3rd Nordic Conference on Peadiatric Medicines
8.-9. October 2019, Helsinki

When does the normal development of adolescents end?

Helena Fonseca MD, MPH, PhD
helenaregalofonseca@gmail.com

FACULDADE DE MEDICINA UNIVERSIDADE DE LISBOA

U LISBOA | UNIVERSIDADE DE LISBOA

Summary

- **Definition of adolescence**
- **Bio-psycho-social development during adolescence**
- **Specific aspects of drug evaluation in adolescents**
- **When does the normal development of adolescents end?**

Definition of adolescence

The adolescent is neither a grown-up child nor a small adult

Adolescents: 10 -19 y

Adolescents: 10 -19 y
Young people: 10 - 24 y
Youth: 15 - 24 y

WHO. The second decade: improving adolescent health and development. Geneva: World Health Organization, 2001: 1–20.

The adolescent is neither a grown-up child nor a small adult

- Progressive acquisition of autonomy + identity
- Developmental stages

Early adolescence (10-13 y)

centred on body changes and marked by poor developed abstract thinking + poor time perspective

Middle adolescence (14-16 y)

intense involvement in peer relationships and encounters and increasing cognitive abilities

Late adolescence (17-19 y)

further dv of intimate relations, vocational planning and completion of abstract thinking and realistic time perspective

Task	Early Adolescence (10-13y)	Intermediate Adolescence (14-16y)	Late Adolescence (17-19y)
Independence	- Decreased interest in parent activity/interaction - Mood swings	- Familiar Conflicts (peak)	- Acceptance of parent's advice, moral values
Body Image	- Worried with body changes - Unsafe	- Body acceptance - Care with appearance	- Acceptance of body image
Peers	- Intense relationship with peers of the same gender	- The group – involvement / commitment - Exploratory behaviours	- Less group more intimae/personal interaction - Share of feelings
Identity	- Need for privacy - Ideals - Loss of control for impulsivity	- Increased intellectual skills - Sense of immortality leading to risk behaviours	- More practical and realistic goals - Definition of moral, religious and sexual values - Capable of commitment

The adolescent is neither a grown-up child nor a small adult

- **Early adolescence** (10-13 y): centered on body changes

Fonseca H. et al. Are adolescent weight-related problems and general well-being essentially an issue of age, gender or rather a pubertal timing issue? J Pediatr Endocr Met, 2011

The adolescent is neither a grown-up child nor a small adult

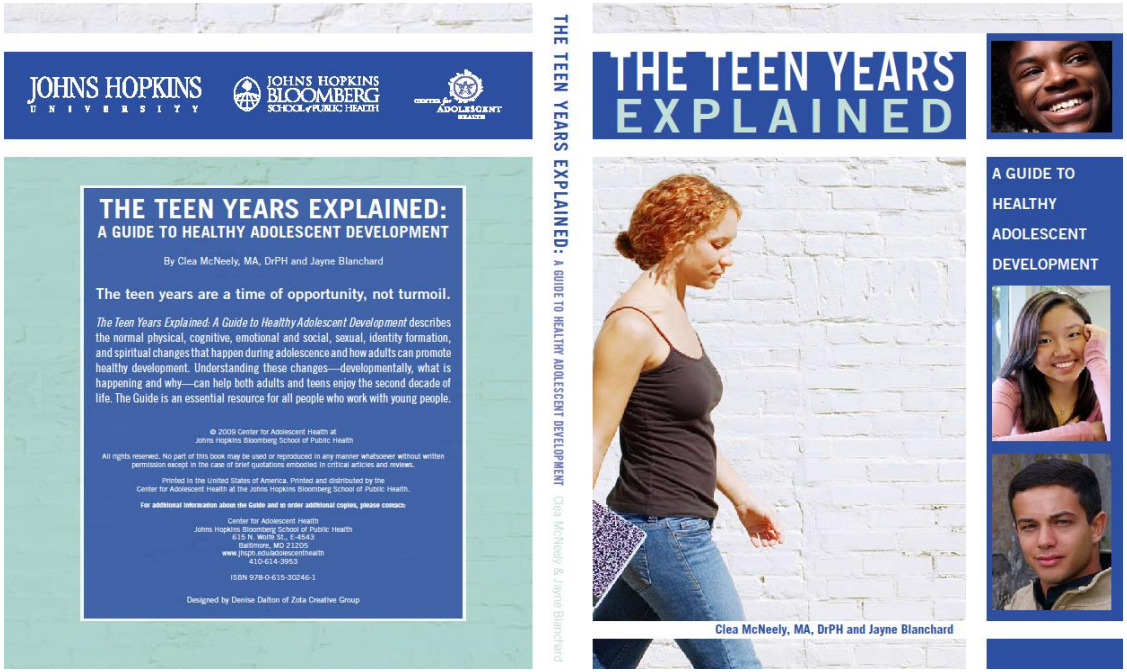
- **Middle adolescence** (14-16 y): intense involvement in peer relationships and encounters and increasing cognitive abilities.

