Endocrine system development susceptibility

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Growth as a marker of child health

Growth failure is

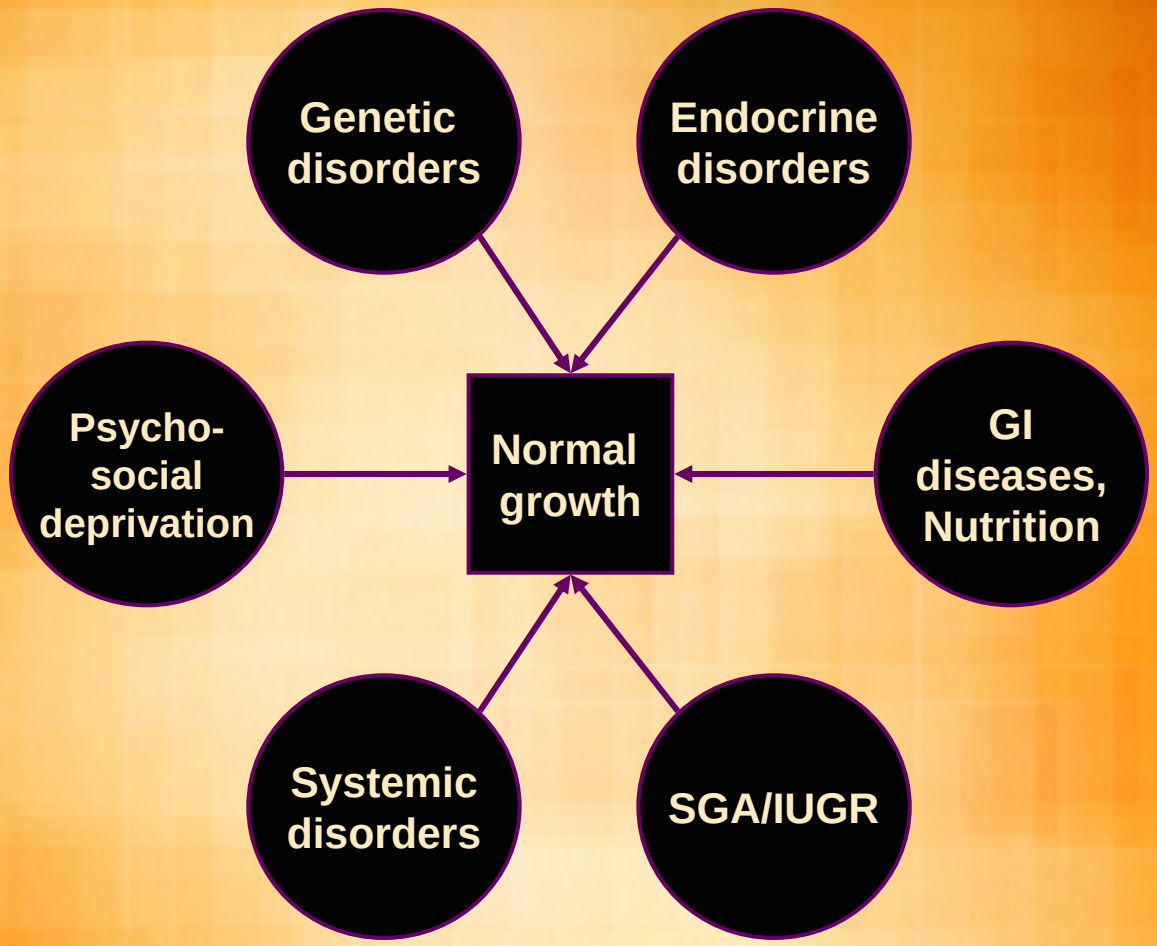
the single most sensitive

physical sign that something

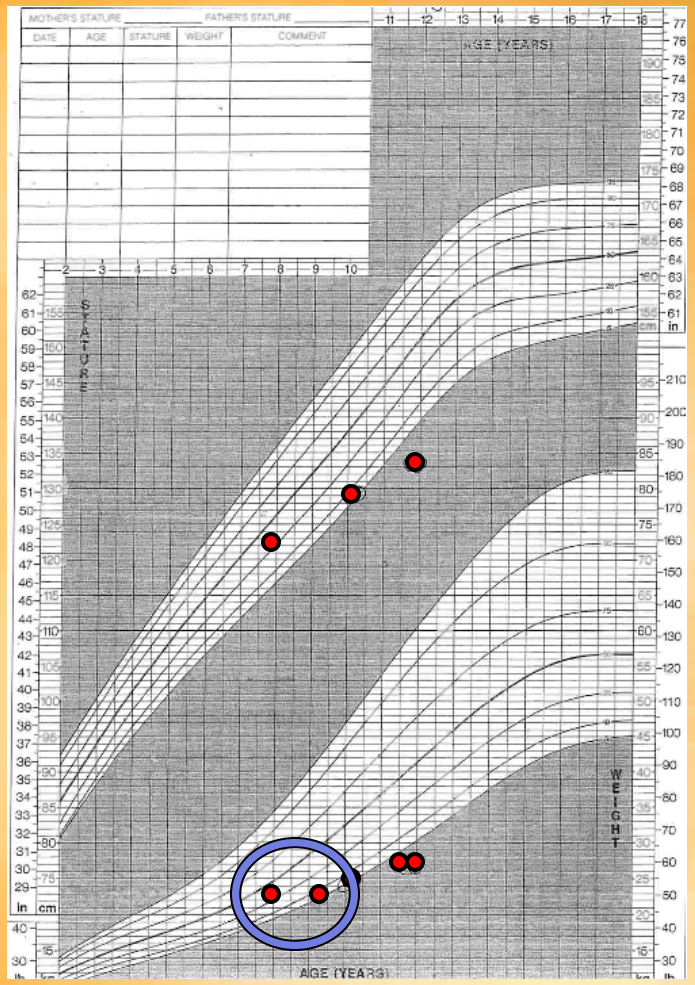
is amiss with a child.

