Pseudohypoparathyroidism

PHP

Pseudohypoparathyroidism

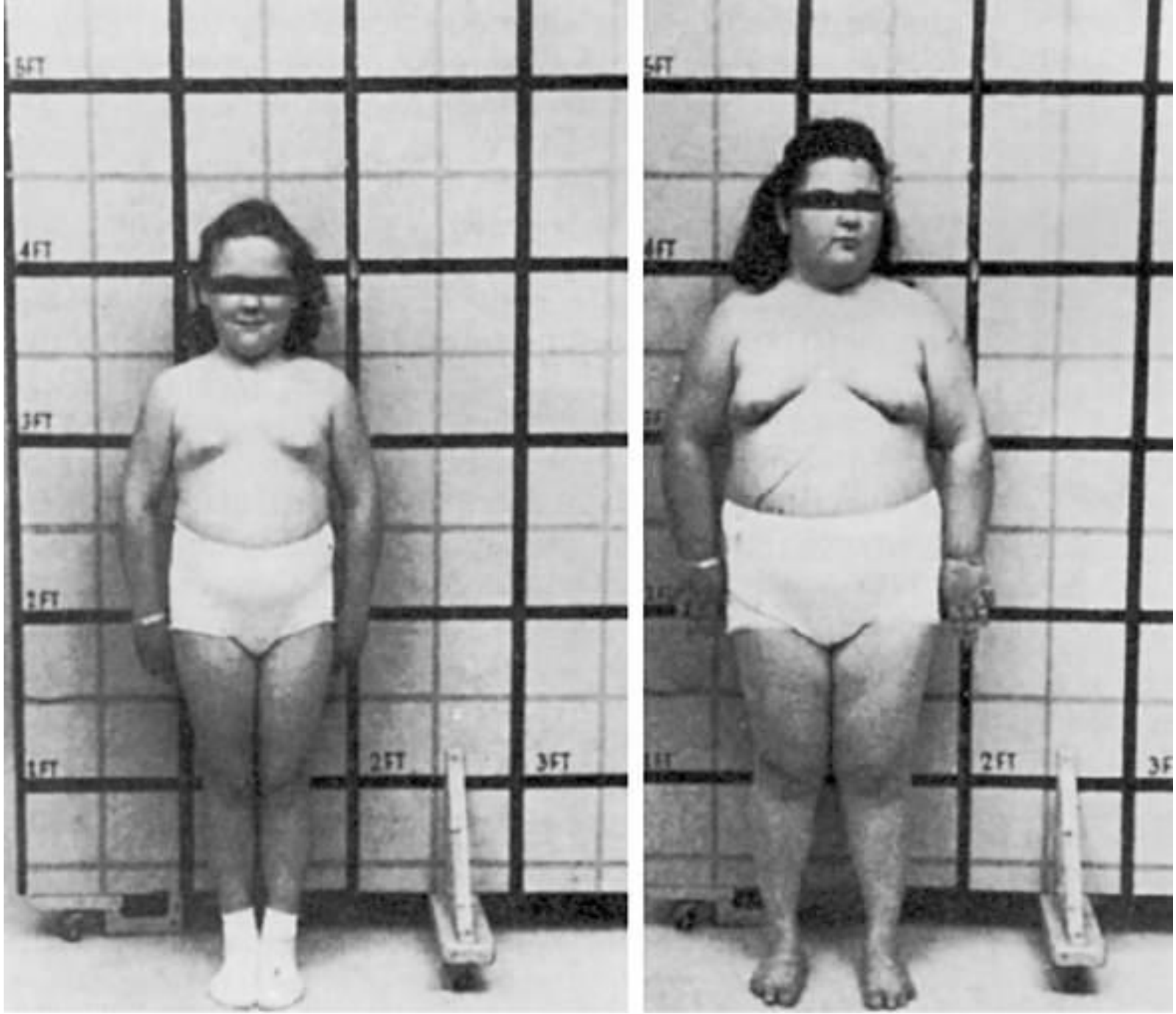
- Idiopathic and inherited forms of PTH resistance
- First described by Albright, Burnett, Smith and Parson in 1942
- **Type 1**
  - resistance to PTH in proximal renal tubule
  - impaired increase in urinary cAMP and urinary phosphate following administration of PTH
- **Type 2**
  - conserved cAMP response to PTH
  - no phosphaturic response, consistent with molecular defect distal to cAMP generation in PTH-mediated signal transduction pathway