The adolescent is neither a grown-up child nor a small adult

- **Late adolescence** (17-19 y): further dv of intimate relations, vocational planning and completion of abstract thinking and realistic time perspective.

Bio-psycho-social development during adolescence

Bio-psycho-social development



- During adolescence, adolescents gain 50% of their adult body weight, become capable of reproducing and experience an impressive transformation in their brains.
- **At no other time except infancy do human beings pack so much development into such a short period !**

Bio-psycho-social development

- **An adolescent's thinking shifts from concrete to abstract** (i.e. thinking about things they cannot see, hear or touch) from early, through middle to late adolescence.

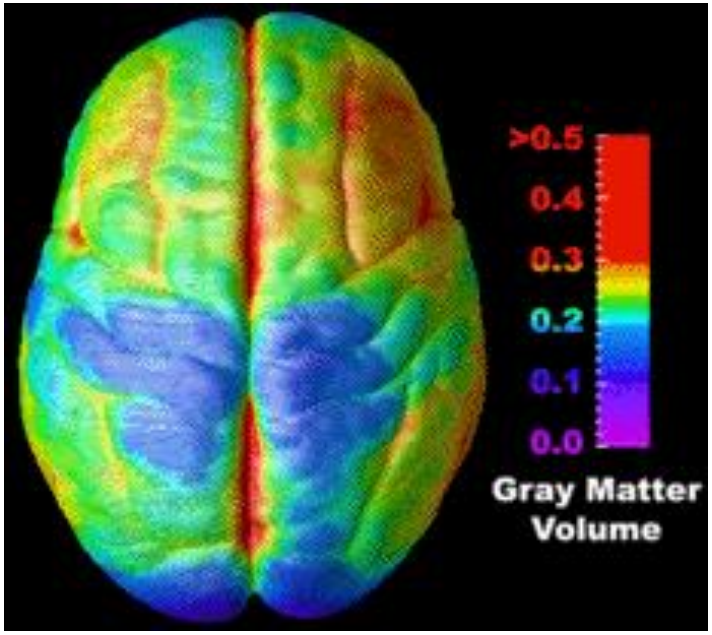
Bio-psycho-social development

"Alice: How long is forever?
White Rabbit: Sometimes, just one second."

Lewis Carroll, Alice in Wonderland

- **Rapid dynamic changes**
  - The adolescent may fluctuate between more or less mature functioning in different circumstances.

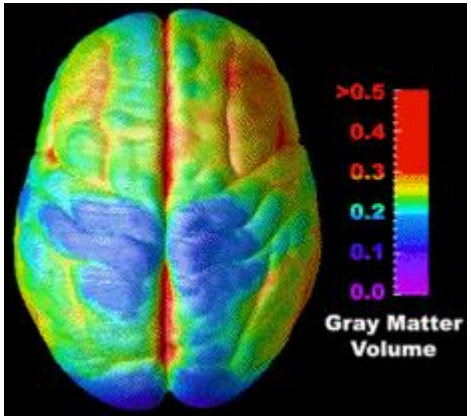
Teenage Brain – a work in progress

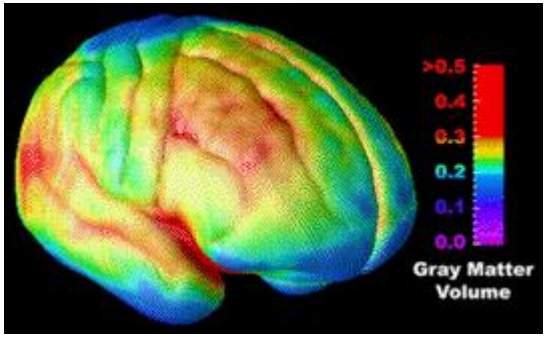


- Red indicates more gray matter, blue less gray matter. Gray matter wanes in a back-to-front wave as the brain matures and neural connections are pruned.
- Prefrontal Cortex development