It is very nonspecific.

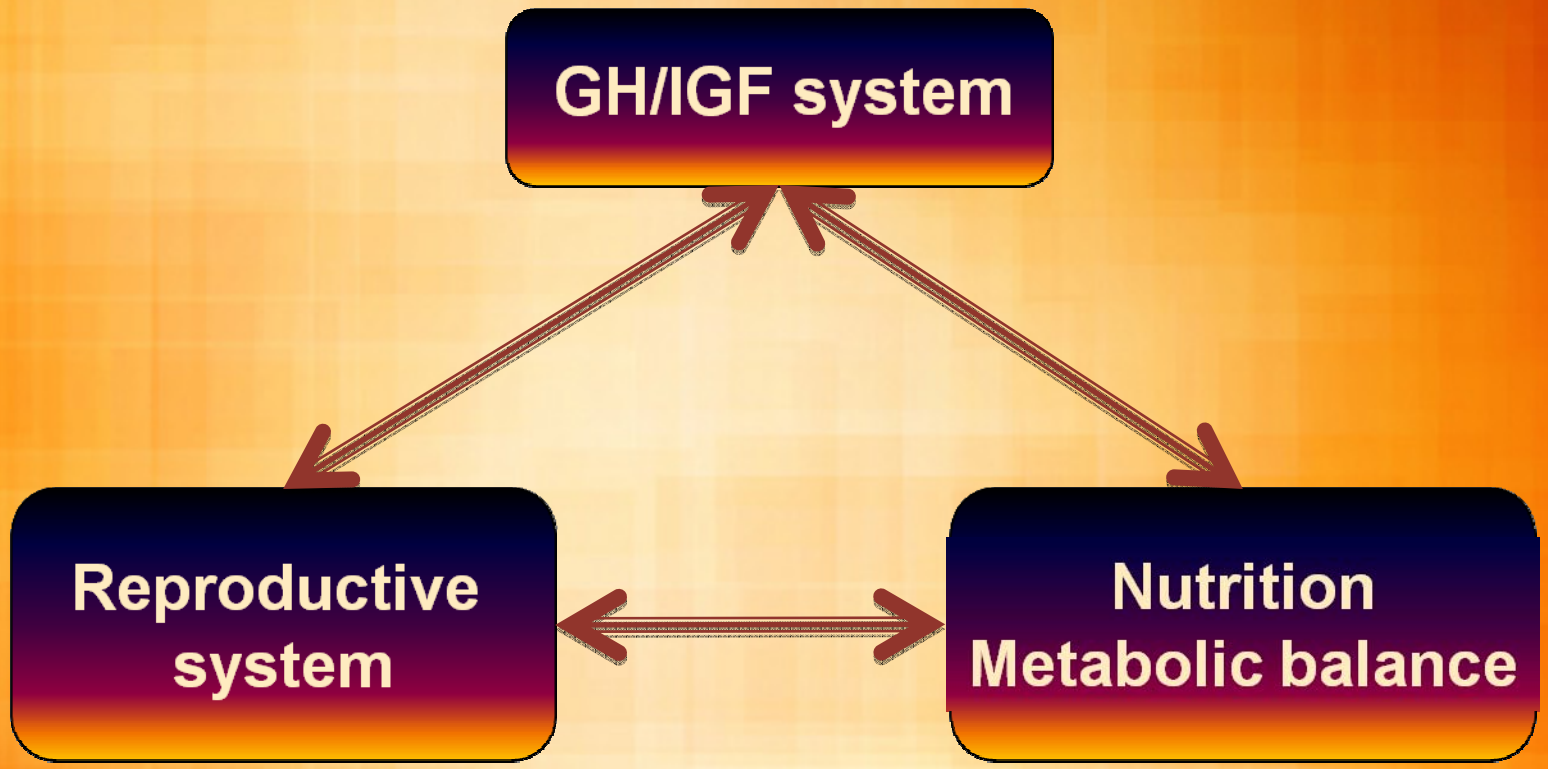
Processes that affect growth



Illustrative patient



Endocrine growth control



Normal growth rates during childhood

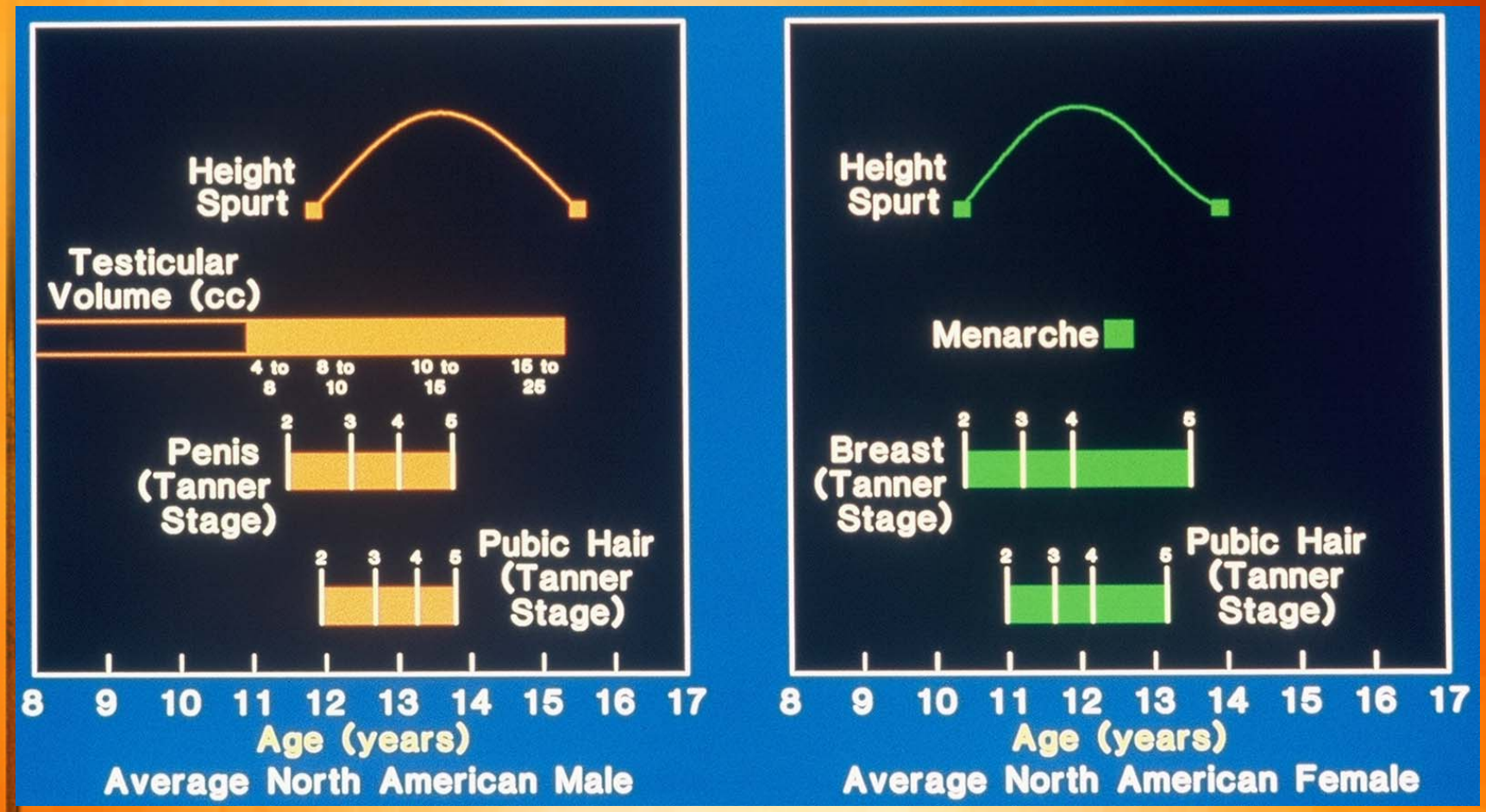
Age	Growth (cm/yr)
Birth to 1 yr	17– 26
1 to 2 yrs	10–13
2 yrs to puberty	5–7
