism is noted once (Gilgore et al., 1962).

Irregular and scanty menstrual blood in female patients with PPHP is noted by Albright et al. (1952), Miles and Elrick (1955), Papadatos and Alivisatos (1960),

Barr et al. (1960), Tanz (1960). Delayed puberty is encountered in some other cases (Laligant, 1957; Gorpe et al., 1961).

Hypogonadism with primary amenorrhea is noted by Adrian et al. (1963).

In some female patients with PPHP there seem to exist a lowered fertility of unknown origin.

An uterus duplex is seen in one case (Gorman et al., 1962).

Low urinary 17-ketosteroids values are noted in some cases (Tanz, 1960; de Sèze et al., 1961; Gilgore et al., 1962; personal case, 1963).

Danowski (1962) found normal values for urinary 17-ketosteroid and 11-oxysteroid excretion.

This low urinary 17-ketosteroid excretion in some patients cannot always be correlated with any readily demonstrable hypofunction of the gonads or adrenal cortex.

Associated clinical conditions in PPHP

Diverse endocrine abnormalities are inconstant but notable constituents of Albright's hereditary osteochondrodystrophy (poly-endocrine insufficiency syndrome).

They do not appear to be directly genetically interrelated.

The association of PPHP with hypertension, diabetes, hypothyroidism polyarthrosis and peripheral arteritis is probably significant.

The hypothetical association with gonadal dysgenesis is discussed in detail.

a) *Hypertension*

Cases of PPHP with hypertension have been described by Mc Gavack and Reinstein (1941), Albright et al. (1952), Todd et al. (1961), Gilgore et al. (1962).

The patient of Ahmed (1961) had a mild hypertension. We observed three patients with PPHP and hypertension.

PPHP with Turner's syndrome (?) and hypertension has been mentioned by van der Werff ten Bosch in the Netherlands (1959). A case of PPHP with hypertension and diabetes has also been described by Smulyan and Raïsz (1959).

Hypertension seems to occur in about 25% of the cases.

b) *Diabetes*

A slight pre-diabetic curve was noted in a child of 7 years by de Meulemeester (1961), by Seringe and Tomkiewicz (1956) in a girl of 10 years and by Laligant (1957) in a girl of 27 years. Pre-diabetes in a case of PPHP is mentioned by Nagant de Deuxchaisnes (1960). Diabetes also existed in the mother or father of patients with PPHP (Tanz, 1959; Nagant de Deuxchaisnes, 1960). Engel et al. (1956) have seen a female with PPHP, gonadal dysgenesis, hypertension and diabetes.

A young female with PPHP, a pheochromocytoma with hypertension and possibly diabetes has been briefly mentioned by Nagant de Deuxchaisnes (1959). The

pheochromocytoma could be responsible for the diabetes (however, there was only a high secretion of noradrenalin in this patient). Danowski (1962) noted also diabetes and hypertension in one case with PPHP.

Minozzi et al. from Italy (1963) described also an extensive pedigree of PPHP with 13 members in 4 generations.

One patient with PPHP and two family members without PPHP also had diabetes.

A review of the literature discloses nearly 25% diabetic cases in PHP (Nagant de Deuxchaisnes et al., 1960) and more than 25% in PPHP (Goeminne, 1963).

In the pseudo-form (PHP) diabetes insipidus has been noted once (Berardinelli, 1951). This association has not been described up to now in the pseudo-pseudo form (PPHP).

c) *Hypothyroidism and other thyroid diseases*

In many patients with PPHP a first clinical diagnosis of hypothyroidism is frequently made. A low basal metabolic rate and a moderate hypercholesterolemia without clearcut hypothyroidism is frequent.

An isolated low fixation of radioactive iodine may occur as seen by Royer et al. (1959).

The association with true hypothyroidism or goitre has been mentioned by Miles and Elrick (1955), Hortling et al. (1960), Barr et al. (1960), Tanz (1960). A patient with PPHP from Gibson (1961) had undergone a strumectomy for goitre. A case with a toxic goitre and another case with a nontoxic goitre are noted by Vartio and Meronen (1961).

Five patients with PPHP and two family members without PPHP suffered also from thyroid disorders (hypothyroidism or goitre) (Minozzi et al., 1963).

Hermans et al. (1964) mentioned soft nodular nontoxic goitre in three subjects with PPHP from 15 cases in one large family pedigree.

The incidence of thyroid disorders in PPHP may be estimated at 25%.

d) *Polyarthrosis*

A case of PPHP with diabetes and polyarthrosis has been studied by Tanz (1960).

PPHP with polyarthrosis or spondylarthrosis has been seen by Wallach (1956), Gorpe et al. (1961), Danowski and Benedek (1962) and Goeminne (1963). Backpain and pain in the arms is noted by Miles and Elrick (1955). Polyarticular complaints are mentioned by de Sèze et al. (1961). In two cases described by Wallach et al. (1956) and Stecher (1961) the association of PPHP with gouty polyarthritis was also observed.

The relationship of gout to PPHP is unknown. It may be fortuitous. In one of these cases a parent had also gout.

e) *Peripheral arteritis*

Peripheral arteritis with aortic and femoral arteries calcification may occur in PPHP (Rubenstein and Cody 1959; personal case, 1963).

f) *Pathogenesis of some clinical associations*

Diabetes in PPHP seems to arise between 35 and 55 years of age, whereas hypertension and polyarthrosis seem to arise in the 5th or 6th decade of life.

So far, no histological examination of the total vascular system in PHP and PPHP has been performed.

The renal biopsy in the 29 years old case of Albright et al. (1952) disclosed a nephrosclerosis.

Wallach et al. (1956) noted a slight decreased renal function test in PPHP.

We found nearly normal renal function tests in our proband.

It appears to us that hypertension, diabetes and arteritis might arise from diffuse ectopic calcifications and sclerosis respectively of the aortorenal, pancreatic and femoral arteries. In this connection it should be mentioned that some rare cases of PPHP are known with calcification of the aorta and femoral arteries (Rubenstein and Cody, 1959; Nagant de Deuxchaisnes, 1960; personal observation, 1963). Rubenstein's patient had also severe peripheral arteritis, but no hypertension.

Urinary lithiasis has thus for never been mentioned in PPHP.

The polyarthrosis (spondylarthrosis, coxarthrosis) and the other polyarticular complaints might arise from the dyschondroplastic anomalies with sclerosis and diffuse calcification in the periarticular ligaments.

Thus, some clinical conditions in PPHP might be secondarily related to the extrarenal effect of the parathyroid hormone or to certain polygenetic defects.