Paul Thompson UCLA Laboratory of Neuroimaging

Waves of synaptic pruning & myelinisation

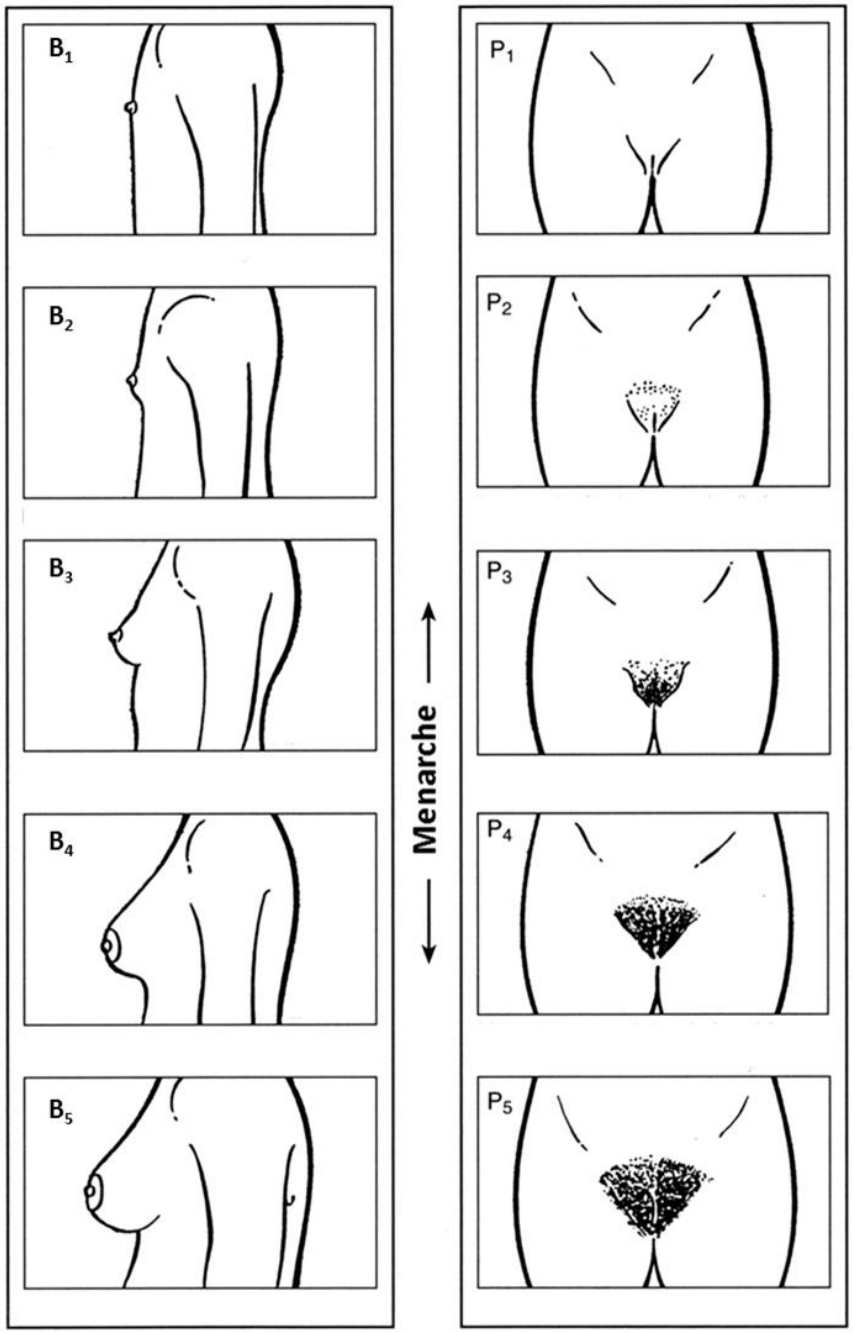




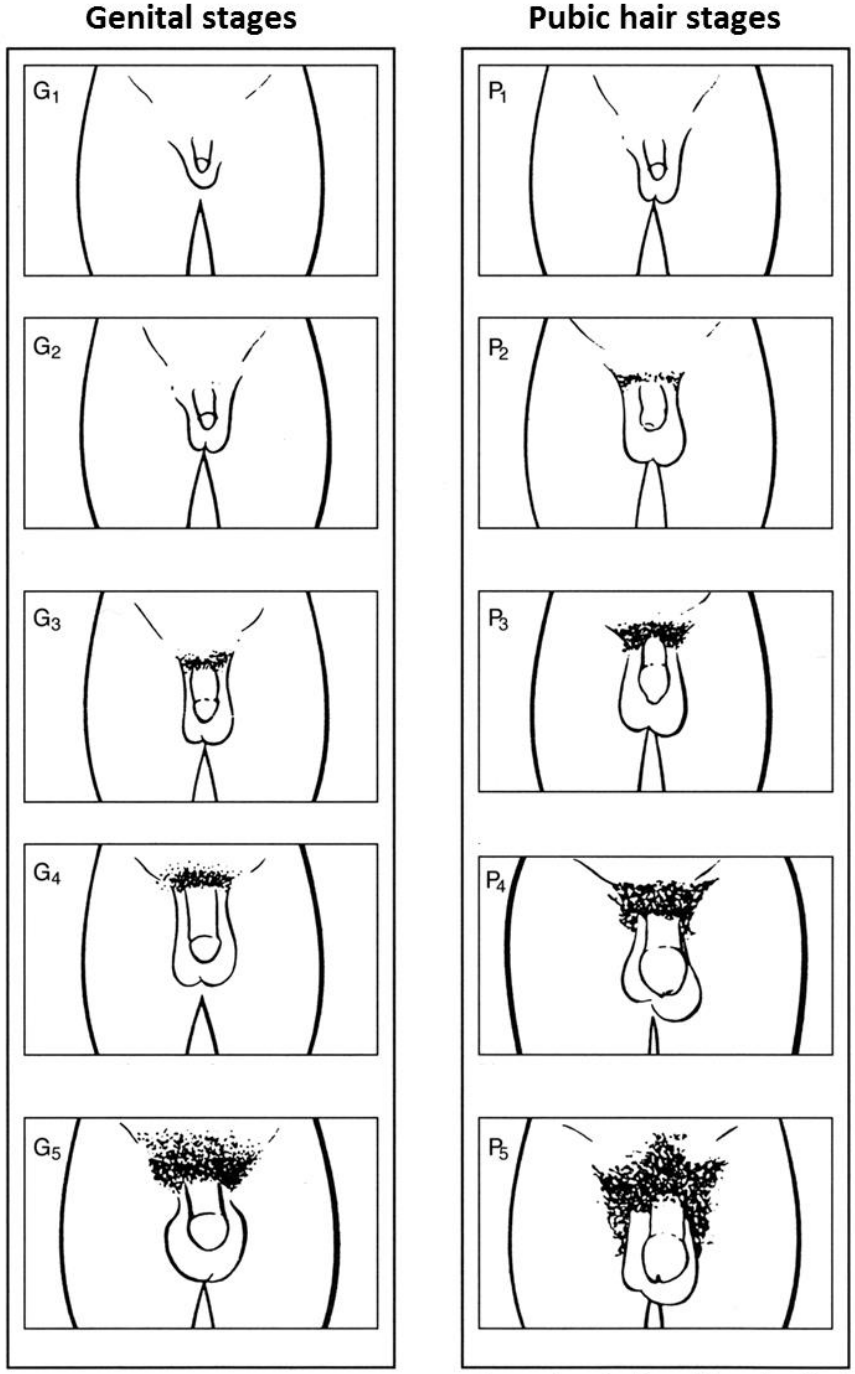
Abstract thinking