J Clin Endocrinol Metab. 2016 Jun;101(6):2284-99

Pseudohypoparathyroidism

- Albright hereditary osteodystrophy (AHO)
  - short stature
  - rounded face
  - shortened fourth and other metacarpals
  - obesity
  - subcutaneous calcifications
  - variable degrees of reduced mental acuity
  - dental hypoplasia

J Clin Endocrinol Metab. 2016 Jun;101(6):2284-99



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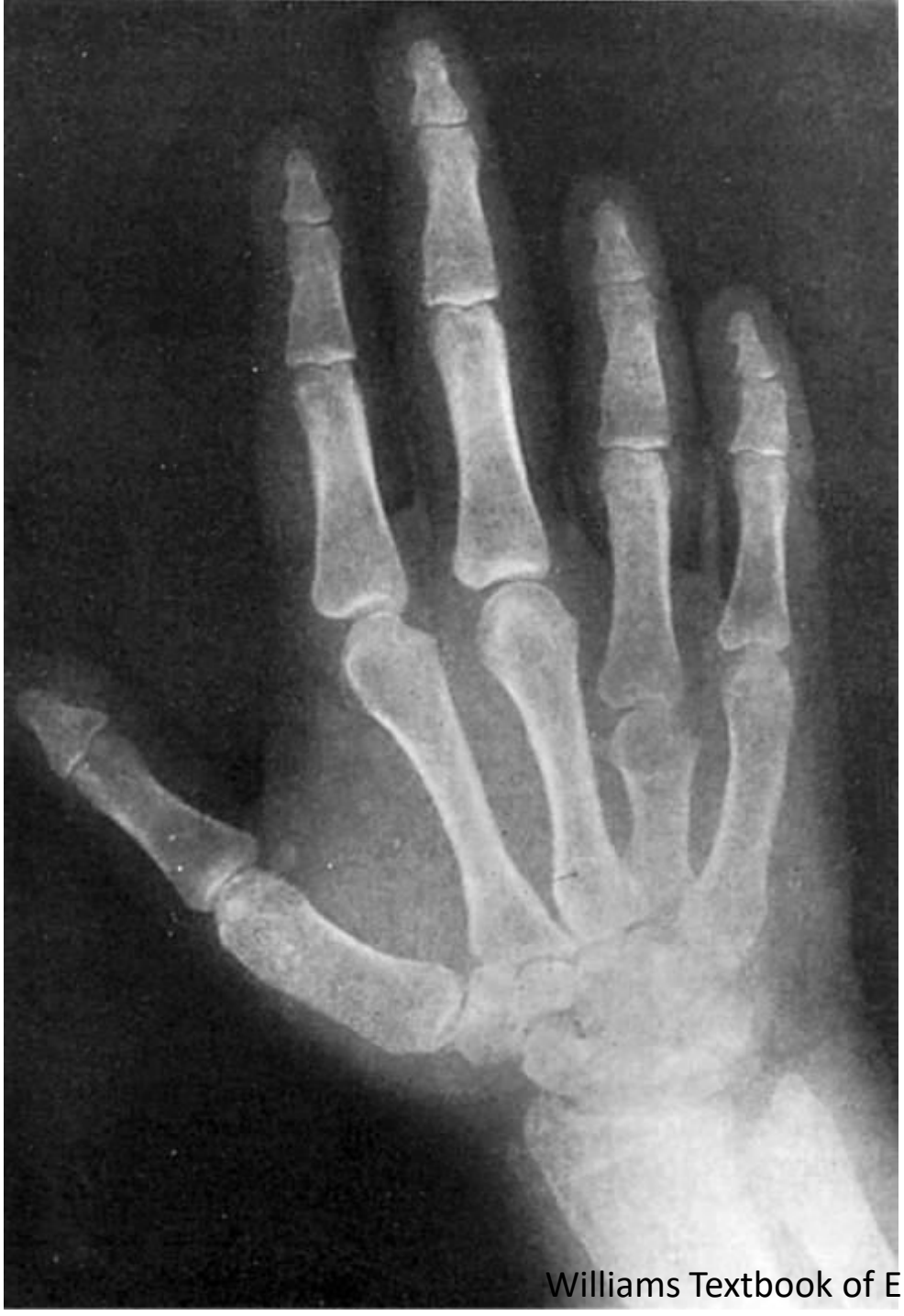