Danowski (1962) claim that the diabetes and hypertension may reflect predispositions stemming from obesity.

g) *Gonadal dysgenesis*

In 1959 van der Werff ten Bosch described 8 cases of PPHP, 4 of which he claimed to have also gonadal dysgenesis (three of them had a negative sex chromatin). However, cases 1 to 4 and case 6 of this author had either Turner syndrome with brachymetacarpy (cases 1 to 3) or brachymetacarpy only (cases 4 and 6) and must be excluded from the list of cases with PPHP, as there may be few findings reported to warrant a firm diagnosis of PPHP. Cases 5, 8 and possibly 7 seem to have PPHP only, where the sex chromatin and gonadotropine values are normal or not stated. Case 7 may have PPHP, although severe skeletal decalcification is uncommon in PPHP. The final height of cases 5,7 and 8 range from 143 to 158 cm.; the highest values in his 8 cases. Further only cases 5 and 8 present the typical dyschondroplastic lesions on the proximal epiphysis of the middle phalanx as frequently seen in PPHP (see further).

More than eight such cases with questionable association of PPHP with gonadal dysgenesis have been described up to now; Engel et al. (1956), van der Werff ten Bosch (1959), Archibald et al. (1959), Hortling et al. (1960), Schwartz and Walter (1962).

Klotz et al. (1962) note without further proof (sex chromatin and gonadotropine values are not stated) 2 cases of PPHP with Turner's syndrome in 14 personal cases of PPHP.

In fact, only two cases (Engel et al., 1956; Schwarz, 1962) have been reported which satisfy exact diagnostic criteria for the coexistence of PPHP and gonadal aplasia.

Some cases of PPHP with primary amenorrhea may have a severe " hypoplasia " of the ovaries instead of a true " dysgenesis ". Histologic examination and chromosome analysis of ovarian tissues are thusfore needed to make a differential diagnosis.

One should be very cautious to diagnose PPHP in Turner's syndrome the latter in itself being characterised by many of the symptoms in PPHP (mainly brachymetacarpy IV). The degree of overlapping of clinical manifestations will be discussed in the following paragraphs.

Brachymetacarpy is an inconstant feature in gonadal dysgenesis and an essential sign in PPHP.

Van der Werff ten Bosch (1959) noted in 29 cases with Turner's syndrome 4 cases with brachymetacarpy (13%). Hortling et al. (1959) noted one case of brachymetacarpy in 10 cases with true Turner's syndrome (10%). The incidence of brachymetacarpy in gonadal dysgenesis lies between 10 and 20%.

But when precise radiographic methods of appraisal are employed, slight brachymetacarpy IV (a positive Archibald metacarpal sign) is said to have been present in 16 of 17 cases of gonadal dysgenesis.

The brachymetapody in gonadal dysgenesis and PPHP is not entirely of the same type. In Turner's syndrome only the metacarpal IV is involved.

Although gonadal dysgenesis is very often associated with chondrodystrofic lesions, typical V shaped dystrophic lesions in the phalanges of cases with gonadal dysgenesis plus brachymetacarpy, are usually absent.

Retarded bone-age (2 to 8 years) is very frequent in patients with Turner's syndrome, over 14 years of age. This seems not be the case in PPHP, where advanced skeletal maturation may exist.

Short stature is a typical feature of Turner's syndrome and PPHP, but not at the same degree. The final height in gonadal dysgenesis ranges generally from 127 to 152 cms. (average: 140 cms.).

In PPHP the average final height is 158.8 cms. for men (Range 150-165 cms.) and 151.8 cms. for women (Range 140-160 cms.) (Tab. 3).

Nevertheless, in both conditions cases with a normal stature are known.

A normal to wide armspan is a feature of gonadal dysgenesis, but not of PPHP, where the armspan: height ratio in generally below 1.

Pterygium colli and a low hairline in the neck are also never present in PPHP.

The following features or congenital anomalies may occur in both syndromes: round face, wide intermammary distance, radius curvus, a cubitus valgus, a slight

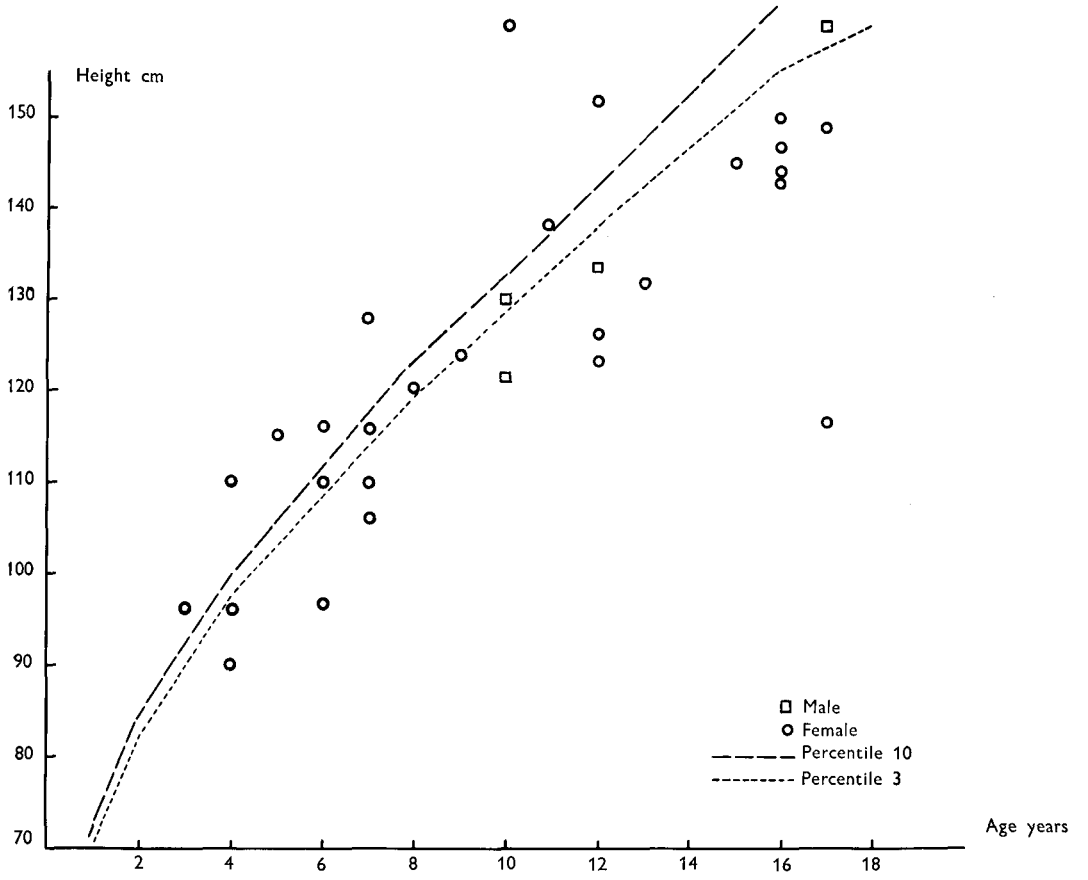

Fig. 37. Relation of body stature to age in 31 children with PPHP (review of the literature and personal observations 1962 and 1963)