Puberty	
Girls	7–12
Boys	8–13

National Center for Health Statistics.

Sequence of pubertal events

Boys' peak growth rate: 9.5 cm / y

Girls' peak growth rate: 8.3 cm / y



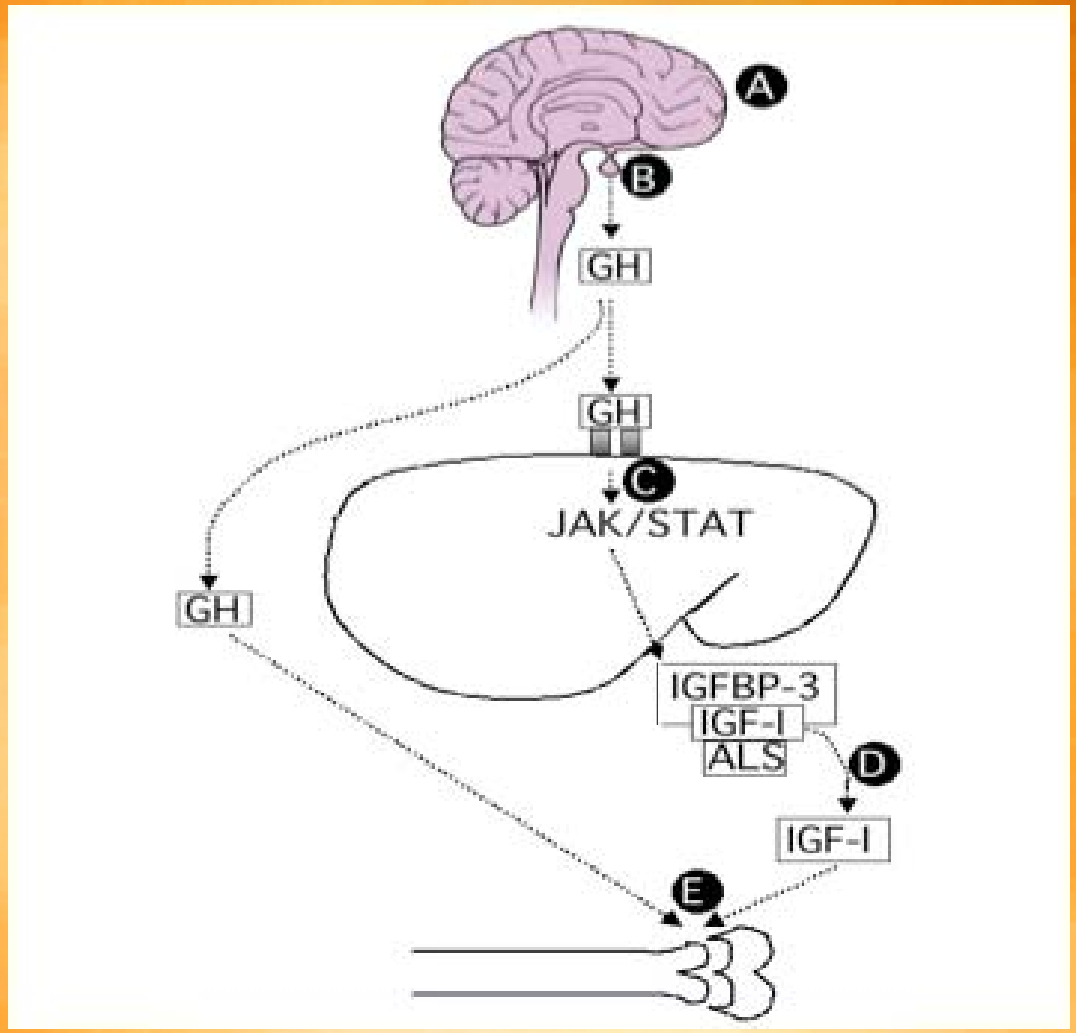
Tanner J. Growth at Adolescence. Oxford, Blackwell Scientific Pub,1962.