Identity development

Ethics: right to be informed + decide on participation in clinical studies



Sexual maturity ratings (females)

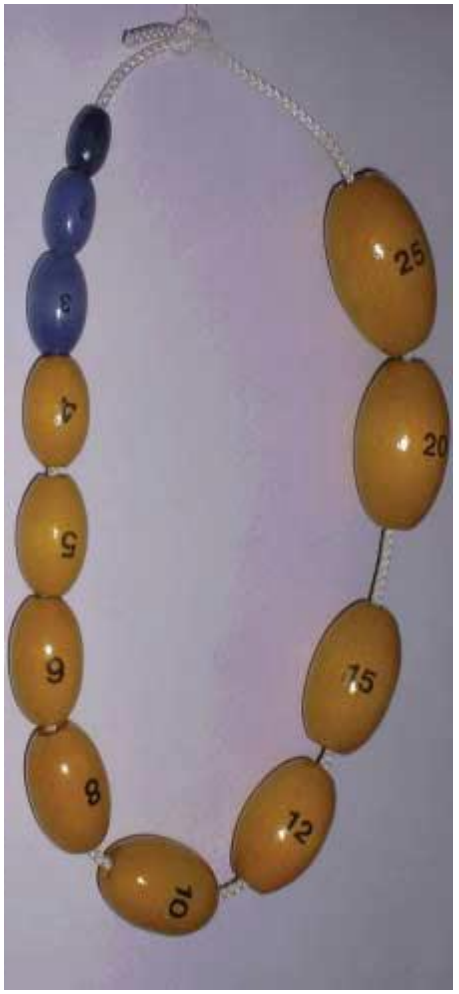


Sexual maturity ratings (males)