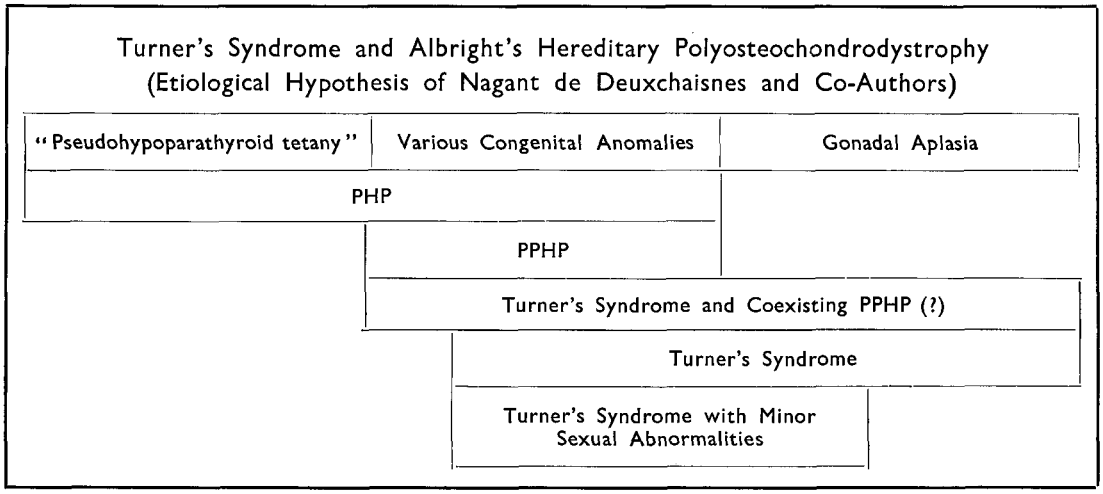

Fig. 38. Possible relationship between gonadal dysgenesis and Albright's hereditary polyosteochondrodystrophy (after Nagant de Deuxchaisnes and Hoet, 1960)

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Madelung's deformity, brachyphalangy, partial cutaneous syndactyly, a slight hypoplasia of the mandibula, hyperostosis frontalis interna ectopic calcifications, tibial exostoses, vertebral epiphysitis, several pigmented naevi, high arch, dental anomalies, blue sclerae and mental retardation.

Hypercholesterolemia, diabetes, hypothyroidism and hypertension of unknown cause also occur more frequently in both syndromes. Moderate hypertension occurred in 14 of 47 patients with gonadal dysgenesis without coarctation.

However, a small sella turcica, osteoporosis, scoliosis with lordosis, fusions of cervical vertebrae, a tibia vara like deformity, muscular hypotonia, ligamentar and cutaneous laxity, cardiac and renal anomalies (frequent in gonadal dysgenesis) do not occur in PPHP.

Forbes (1964) studied fingerprints, palm prints (Dermatoglyphics) and palmar-flexion creases in patients with either gonadal dysgenesis, PHP or PPHP. She found many resemblances between the hand features of these conditions. She noted that thus a new area of overlap between gonadal dysgenesis and PHP or PPHP has been found, suggesting a chromosomal disorder in PHP to. However, in 1961 and 1962, prior to her conclusions the karyotype had already been found normal in both PHP and PPHP (see further).

It is conceivable that some cases reported as PPHP, in childhood may have had gonadal dysgenesis, which undetected in the absence of nuclear sexing or gonadotropine determinations.

Only in the presence of a clearcut pedigree of PPHP, can one accept the simultaneous occurrence of PPHP and Turner's syndrome in different members of one family.

Turner's syndrome with gonadal aplasia coexisting with PHP has not thus far been reported.

Nagant de Deuxchaisnes and Hoet (1960) have proposed an ingenious explanation for these facts. The critical period for gonadal development and for development of responsiveness of tissues to parathyroid hormone may each occupy a temporal location near to each other in the ontogenetic sequence adjoining the period for osseous and other developments deranged in PPHP but adjoining it on opposite sites. A small variation in the timing and duration of a deleterious influence could then explain, the overlapping of certain features of Turner's syndrome and Albright's hereditary osteochondrodystrophy (Fig. 38).

These authors postulated a metabolic acquired disorder of the mother (diabetes or hypothyroidism) as the primary cause of the postulated harmful influence to fetal development.

Our extensive pedigree infirms this ingenious theory of nonhereditary phenocopy, and may confirm on the other hand the modified hypothesis put forward by Mann et al. (1962) suggesting that the metabolic abnormality affecting fetal development is a consequence of a fetal genetic defect.

In these cases it seems that the phenotype is not only determined by the presence of an abnormal gene but also by the temporal location of its deleterious effect.

In this way Turner's syndrome may be pathogenetically related to true Albright's hereditary osteochondrodystrophy, but genetically wholly distinct (Mann et al., 1962); Goeminne, 1963).

We have to resist to apply to the cases of gonadal dysgenesis with brachymetacarpy IV the term PPHP.

h) *Heart defects*

Congenital heart defects are unusual in PPHP (Todd et al., 1961).

Only in rare cases a congenital heart defect occurs with PPHP (acyanotic tetralogy of Fallot in the case of Cruz and Barnett, 1962). We can hardly accept the case of Bazex et al. (1962) with a fundibular pulmonary stenosis as a case of PPHP. Indeed chondromas, metaphyseal hypertrophy and cubital aplasia have never been cited as features of PPHP.

i) *Renal anomalies*

Renal anomalies are generally not associated with PPHP.

Rohde and Lange (1964) described two sibs with brachymetapody, a slight stunted stature and familial cystinuria. They represent probably no cases of PPHP, but a fortuitous association of hereditary brachymetapody with cystinuria.