Bone Age

Male, 8 yrs

Male, 14 yrs

The GH / IGF axis



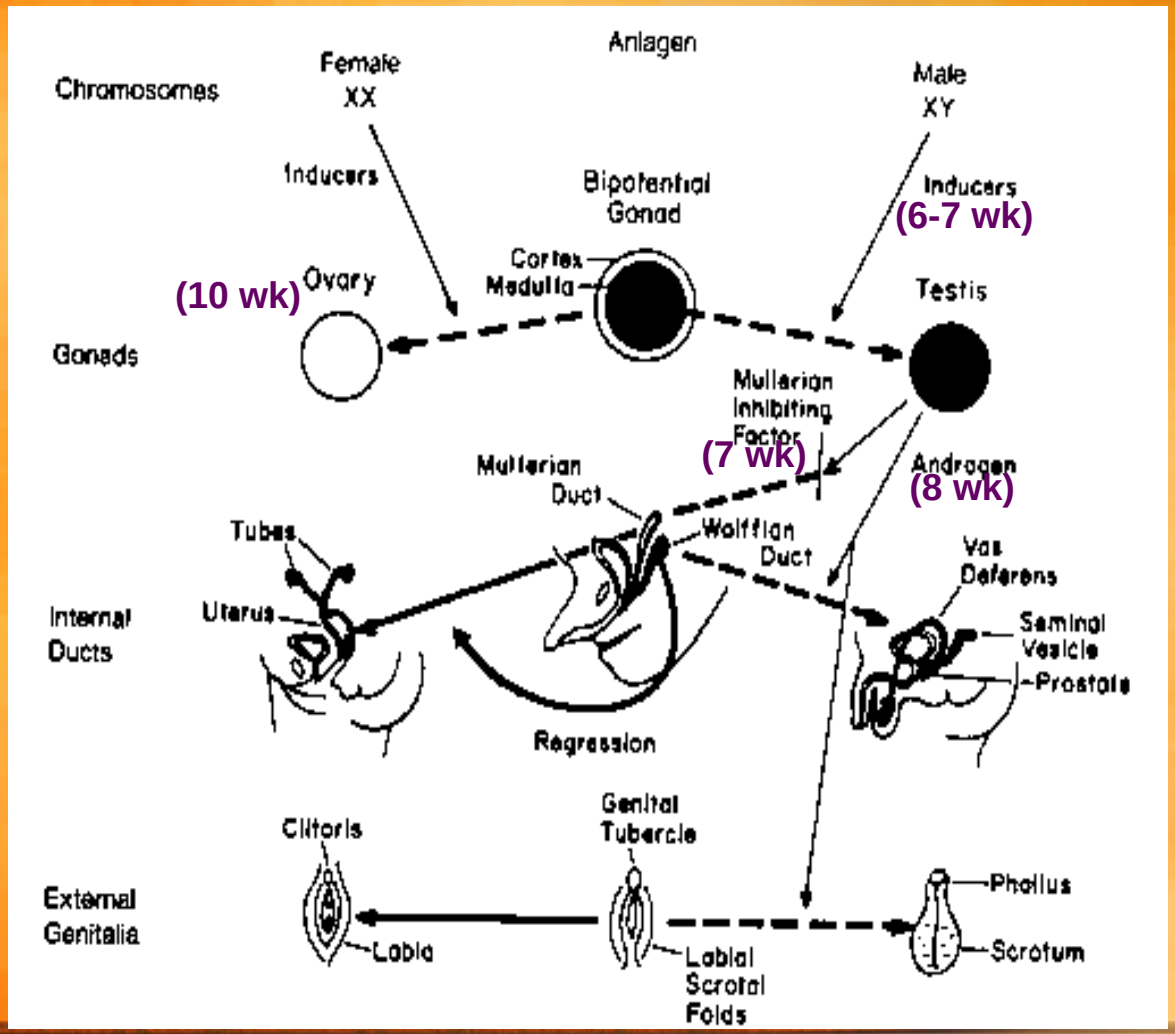
Henwood M, Grimberg A, Moshang T. Curr Opin Pediatr. 2002;14:437-442.