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Pseudohypoparathyroidism

- PTH administration failed to provoke a phosphate diuresis or an increase in serum calcium
- Defect in PTH receptor or cAMP-mediated signal transduction
- Measurement of cAMP in urine in response of PTH infusion
  - Chase-Aurbach test
  - diagnosis of PTH resistance
  - Measure urine phosphate by Ellsworth-Howard test

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Classification of Pseudohypoparathyroidism

Type	Hormone Resistance	AHO	Response to PTH	GNAS defect	Molecular defect
PHP Ia	PTH, TSH, GnRH, GHRH	**Present**	Blunt cAMP and phosphaturic response	Maternal inactivating mutation	Reduced functional Gs-alpha levels
PHP Ib	PTH (± TSH)	Absent	Blunt cAMP and phosphaturic response	Imprinting dysregulation	Abnormalities in Gs-alpha gene transcription STX16/GNAS
PHP Ic	PTH, TSH, GnRH	**Present**	Blunt cAMP and phosphaturic response	Few inactivating mutations reported	?adenyl cyclase
PPHP	None	**Present**	Normal response	**Paternal inactivating mutations**	Gs-alpha
PHP II	None	Absent	Normal cAMP response, blunted phosphaturic response	-	?cAMP targets

J Clin Endocrinol Metab, October 2011, 96(10):3020 –3030

J Clin Endocrinol Metab. 2016 Jun;101(6):2284-99

Classification of Pseudohypoparathyroidism

Type	Serum Calcium	Serum Phosphate	Serum PTH	Inheritance	Parental Origen of *GNAS allele*
PHP Ia	L	H	H	AD	Maternal
PHP Ib	L	H	H	AD / Sporadic	Maternal
PHP Ic	L	H	H	AD	Maternal
PPHP	N	N	N	AD	Paternal
PHP II	L	H	H	Sporadic	