Ahmed (1961) noted a bilateral congenital idiopathic type of hydronephrosis in a patient with PPHP, what he called a possible related (?) genetic abnormality.

j) *Gastrointestinal anomalies*

The association of PPHP with gastroduodenal ulcer in some cases seems fortuitous.

Nosologic entity of PHP and PPHP

PPHP is most probably an incompletely penetrant form of PHP which represents the complete clinical syndrome (Bergstrand et al., 1958; Gerschberg and Weseley, 1960; Schwarz and Bahner, 1961). Ray and Gardner (1959) believe that PHP and PPHP belong to a *continuum* of genetic disorders. Both syndromes show a similar dysmorfic habitus and identical chondrodystrofic lesions.

Both syndromes have a similar sex distribution (Mann et al., 1962) and very probably a similar inheritance.

Both syndromes may occur in the same family as reported by many authors (Selye, 1949; Browne, 1950; Buchs, 1954; Frame and Carter, 1955; Cusmano et al., 1956; Klotz and Kahn, 1957; Moreau et al., 1958; Bergstrand et al., 1958; Dickson et al., 1960; Mackay, 1960; Rosan and Dascalu (1964), Dechaume et al. (1964).

Instances of conversion of PHP into PPHP in the same patient is recorded by Cusmano et al. (1956), Palubinskas and Davies (1959), Gerschberg and Weseley

(1960), Enthoven (1960), Forbes and Moldawer (1960). The patient may have had hypocalcemic convulsions in childhood and became normocalcemic in the adult life.

Conversion of PPHP into PHP is seldom seen. A case is recorded by Ray and Gardner (1959).

Cases with PHP, PPHP and also intermediate forms between PPHP and PHP were recorded in the same family (Schöngut and Scerhati, 1963).

Gerschberg and Weseley (1960) suggest that some cases of the disease may have a mild disorder of calcium and phosphate metabolism, so that hypocalcemia appears only during periods of increased calcium requirements such as growth with ageing.

This view is further supported by the fact, noted by the same authors, that most cases of PHP have been described in children or adolescents while most reported cases of PPHP have occurred in adults.

PPHP in children is only noted by Seringe and Tomkiewicz (2 cases in 1956), Ray and Gardner (1959), Royer et al. (3 cases in 1959) and de Meulemeester (1961). In our family, however, we observed at least 3 children with PPHP.

Gershberg and Weseley (1960) postulated that PHP may occur also in a patient when his calcium demand is great for other reasons than growth, whereas PPHP would occur if the patient had lower or normal calcium requirements.

This theory is based on their observation of a 16 years old female, diagnosed as PHP but requiring therapy for hypocalcemia, only during pregnancy, and who could be classified as having PPHP before pregnancy. Hypocalcemia, therefore, may be an inconstant feature in an individual case, which thus must be classified as one or the other at different times (Palubinskas and Davies, 1959).

Intermediate states between PHP and PPHP also exist.

Some cases of PPHP named pseudo-pseudo-pseudo-hypoparathyroidism (!) or PPPHP by Ray and Gardner (1959), showing a slight hyperphosphatemia between 6 and 8 mg.% without hypocalcemia are stated by Selye (1949), Ray and Gardner (1959), Papadatos and Alivisatos (1960), de Meulemeester (1961) and Schöngut and Scherhati (1963).

A decreased basal calciuria and/or phosphaturia in PPHP as in PHP is also noted by some authors.

Both syndromes also happen to be associated with the same clinical or endocrinological conditions; hypertension, arteritis, diabetes and hypothyroidism.

Pathogenesis of Albright's hereditary polyosteochondrodystrophy

According to Albright's original view (1952), it is generally agreed that the multiple anomalies in PHP and PPHP (renal tubule defect, dysmorfic habitus, dyschondroplastic lesions and ectopic calcifications) are metabolically unrelated to the parathyroid gland and more probably the result of a polygenetic defect (Elrick et al., 1950). Associated hypothalamic lesions are also possible (Klotz and Kahn, 1957).

Nagant de Deuxchaisnes and his associates (1960), following Wallach et al. (1956)

think it probable that the multiple congenital anomalies of the disease are due to maternal metabolic conditions which result in a fetal environment unfavorable to normal embryogenesis at certain periods critical for development of one or another of the affected tissues or organs.

Our extensive pedigree including a clear male-to-male transmission, infirms however this theory of nonhereditary phenocopy.

Dickson et al. (1960) advanced that possibly there is one genetic defect that affects the renal tubule and one, or more others, that affect the habitus and dyschondroplastic lesions.

The short stature is probably due not only to the early closure of pseudo-epiphyses but also to a disturbance of the enchondral bone growth as seen in cases of familial multiple exostoses (osteodysplasia exostotica).

The cataracts in PPHP may be caused by an early slight hypocalcemic state in the past. Cataract is however for more frequent in the pseudo-form (PHP) than in the pseudo-pseudo-form (PPHP). It seems therefore that only in some rare instances of PPHP a pre-existing hypocalcemic period could have occurred.

The ectopic calcifications, but not the subcutaneous ossifications may have a similar origin.

The level of serum-calcium at which cataract forms is uncertain, although some workers cited that 7.5 mgs. per 100 mls. is the critical level.

Furthermore, in some cases, cataract and ectopic calcifications had developed in patients with PPHP and normal serum calcium, suggesting a genetic origin for their occurrence.

The cause of the occurrence of intracerebral calcifications in certain cases of PPHP is unknown.

The cause of the associated clinical conditions in PPHP was discussed in a preceding paragraph.

The idea originally put forward by Albright et al. (1942) remains current, that in the condition of PHP normal or supernormal amount of active parathyroid hormone in circulation is ineffective, owing to an inherent refractoriness of the end organ the renal tubule (relative parathyroid insufficiency in spite of a parathyroid hyperplasia).

This renal tubule defect is studied by the Ellsworth-Howard test (see further).

Gilgore et al. (1962) and Goeminne (1963) speculate that in PPHP there may be some abnormality of end organ (renal tubulu) responsiveness qualitatively akin to that manifested by patients with PHP, but of a much lesser order of magnitude (see Fig. 39).

The evidence of inherent end-organ refractoriness is supported by the demonstration that the chemical changes in PHP are not corrected by administration of exogenous hormone, and by the indirect evidence of the biopsies showing normal or hyperplastic tissue, suggesting that the parathyroid glands are releasing parathyroid hormone at a normal or possibly an accelerated rate.