Control of GH secretion

class of neuromodulator	example	second messenger or mechanism	effect on GH secretion
growth hormone releasing hormone	GHRH	calcium influx	stimulatory
somatostatin	SRIH	G proteins	inhibitory
a_2-adrenergic agonist	clonidine, norepi/epinephrine	G proteins; stimulate GHRH	stimulatory
b_2- adrenergic agonist	epinephrine	G proteins; increase SRIH	inhibitory
dopaminergic agonist	dopamine	adenyl cyclase (pituitary receptors);increase SRIH	inhibitory
serotonergic agonist	serotonin	G proteins, K channel	stimulatory
cholinergic agonists	acetylcholine	G proteins (muscarinic receptors); inhib SRIH	stimulatory
histaminergic agonists	histamine	H_1 receptors	stimulatory
gamma amino butyric acid	GABA	chloride influx	stimulatory
amino acids	arginine	depress SRIH	stimulatory
hypoglycemia	insulin		stimulatory
hyperglycemia	diabetes mellitus	suppress GHRH	inhibitory
free fatty acids		inhibit GHRH	inhibitory
calcitonin	calcitonin	block GHRH	inhibitory
prostaglandins	E series	adenyl cyclase (pit); increase GHRH	stimulatory
insulin-like growth factors	IGF-1, IGF-2	negative feedback: stimulate SRIH, inhibit GHRH	inhibitory
exercise, stress		?catecholamines	stimulatory

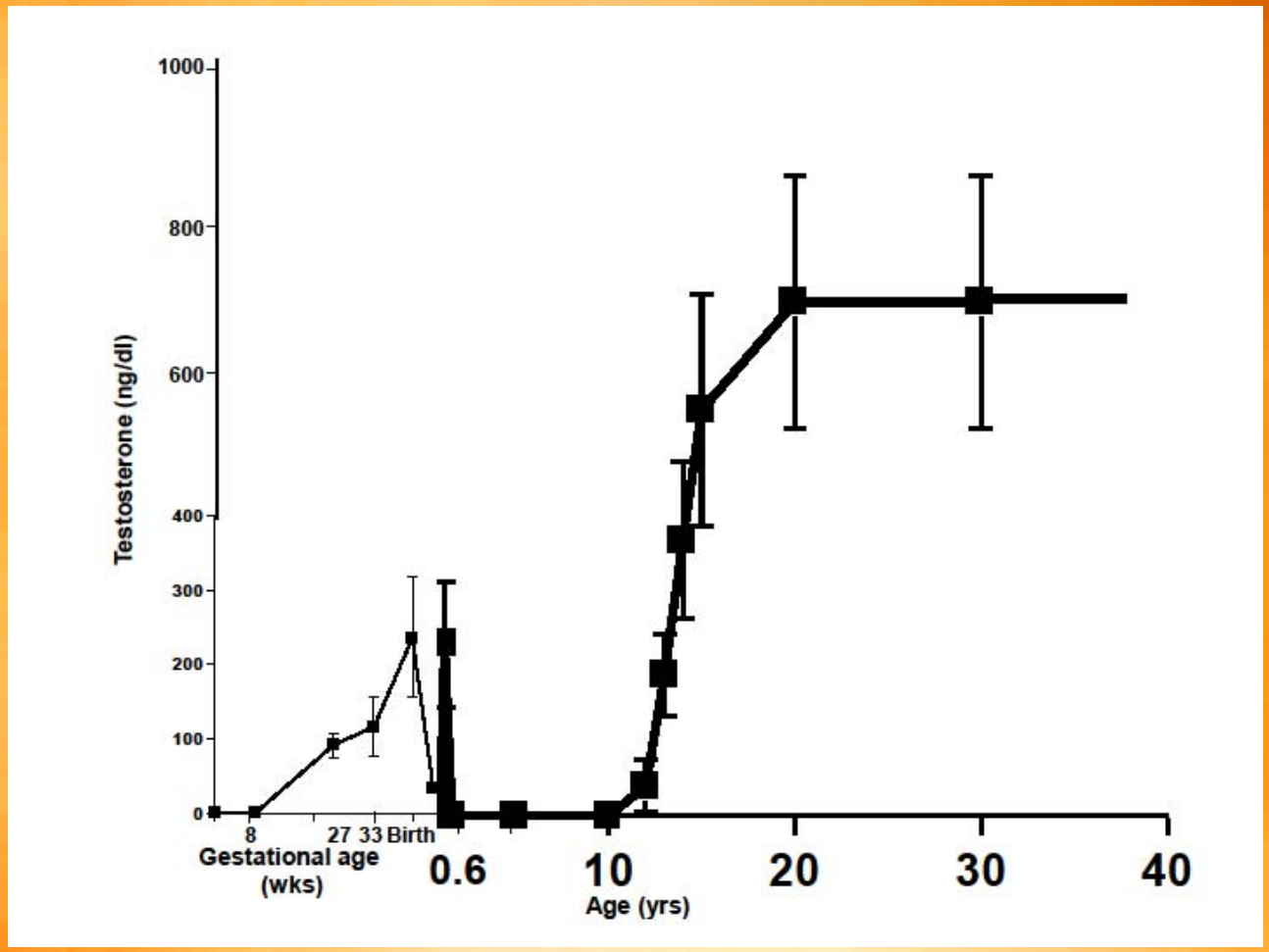
Moshang T, Grimberg A. Oski's Pediatrics, 4th Ed. 2006.

Sequence of sexual differentiation



Hypospadias
8-14 wks
Cryptorchidism
3rd trimester
(gubernaculum)

Testosterone levels in male development



Mean ± SD, based on normative data from Esoterix Laboratories, CA, 2005.