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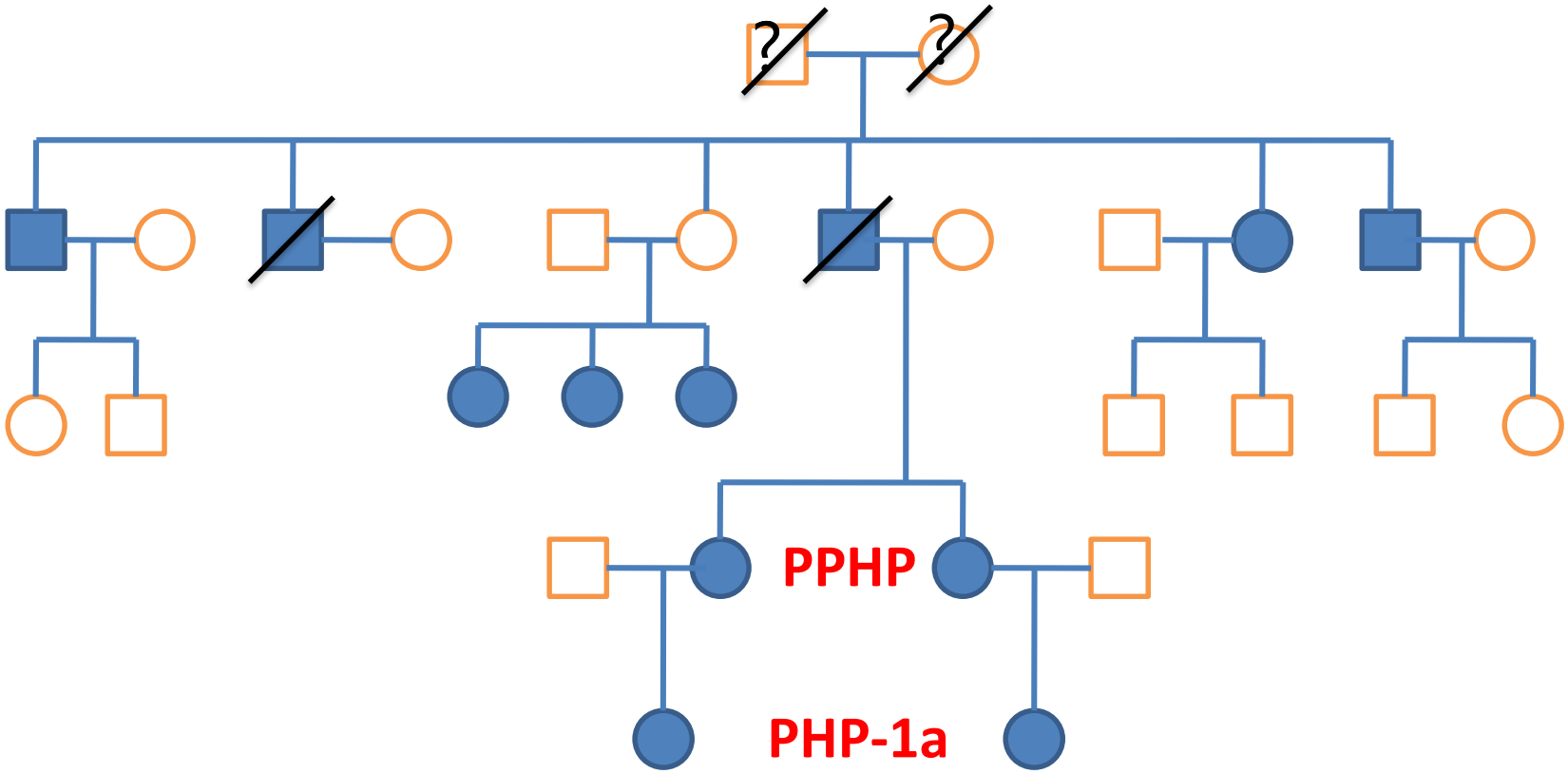
tissue-specific genetic imprinting



PHP type 1a

- GNAS mutations affecting exons 1–13 lead to diminished Gsα activity
- AHO feature
- Mutations that inactivate one allele of the Gsα coding region through a variety of mechanisms
  - missense mutations, chain-terminating mutations, changes that induce abnormal splicing, small insertions, deletions, or inversions
- Demonstrated in several tissues
  - kidney, fibroblasts, transformed lymphocytes, platelets, and erythrocytes
  - resistance to other hormones such as TSH, glucagon, and gonadotropins

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Pseudo-pseudohypoparathyroidism (pseudo-PHP)

- Phenotype of AHO but without evidence of PTH resistance
- Often found in the same kindreds as those with PHP 1a
- Inherit mutant Gsα gene from their fathers
  - tissue-specific genetic imprinting

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Treatment consideration

- Selectivity of PTH resistance for proximal tubule guides management
  - renal resistance to PTH limited to proximal tubule, active vitamin D analogues should be considered
  - goal of normalizing PTH (upper end normal) levels to avoid bone disease
  - calcium supplement
- Genetic counseling

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ALBRIGHT HEREDITARY OSTEODYSTROPHY (AHO) ORAL MANIFESTATION

AHO : Phenotype spectrum

- Short stature
- Obesity, round face
- Shortening of the metacarpal and metatarsal bone (most frequently the 4th and 5th)
- Calcification in the subcutaneous tissue
- Short neck, low nasal bridge
- Mental retardation
- Cataract
- Hyperphosphatemia
- Cone shaped epiphysis
- Osteoporosis