In this condition (PHP) the glands may be under constant stimulation as a di-

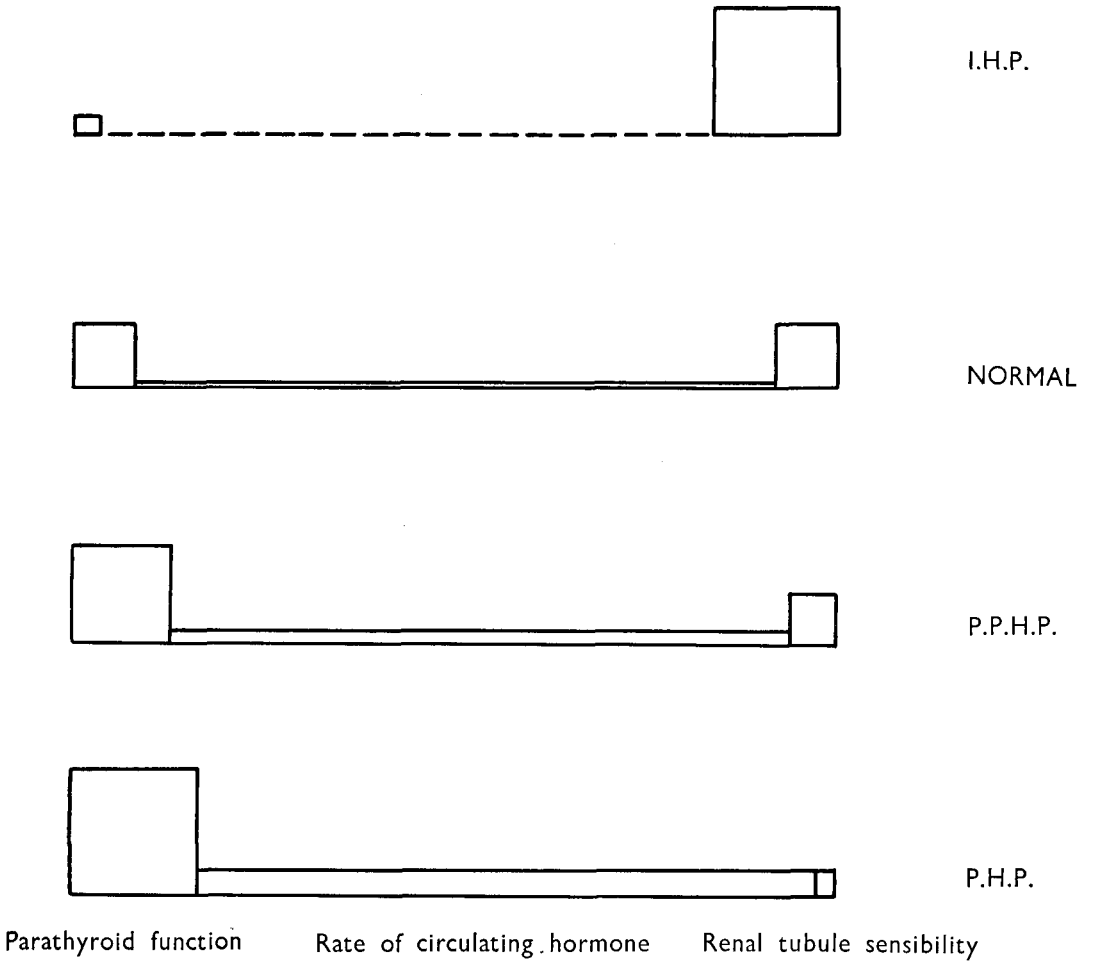

Fig. 39. Possible quantitative relationship between IHP, normal state, PHP and PPHP, concerning the renal tubule sensibility. PPHP possibly represents an intermediate state between normal and PHP

rect result of hypocalcemia and possibly also of hyperphosphatemia or other still unknown factors.

Treated patients with PHP might therefore not have hyperplastic glands (first patient of Albright et al., 1942).

No methods, however, are at present available for directly determining the rate of secretion of the parathyroid hormone, or hormones, nor for measuring the concentration of the active hormone in body fluids. Inferences in regard to the physi-

ological activity of the parathyroid gland on the sole basis of its morphology are somewhat hazardous.

This concept of inherent end-organ insensitivity in PHP must by broadened to include other cells, as well as those of the renal tubule. Osteitis fibrosa should develop, unless the bones as well as the renal tubules are insensitive to parathyroid hormone.

Indeed, the incidence of bony demineralisation in PHP is mentioned in 15% of the cases (Bronsky et al., 1958).

In PHP with such extensive demineralisation of bones the following postulation has been made by Reynolds et al (1952), Kolb and Steinbach (1960), Singleton and Ching Tseng Teng (1962), Bell et al. (1963).

The inability of one end-organ (kidney) to respond to parathyroid hormone could lead to parathyroid hyperplasia, and the oversecretion of the hormone might affect another more responsive end-organ (bone) and thus cause demineralisation in a certain number of cases.

This cases have been named pseudo-hypo-hyperparathyroidism or PHP with secondary hyperparathyroidism (Kolb and Steinbach, 1960) (see Tab. 5).

Recently Fanconi et al. (1964) described 3 cases of familial PHP with radiological signs of hyperparathyroidism.

These cases lend support for a dissociation in man of the effects of parathyroid hormone on bone and kidney.

Smulyan and Raïsz (1959) reported a case with PPHP who did not show the renal response to injected parathyroid extract but did respond with hypercalcemia (skeletal response).

PPHP with extensive demineralisation is uncommon as to be expected. It has been described in one patient with questionable PPHP (van der Werff ten Bosch, 1959). This may be a chance observation.

Indeed, we suggest that in PPHP there exists only a slight hyperplasia of the parathyroid gland with a slight or partial end-organ irresponsiveness (incomplete expression of a genetic syndrome) (see Fig. 39).

As to be theoretically expected bone demineralisation must be very rare in IHP (5% of the cases after Bronsky et al., 1958).

Costello and Dent (1963), and Fanconi et al. (1964) described however typical examples of IHP with hyperparathyroid bone disease.

In these cases Fanconi raises the hypothesis of parathyroid hyperplasia with overproduction of both the hypo calcemic factor " calcitonin " and (secondarily?) the classical parathormone.

Nothing however is known at present about the " calcitonin " secretion in patients with IHP, PHP and PPHP.

A number of still other extra-renal and extra-osseous effects of parathyroid hormone might be expected to lead to, among other things, demonstrable abnormalities of calcium absorption, lactation and of phosphate distribution in liver and muscle (Mann et al., 1962).