Timing

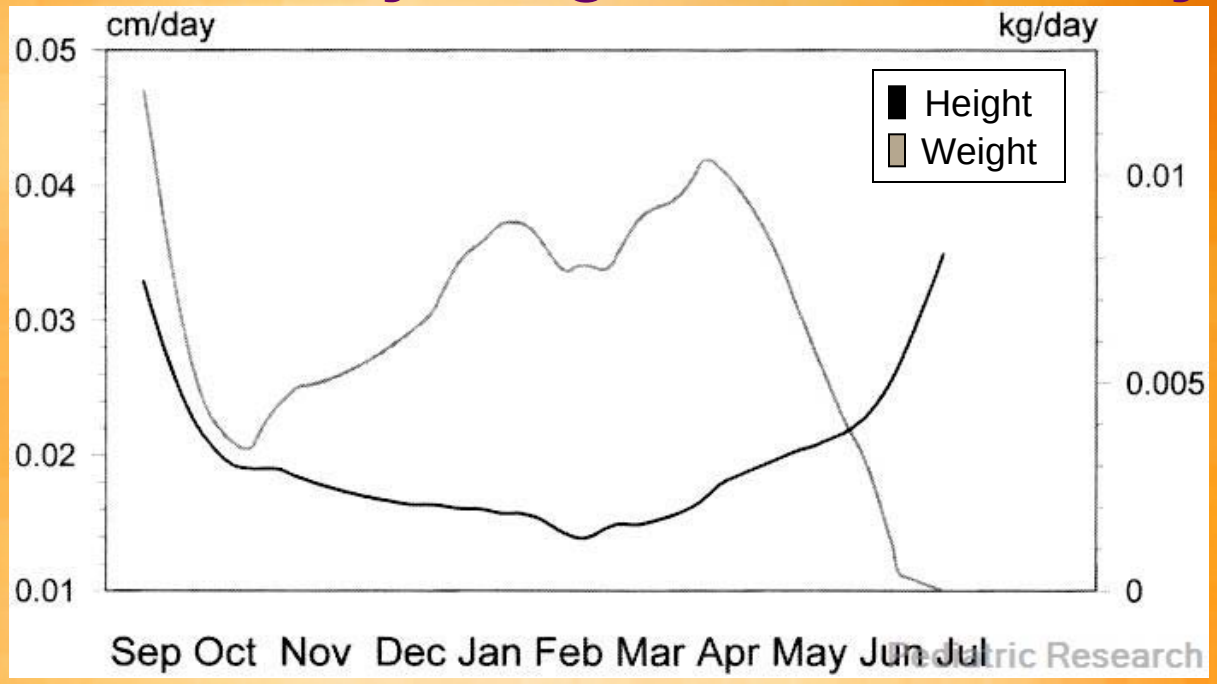
At time of exposure: Loss of function

- **Phthalate esters**
  - *Hold color & scent in personal care products*
  - *Solvents in paints, glues, insect repellents, lubricants, adhesives*
  - *Soften plastics*
- **Anti-androgenic**
  - *Decrease testosterone biosynthesis*
- **Measure exposure**
  - *maternal urinary excretion of metabolites*
  - *in breast milk*
- **Testicular dysgenesis syndrome**
  - *Most sensitive = decreased anogenital distance*
  - *Hypospadias, cryptorchidism*
  - *Testicular cancer, poor semen quality*

Toppari J, et al. Birth Defects Res 2010;88. Main KM, et al. Best Pract Res Clin Endocrinol Metab 2010; 24.

At time of exposure: Gain of function

- **Seasonality of growth velocity**



- **43 normal prepubertal children**
  - *17 M, 26 F; age 5.7-7.7 yrs; Ht -2.9 to +2.3 SD*
- **Measured 3X/wk X1 academic yr**

Tillmann V, et al. Pediatr Res. 1998;44:882-886.

At time of exposure: Gain of function

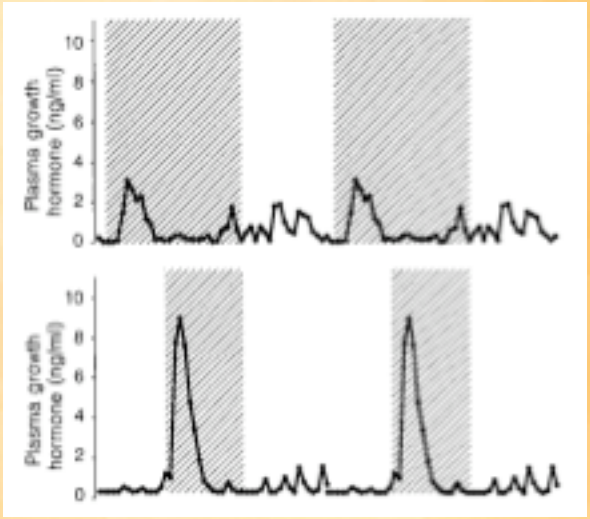
- **Seasonality of growth velocity**

Retinohypothalamic tract

Supra-chiasmatic nucleus

Long scotoperiod (14 hr)