ORAL MANIFESTATIONS OF ALBRIGHT HEREDITARY OSTEODYSTROPHY
REV. HOSP. CLÍN. FAC. MED. S. PAULO 57(4):161-166, 2002

Albright hereditary osteodystrophy (AHO) Oral manifestation

- Changes affecting dentition found in 37-50% of PHP
- Premolars and molars affected most severely
- Severe periodontal disease with gingivitis
- Xerostomia
- Malocclusion
- Labial hypotonicity
- Deep hard palate

Ambika L, Vaishali keluskar, JIAOMR Dec 2010
Wesley et al, PEDIATRIC DENTISTRY: March 1986

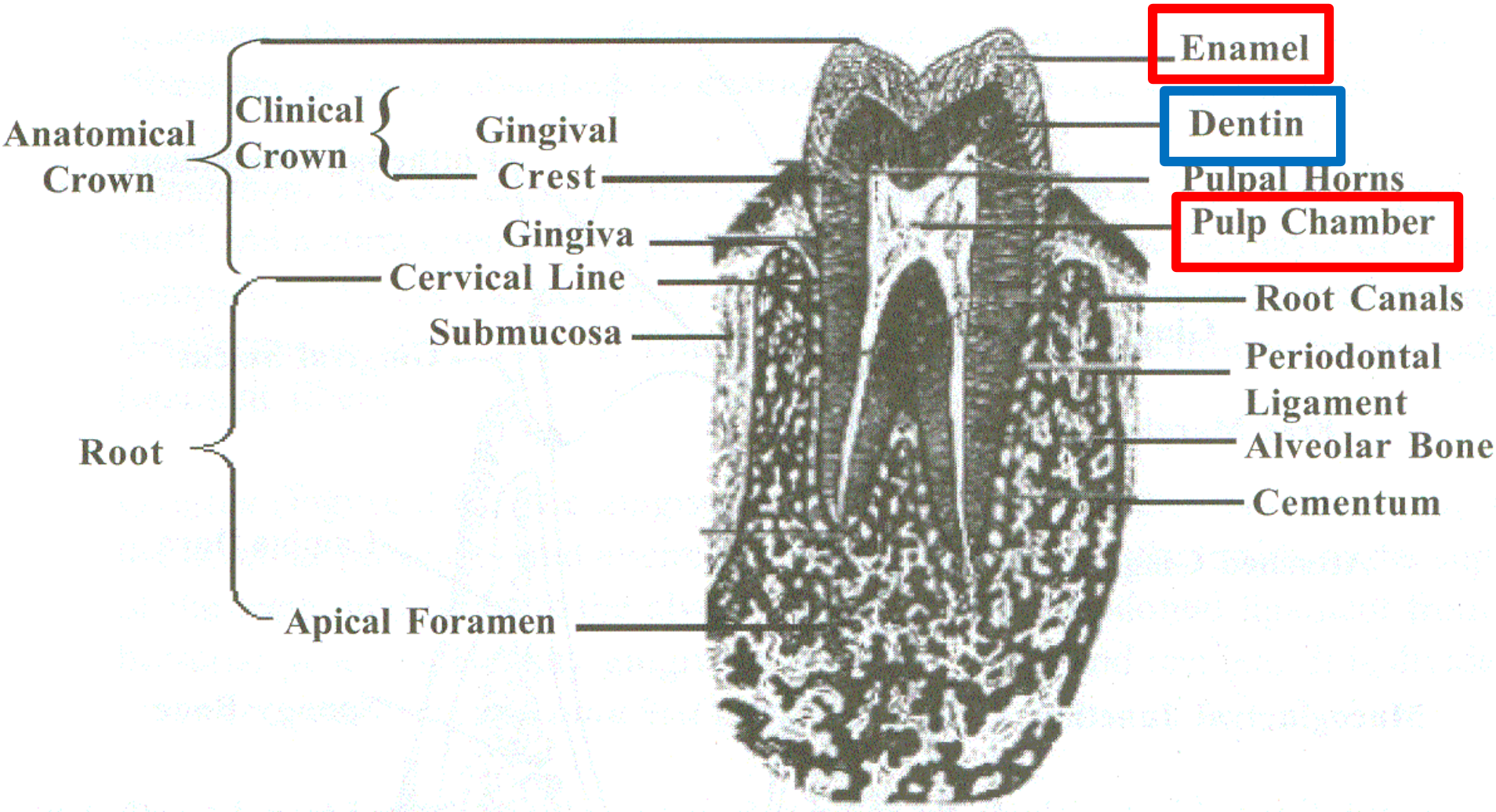


Figure 2-5. Structure of the Teeth and Supporting Tissues

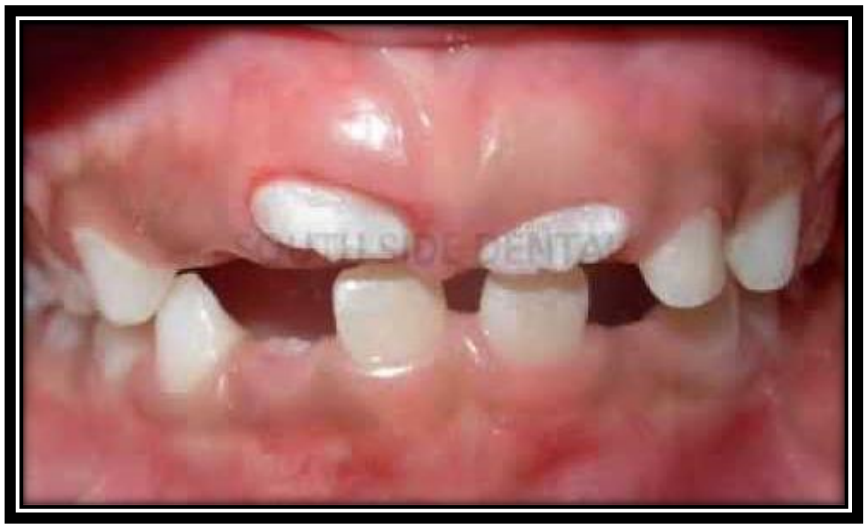
Oral manifestation of AHO

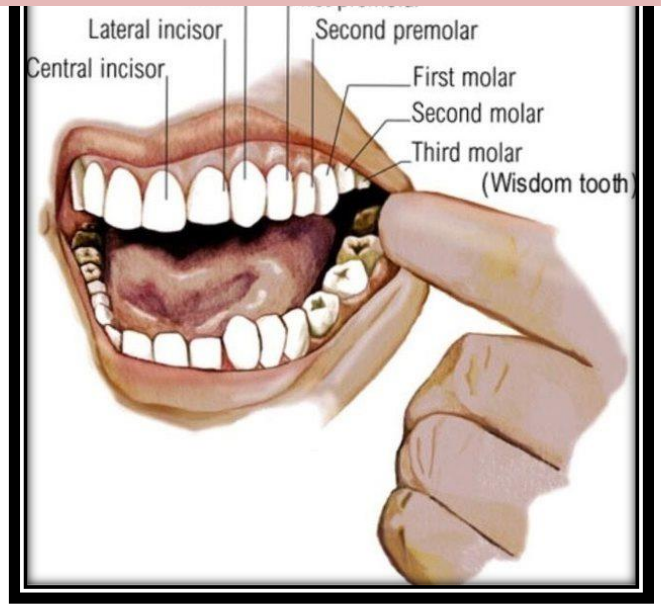
Enamel hypoplasia

- Dull white color
- Wedge-shaped teeth with hypocalcified and exhibit random pits and grooves in enamel
- Extensive caries
- Small crowns and short with blunt end roots