Tab. 5. Nomenclature related to parathyroid glands with or without functional disturbance

	Hyper-parathyroidism	Pseudohypo-hyperpara-thyroidism	Pseudohypo-parathyroidism	Hypopara-thyroidism	Pseudo-pseudohypo-parathyroidism
Etiology and pathologic physiology	Adenoma Hyperplasia Carcinoma	Failure of renal response to normally functioning parathyroid glands		Post-thyroid-ectomy Idiopathic Moniliasis?	Normally functioning parathyroid glands
		Secondary hyperplasia			
PTH Output	Increased		Normal	Decreased	Normal
Serum alkaline phosphatae	Increased	Normal or increased	Normal or decreased		Normal
Serum Ca P Urinary Ca P	Increased Decreased Increased Increased	Decreased Increased Decreased Decreased			Normal Normal Normal Normal
Tetany	Absent	Present			Absent
Bone changes	Increased osteoclastic resorption: Osteitis fibrosa generalisata		Decreased osteoclastic resorption: increased density of bones		None
Pathologic calcification	Renal	Basal ganglia, periarticular soft tissues, lenticular			Soft tissues Lenticular
Brachydactyly Exostosis Round facies Short stature	None	Present		None	Present
Ellsworth-Howard test	No response	No response		Positive response	Positive response

Two hypotheses other than innate end-organ insensitivity are discussed by Mann et al. (1962).

Hyperplasia of the parathyroid gland can be seen when the hormone manufactured by the gland is defective and, to a greater or lesser extent, physiologically ineffective, and if the abnormal secretory product of the gland is capable of functioning as a chemical analogue to block the effect of injected parathyroid hormone on the end-organs.

This assumption, however, cannot explain these cases with PHP with bone dimineralisation where other end-organs (bones) are sensitive to the secretory product of the parathyroid gland.

An hypothetical substance present in the blood of these patients, which could render parathyroid hormone, whether exogenous or endogenous, physiologically ineffective, by combining with it or by degrading it, has twice been sought in vain. This subject is discussed by Mann et al. (1962).

In PHP there also is at present no auto-immunological basis to assume this hypothesis.

An auto-immunologic mechanism is however possible in IHP (Pinsky, 1963).

Nosologic interrelations of PHP, PPHP and IHP

It is yet unknown if there exists a nosologic relationship between IHP and PHP. Dickson et al. (1960) supposed a genetic relationship between IHP and PHP and suggest to perform an Ellsworth-Howard test in each patient with IHP, especially if he responds poorly to therapy with Vitamine-D or AT-10.

Until 1960, cases of PHP and IHP were not seen in the same family.

However, Nichols et al. (1961) reported a family in which members of three generations had a syndrome of calcification of the basal ganglia and hypocalcemia. One subject presented signs and symptoms similar to those of IHP, two had calcification of the basal ganglia without hypocalcemia and six presented a clinical picture suggestive of PHP. They found it " tempting to speculate that the involved members represent examples of varying stages of the natural history of and inherited defect of calcium metabolism resulting in: ectopic calcification only, ectopic calcification with parathyroid overactivity insufficient to maintain normo-calcemia, and ectopic calcification with ultimate parathyroid atrophy ".

Palubinskas and Davies (1959) reported that in their case of PHP, whose blood chemistry reverted spontaneously to normal, transferring her to the pseudo-pseudo group, while at the same time calcification of the basal ganglia, not previously present, developed.

Chronic hypoparathyroidism of any etiology may give rise to a number of complications which are included in IHP and PHP.

These include calcifications in the basal ganglia, lenticular opacities, defective dentition, mental retardation and convulsions. All these phenomena with the exception of mental retardation and dental abnormalities are without doubt consequences of the disturbed calcium or phosphorus metabolism, since they are well established sequelae of parathyroidectomy in man.

Mental deficiency and defective dentition are not recognized complications of post-operative hypoparathyroidism, because they require that parathyroid function be depressed in early childhood, when inadvertant parathyroidectomy must be increasingly rare.

The presence of some of these complications in the normo-calcemic form of Albright's hereditary polyosteochondrodystrophy is evidence that a hypoparathyroid-like state has possibly been present at some previous time. Indubitable instances of such a transformation are recorded.

Short stature is present both in IHP (mean height 157 cms.; data from Lachmann, 1941) and Albright's hereditary polyosteochondrodystrophy (PHP and PPHP forms).

However, the typical dyschondroplastic skeletal anomalies and the subcutaneous calcifications are usually not present in IHP.

The sex incidence is possibly 1 : 1 in IHP and about 2 : 1 in PPHP and PHP.

The age of onset or diagnosis also differs (first decade in the idiopathic form, second decade in the pseudo form, and the third decade in the pseudo-pseudo form).

It should be noted that, although the 3 disorders are related, the relationship is like that of 3 links in a chain (Hanno and Weis, 1961); IHP and PPHP share no features in common, whereas PHP combines the clinical features of both the other disorders (Tab. 6).

Moniliasis and Addison's disease occur almost only in the idiopathic form. Diabetes occurs also in patients and family members of IHP as in the PHP and PPHP forms.

Eleven familial cases of IHP are on record (Bethénod et al., 1964).

The exact inheritance may be autosomal dominance with low penetrance, but further study is needed in this field.

Tab. 6. Albright's hereditary polyosteochondrodystrophy

	Familial cases of idiopathic hypoparathyroidism (IHP) Type O (?)	Pseudo-hypoparathyroidism (PHP) Type I	Pseudo-pseudo-hypoparathyroidism (PPHP) Type II
Biological syndrome (hypocalcemia, hyperphosphatemia)	+	+	—
Clinical syndrome (tetany)	+	+	—
Morphological syndrome (short stature, brachymetacarpy)	±	+	+
Trophic disturbancies (basal ganglia, lenticular and subcutaneous calcifications)	±	+	+

It seems to us that IHP, PHP and PPHP are clinically only distinct by the different frequency of the dysmorfic syndrome, the associated neurological and endocrinological disturbancies, and the different incidence of hereditary factors.

Differential diagnosis

PPHP must be differentiated with some other clinical conditions. This subject is extensively reviewed by Nagant de Deuxchaisnes et al. (1960) and Mann et al. (1962).