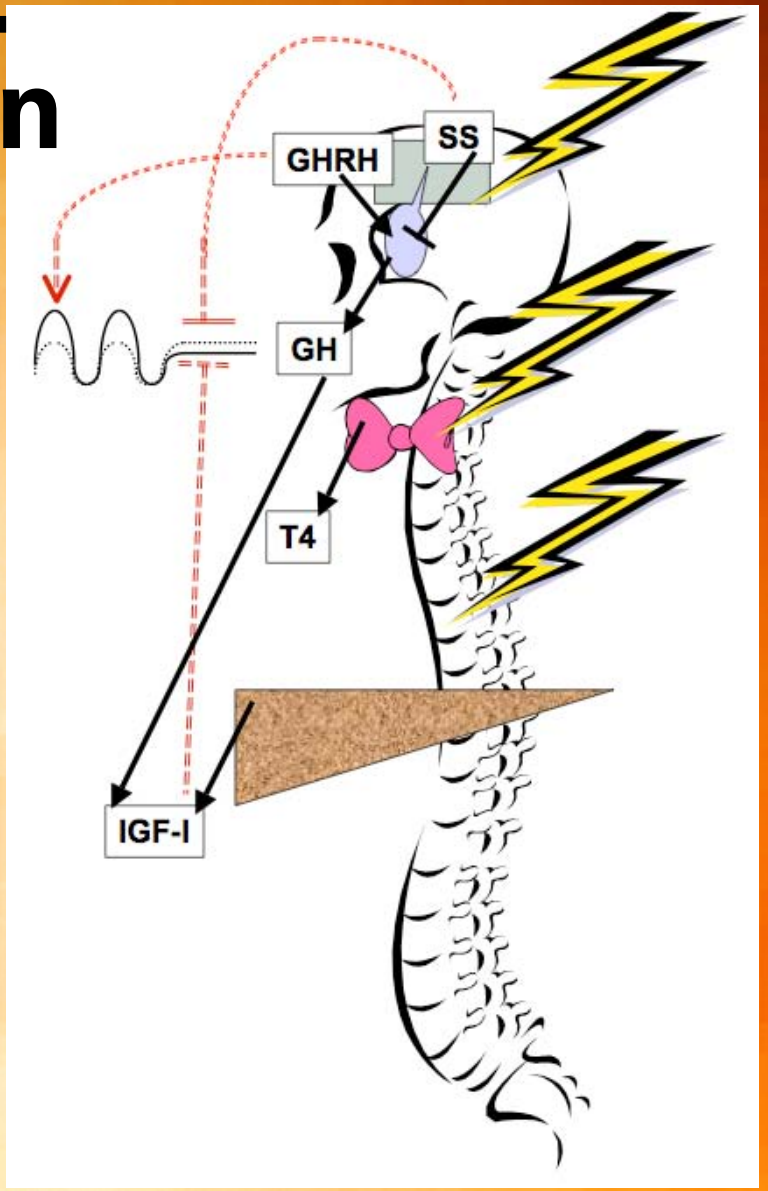
Short scotoperiod (8 hr)



Wehr TA. Horm Res. 1998;49:118-124.

Delayed effect: Loss of function

- Craniospinal irradiation



Mostoufi-Moab S, Grimberg A. Pediatr Endocrinol Rev. 2010;8:6-17.

Delayed effect: Gain of function

- **Exposure**
  - *Obesity*
  - *Androgens*
    - Transdermal testosterone
    - Adrenal extracts
  - *Estrogens/ Phytoestrogens*
    - OCPs, menopausal
    - Transdermal estrogen
    - Cosmetics
    - Isoflavones in soy
    - Tenderized meat

Advanced bone age

Activate central puberty early

DiMeglio L, Grimberg A. When Puberty is Precocious: Scientific and Clinical Aspects. 2007.

Developmental origins of health and disease

Anne Geddes. Beginnings. 2011.

Developmental origins of disease: Barker hypothesis

- **SGA**
  - *Increased risk metabolic syndrome*
  - *Increased risk of sexual precocity*
- **Refeeding/rate of weight gain**
  - *risk of future obesity/metabolic syndrome*
- **Epigenetics and transgenerational effects**

Dutch famine 1944-1945

- **Dutch Hunger Winter**
  - *German occupation limited rations after a railway strike*
  - *400-800 kcal/day*
  - *affected people of all socioeconomic classes*
  - *liberation May 1945: abrupt food abundance*
- **Population study; 1st results 1976**
- **Critical periods of development**
  - *Mid to late gestation:*
    low BW, small thruout life
  - *Early gestation only:*
    normal BW, but increased rates of obesity, dyslipidemia, CVS disease,
    impaired selective attention at age 56-59 yrs

Schultz LC. PNAS. 2010;107:16757-16758.

Dutch famine 1944-1945

Menstruation

TABLE 2

Famine and concurrent regularity of the menstrual cycle (cohort A).

Famine score	Irregular menses during famine, %		Crude OR (95% CI)	Adjusted OR (95% CI)[a]
	No	Yes		
Unexposed (n = 3,252)	94	6	1.00	1.00
Moderately exposed (n = 3,318)	81	19	3.46 (2.93–4.09)	3.57 (3.02–4.22)
Severely exposed (n = 1,091)	64	36	8.38 (6.94–10.11)	8.85 (7.31–10.70)

[a] Adjusted for age during the famine, age at menarche, and socioeconomic status.

Born 1932-1941;
excluded women with menarche ≤1 yr after the famine

TABLE 3

Famine during childhood and time from menarche to regular menses (cohort B1).

Famine score	Time to regular menses, %		Crude OR (95% CI)	Adjusted OR (95% CI)[a]
	≤2 years	>2 yrs		
Unexposed (n = 2,082)	78	22	1.00	1.00
Moderately exposed (n = 1,350)	75	25	1.17 (0.99–1.37)	1.15 (0.98–1.36)
Severely exposed (n = 302)	70	30	1.54 (1.18–2.01)	1.51 (1.15–1.98)

[a] Adjusted for age during the famine, age at menarche, and socioeconomic status.

Elias SG, et al. Fertil Steril. 2007;88:1101-1107.