Wesley et al, PEDIATRIC DENTISTRY: March 1986

Oral manifestation of AHO



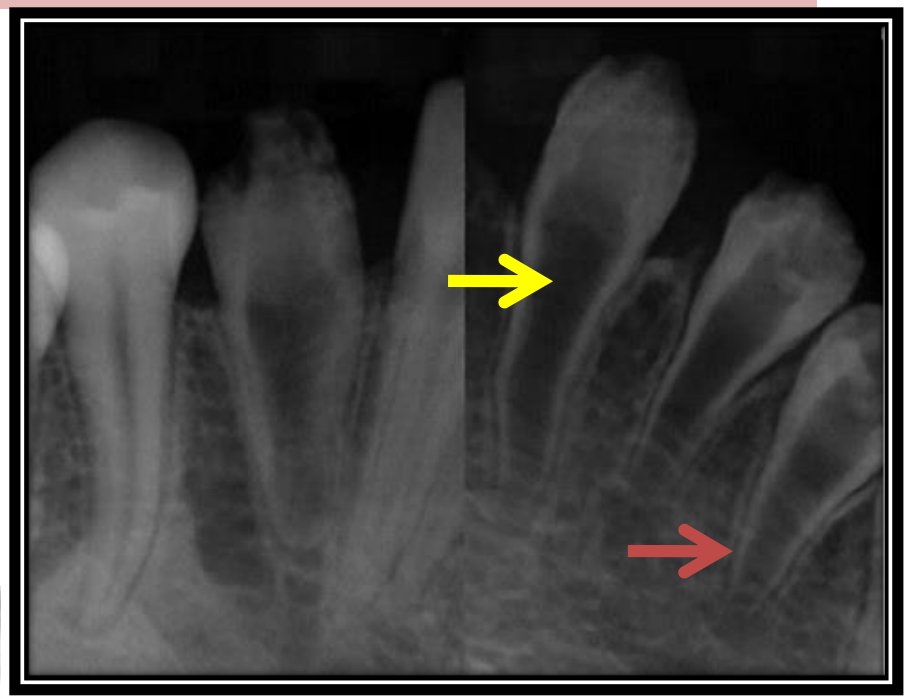


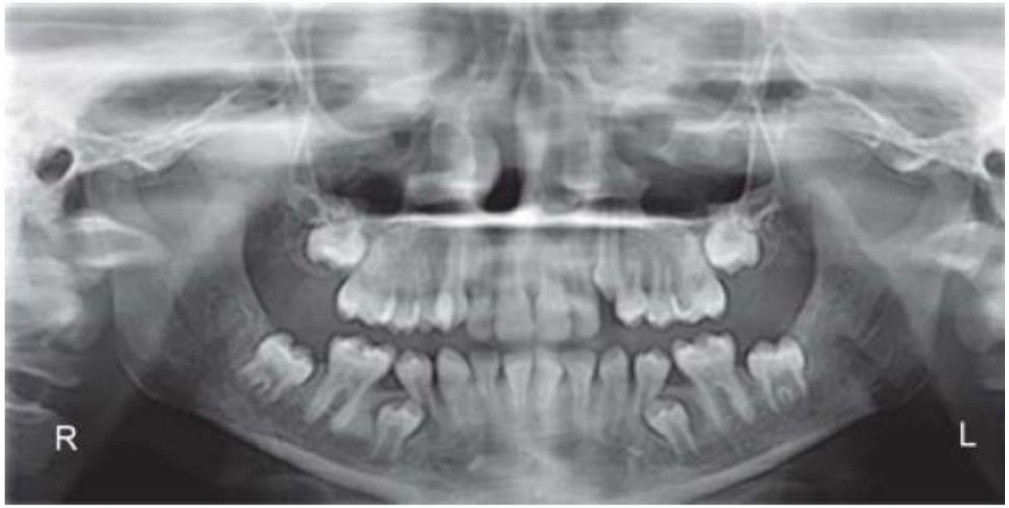
- Overall delay in eruption of permanent teeth with short, incomplete root formation
- Teeth lost early due to caries
- Jaws are short and wide in all cases

Wesley et al, PEDIATRIC DENTISTRY: March 1986

Oral manifestation of AHO

- Thin enamel
- Increased density of lamina dura and enlarged pulp chamber
- Impacted mandibular premolars





Arch. Dis. Childh., 1965, 40, 565.
Ambika L, Vaishali keluskar, JIAOMR Dec 2010

THANK YOU