We may cite only:

1. Hypothyroidism: (previous diagnosis most often made);
2. Gonadal dysgenesis, as discussed in another paragraph;
3. Hereditary multiple exostoses. Genetically separate and clinically distinct. Some similarity in pathogenesis is not excluded. Short stature (from 140 to 150 cms.

and a high US/LS ratio is also characteristic of this condition). A short ulna and a radius curvus may also occur;

4. Bilateral symmetrical brachymetapody (Boorstein, 1916);

5. Familial calcification of the basal ganglia (Fahr syndrome). Clinically unrelated;

6. Multiple epiphyseal dysplasia (Waugh, 1952). Genetically and clinically clearly unrelated;

7. Familial brachydactyly (Brailsford 1945). Clinically distinct;

8. Congenital mesodermal dysmorphodystrophy of brachymorphic type (Feinberg, 1960);

9. Congenital chondrodystrophy with calcifications;

10. Ellis-Van Creveld syndrome;

11. Myosisitis ossificans progressiva. A fundamentally entirely distinct syndrome;

12. Laurence-Moon-Biedl syndrome.

Heredity of PPHP

PPHP arise from a polygenetic pleiotropic deficit with probably early subclinical hypoparathyroidism (without clinical findings).

The first familial cases of PHP were observed by Lachmann (1941), Elrick et al. (1950) and Uhlemann (1950). The first familial cases of PPHP were recorded by Seringe and Tomkiewicz (1956).

The simultaneous occurrence of cases with PHP and PPHP in the same family in two or more generations has been first recorded by Selye (1949) and Browne (1950).

The fully expressed syndrome of PHP or PPHP alone in 2 or more successive generations has been first reported respectively by Béhague and Soulas (1956) and by Mann et al. (1962).

Still less attention has been payed to the genetic mechanism which underlies the transmission of this disease. Thorough studies of relatives of affected persons have not been made until 1963.

A review of limited pedigrees of Albright's hereditary polyosteochondrodystrophy is provided by Mann et al. (1962) and by Schwarz and Bahner (1963).

Consanguinity of parents in PHP is reported only once (Martin, 1957) in about the total number of 50 publications until 1964.

The recent publications of more extensive pedigrees with the appearance of the disease in two or more successive generations leave no doubt that this condition is essentially genetically determined, and is not the result of an intra-uterine phenocopy, as put forward by Nagant de Deuxchaisnes et al. (1960).

Ray and Gardner (1959), Dickson et al. (1960) and Mc Kusick, quoted by Uhr and Bezahler (1961), have considered that the inheritance of PPHP may be autosomal dominant, without excluding a sex linkage.

This condition appears more often in females than in males, and was previously found to approach the 2 : 1 ratio. Furthermore, until our observation in 1963, male-

to-male transmission in PPHP was not recorded. The condition was also more commonly transmitted by the mother than by the father.

For all these reasons Mann et al. (1962), Schwarz and Bahner (1963), Schöngut and Scérhati (1963) and Lehmann (1964) supposed a sex-linked dominance.

Our extensive pedigree and more recent data lead us to exclude sex-linked inheritance in this condition (see further).

In rare sex-linked dominant conditions each of the paired sex chomosomes of the female has a probability equal to that of the male chromosome of carrying the mutant gene. The sex ratio of females to males affected may therefore approach the 2 : 1 ratio.

This was indeed observed for PHP in a review by Cohen and Donnell (1960) comprising 45 females and 22 males.

Mann et al. (1962) claimed a F : M ratio in PPHP close to 2 : 1 (28 females and 10 males: a ratio not differing significantly by the chi-square test from a theoretical 2 : 1).

Of the 22 members of the family with PPHP studied by Hermans et al. (1964) 15 were females and 7 were males.

Cruz and Barnett (1962), however, noted a ratio close to 4 : 1 from a review of 51 accepted cases. In our review (see Tab. 3) we note 68 females and 24 males: a ratio close to 3 : 1.

More cases are therefore needed to establish definitely the exact F : M ratio. It may be different of the 2 : 1 value suggesting sex predominance or partial sex limiting instead of true sex linkage.

In some but not all sex-linked disorders the disease is more severe in males. In PPHP, however, males are no more phenotypically affected than females, just what is seen in autosomal inheritance (Goeminne, 1963, Hermans et al., 1964).

Contrary to the previously accepted opinion, male-to-male transmission in PPHP may occur. Also, paternal affected collaterals of affected male sibs have been observed.

Our extensive pedigree of PPHP (studied in 1962 and 1963) discloses for the first time a clear male-to-male transmission.

Two cases, although rather poorly documented, of apparent male-to-male transmission of PHP, have been observed, one in Basel by Buchs (1954) and the other in Los Angeles by Mackler, Fouts and Birsner (1952).

A clear male-to-male transmission also appeared in an extensive pedigree of PPHP, published in Italy by Minozzi et al. (1963).

Moreover, it should be pointed out that Wallach et al. (1956) described a male patient with PPHP, whose father had short thumbs, whereas Schwarz (1960) described a young male with PPHP, whose paternal grand-father was short. The family trees of Cruz and Barnett (1962) and Hermans et al. (1964), also suggest a male-to-male transmission.

Klotz et al. (1962) note without further statement, brachydactyly in the father and paternal grand-father of a male patient with PPHP.

Royer et al. (1959) reports a male child with PHP, whose paternal uncle presented an isolated mental retardation with a nanism (130 cms.): forme fruste of PPHP?

Forbes (1964) is quoted to have seen a male with PHP; his only son has radius curvus and one short metacarpal and is otherwise well (" forme fruste " of PPHP?).

There only exist few observations where PHP was inherited through the father in female children: Bergstrand et al. (1958), Todd et al. (1961) and Nichols et al. (1961).

Inheritance of PPHP though the father in female children is noted only by Schwarz and Bahner (1963).

In some cases of male siblings with PPHP unfortunately nothing is mentioned concerning the father (Gilgore et al., 1962). Therefore, the father and paternal collaterals of male affected cases have to be explored more thouroughly, to check if the condition is really more than two or three times more commonly transmitted by the mother than by the father, as to be statistically expected by the sex-ratio.

That the apparent male-to-male transmissions are not the result of consanguineous marriages where both parents carry the gene is expressly ruled out in our pedigree.

There is virtually also no likelihood of a random coupling of two gene carriers for so rare a disorder.

Our pedigree (1962 and 1963) and also the observation by Minozzi et al. (1963) clearly shows that a male-to-male transmission may occur; PPHP may thus also show an autosomal dominant transmission, as seen in the other rare pedigrees of isolated or familial brachymetapody with normal stature.

The mode of inheritance of PPHP seems to be further characterized by an incomplete penetrance of about 50%, a varying expressivity and a weak familial specificity.