Dutch famine 1944-1945

Breast cancer

Table 3. Famine and subsequent breast cancer risk according to age during famine*

Age group and famine score	No. of breast cancer cases	Person-years†	Hazard ratio (95% CI) Crude model	Hazard ratio (95% CI) Adjusted model‡
Aged 2–9 years during famine				
Not exposed	77	32 818	1.00 (referent)	1.00 (referent)
Moderately exposed	49	16 985	1.23 (0.82 to 1.83)	1.14 (0.74 to 1.76)
Severely exposed	14	2465	2.44 (1.25 to 4.76)	2.01 (0.92 to 4.41)
P_{trend}			.023	.121
Aged 10–18 years during famine				
Not exposed	91	42 265	1.00 (referent)	1.00 (referent)
Moderately exposed	70	27 929	1.16 (0.83 to 1.64)	1.24 (0.86 to 1.78)
Severely exposed	23	6764	1.59 (0.95 to 2.68)	1.55 (0.89 to 2.73)
P_{trend}			.089	.090
Aged 19 years or older during famine				
Not exposed	97	34 419	1.00 (referent)	1.00 (referent)
Moderately exposed	115	38 461	1.08 (0.80 to 1.46)	1.04 (0.76 to 1.42)
Severely exposed	42	12 186	1.25 (0.83 to 1.88)	1.18 (0.77 to 1.80)
P_{trend}			.306	.482

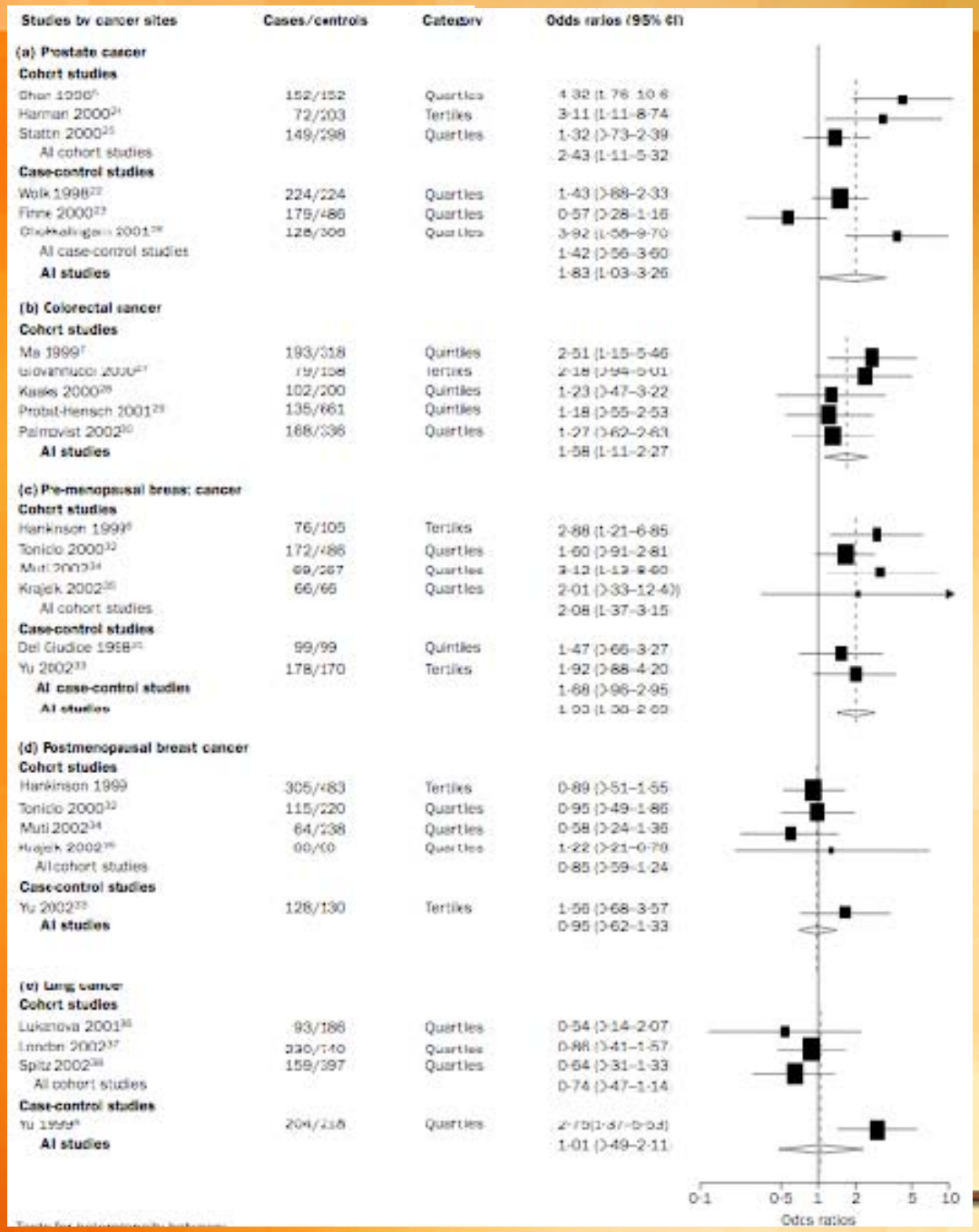
Elias SG, et al. J Natl Cancer Inst. 2004;96:539-546.

Levels of IGF-1 and its major binding protein-3 (expressed in nmol/L geometric means) according to famine exposure[1]

Adjusted hormone levels	Unexposed $n = 45$	Moderately exposed $n = 28$	Severely exposed $n = 14$	P trend
IGF-1	17.41	18.60	21.26	0.04
IGFBP-3	133.00	141.97	162.28	0.05

Van Noord PAH. J Nutr. 2004; 134:3399S-3406S.

IGF-I & cancer risk: meta-analysis



Renehan et al. Lancet 2004.

The endocrine system