Karyotype in PPHP

Schleich, Pfitzer and Schwartz (1963) found a karyotype XO in a case of Turner's syndrome with brachymetacarpy (PPHP?) and a complete normal karyotype in a female with PHP alone. The karyotype of PPHP alone had been found normal too (Rosenthal, 1961).

Linkage studies in PPHP

In 16 members of our family (9 women and 7 men) we also made an ophthalmological examination, especially in order to detect possible congenital colour defects. This investigation was completely negative: none of them had a colour defect. Nothing thus can be said about a linkage with daltonism.

As expected, the family further does not give a linkage score for the Xg^a blood-group (16 persons were investigated). Other blood group determinations were not systematically performed.

Treatment

We don't agree with the statement by Ahmed (1961) and some other authors that PPHP does not need any treatment.

Although there is no tetany, the clinical conditions such as diabetes, hypertension and hypothyroidism should be treated early. Short stature is also a serious social handicap in such patients.

Royer et al. (1959) suggested that in PPHP with nanism moderate doses of thyroid extract may influence the growth rate.

Calciferol or extra-calcium do not influence the growth rate in PPHP.

If it could be proved that in PPHP the early childhood growth pattern fulfils the criteria of " primordial " dwarfism, i.e. retarded height development associated with normal skeletal maturation, it will be interesting to see whether human growth hormone will stimulate height development in these cases.

Terminology

The terms PPHP and PHP were claimed by many authors to be inappropriate and to incarnate much semantic confusion (Mann et al., 1962).

We believe with Ahmed (1961) that until the pathogenesis of the syndrome is unknown, there is no use in changing the term pseudo-pseudo-hypoparathyroidism or Albright's hereditary polyosteochondrodystrophy. Many other purely descriptive but still more inacceptable and inappropriate names have been proposed.

We may cite the following terms proposed in the literature. Pseudo-pseudo-hypoparathyroidism or a-hypocalcemic pseudo-hypoparathyroidism; Albright (1952).

Dyschondroplasia with soft tissue calcifications and ossification; Mc Neely (1956).

Dyschondroplasia and exostoses with metaphyseal dysplasia or congenital skeletal malformations (Fromm, 1956).

Brachymetacarpal dwarfism without tetany; van der Werff ten Bosch (1959).

Dystrophie (polyviscérale) " d'Albright type II " (Seringe and Tomkiewicz, 1956). Type I is the PHP form. We propose the name " type O " for the IHP form.

" Nanisme oligophrène dyschondroplasique " (Nagant de Deuxchaisnes et al., 1960).

Cerebro-metacarpo-metatarsal dystrophy (Jancar, 1965).

We may note here that there is no real " nanosomia " or " dwarfism " and very seldom " true oligophreny " in PPHP.

Summary

A large kindred (4 generations) with pseudo-pseudo-hypoparathyroidism (PPHP) and the clinical, biological and anthropometric features of this syndrome are extensively described.

The association of PPHP with diabetes, hypertension, hypothyroidism, polyarthrosis and peripheral arteritis is very probably significant.

Gonadal dysgenesis with brachymetacarpy must clearly be distinguished from PPHP.

The transmission of PPHP is probably not sex-linked dominant but autosomal dominant with an incomplete penetrance of about 50%, a varying expressivity and weak familial specificity. Partial sex limiting or sex predominance may occur, instead of true sex-linkage in this condition.

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RIASSUNTO

L'autore descrive nuovi casi di pseudo-pseudoipoparatiroidismo in quattro generazioni di una stessa famiglia, facendo una esposizione dettagliata e completa dei dati clinici, biologici e antropometrici di questa sindrome.

Egli insiste sull'associazione significativa del diabete, dell'ipertensione, dell'ipotiroidismo, della poliartrosi e della arterite periferica nella poli-osteo-condro-distrofia ereditaria di Albright, riportando numerosi esempi.

Nota le differenze fondamentali tra la sindrome di Turner con brachimetacarpia e lo pseudo-pseudo-paratiroidismo, la cui trasmissione ereditaria non ha caratteristiche identiche.

Dalle premesse dell'autore risulta comprovata per la prima volta la trasmissione con dominanza autosomica, non legata al sesso, di questa sindrome.

La penetranza è del 50%, l'espressività è variabile, la specificità abbastanza debole e la predominanza molto netta. Dei casi esaminati il 75% è costituito da soggetti femminili.

RÉSUMÉ

L'auteur rapporte plusieurs nouveaux cas de pseudo-pseudo-hypoparathyroïdisme dans 4 générations d'une seule famille.

Il fait la description complète des signes cliniques, biologiques et anthropométriques de ce syndrome.

Il insiste sur l'association significative du diabète, de l'hypertension, de l'hypothyroïdisme, de la polyarthrose et de l'artérite périphérique dans la poly-osteo-chondro-dystrophie héréditaire d'Albright. Il en décrit plusieurs exemples.

Il insiste sur les différences fondamentales entre le syndrome de Turner avec brachymétacarpie et le pseudo-pseudo-hypoparathyroïdisme. Leur transmission héréditaire n'est pas identique.

Pour la première fois, la transmission en dominance autosomale non liée au sexe est ainsi établie pour ce syndrome. La pénétrance est de 50%, l'expressivité est variable, la spécificité est assez faible, la prédominance sexuelle est assez nette (75% des cas sont de sexe féminin).

ZUSAMMENFASSUNG

Verf. hat etwa 15 neue Fälle mit Pseudo-pseudo-hypo-parathyreoidismus in einer grossen Sippe mit 4 Generationen beschrieben. Eine klare Vater-Sohn-Übertragung kommt dabei vor. Bisher liegen keine umfangreichen Sippenuntersuchungen über dieses Syndrom vor. Verf. gibt eine umfangreiche Beschreibung der klinischen erkmale dieser Erkrankung. Diabetes, Hochdruck, Hypothyreoidismus, Polyarthrosis und periphere Arteriitis kommen häufig vor in der Albright' schen Polyosteochondrodystrophie. Mehrere Fälle kamen zu Beobachtung.

Sicher sind Pseudo-pseudo-hypoparathyreoidismus und Gonadendysgenesie mit Brachymetacarpie ganz verschiedene Krankheiten. Auch der Erbgang ist grundverschieden.

Durch unsere Beobachtungen besteht heute kein Zweifel mehr darüber dass diese Erkrankung autosomal dominant und nicht X-chromosomal verebt wird. Die Penetranz ist 50%. Das Krankheitsbild ist wechselnd. Die Spezifizität ist schwach. Die Frauen sind dreimal so haüfig befallen wie die Männer (sexuelle Prädominanz).