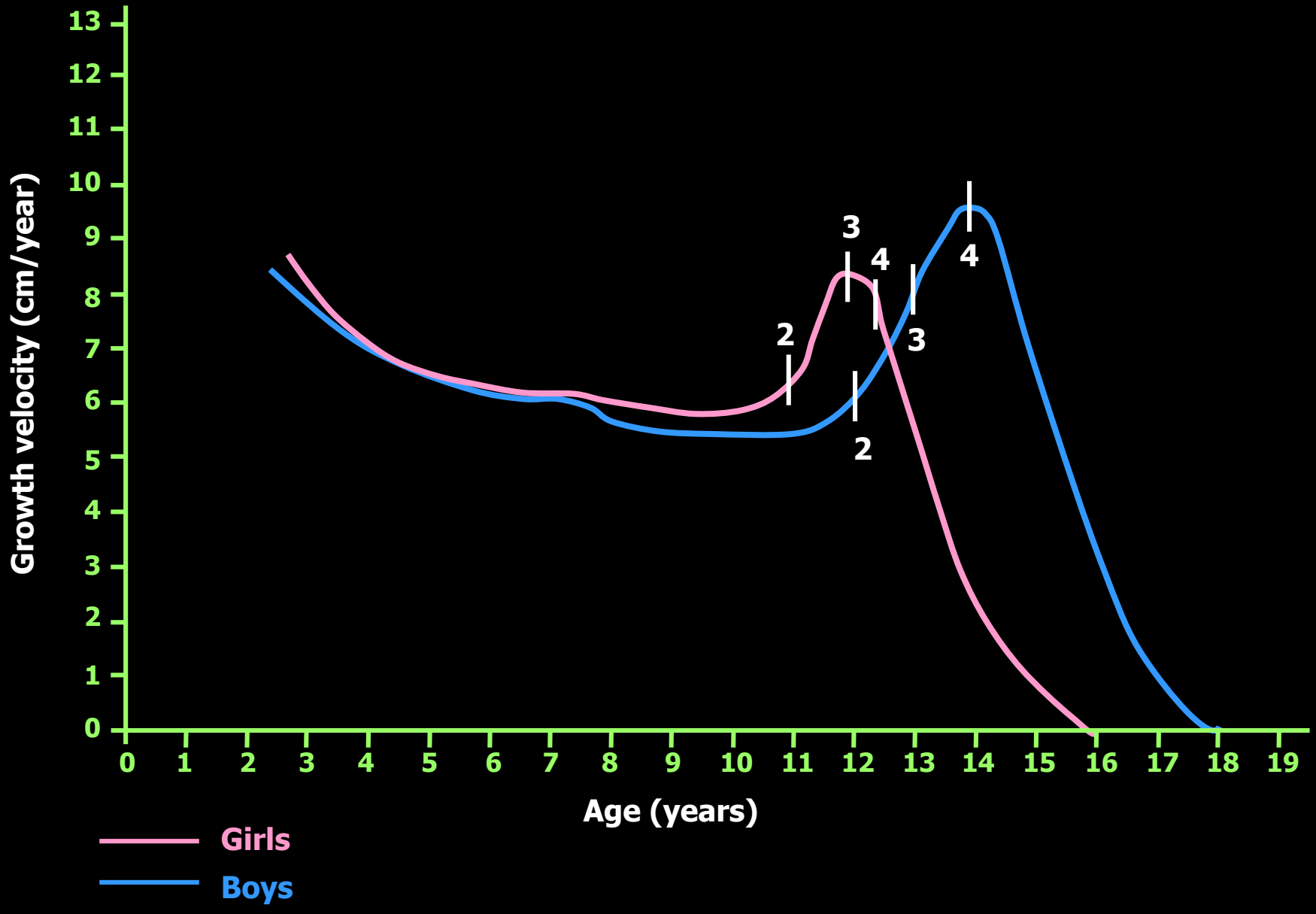
Male puberty

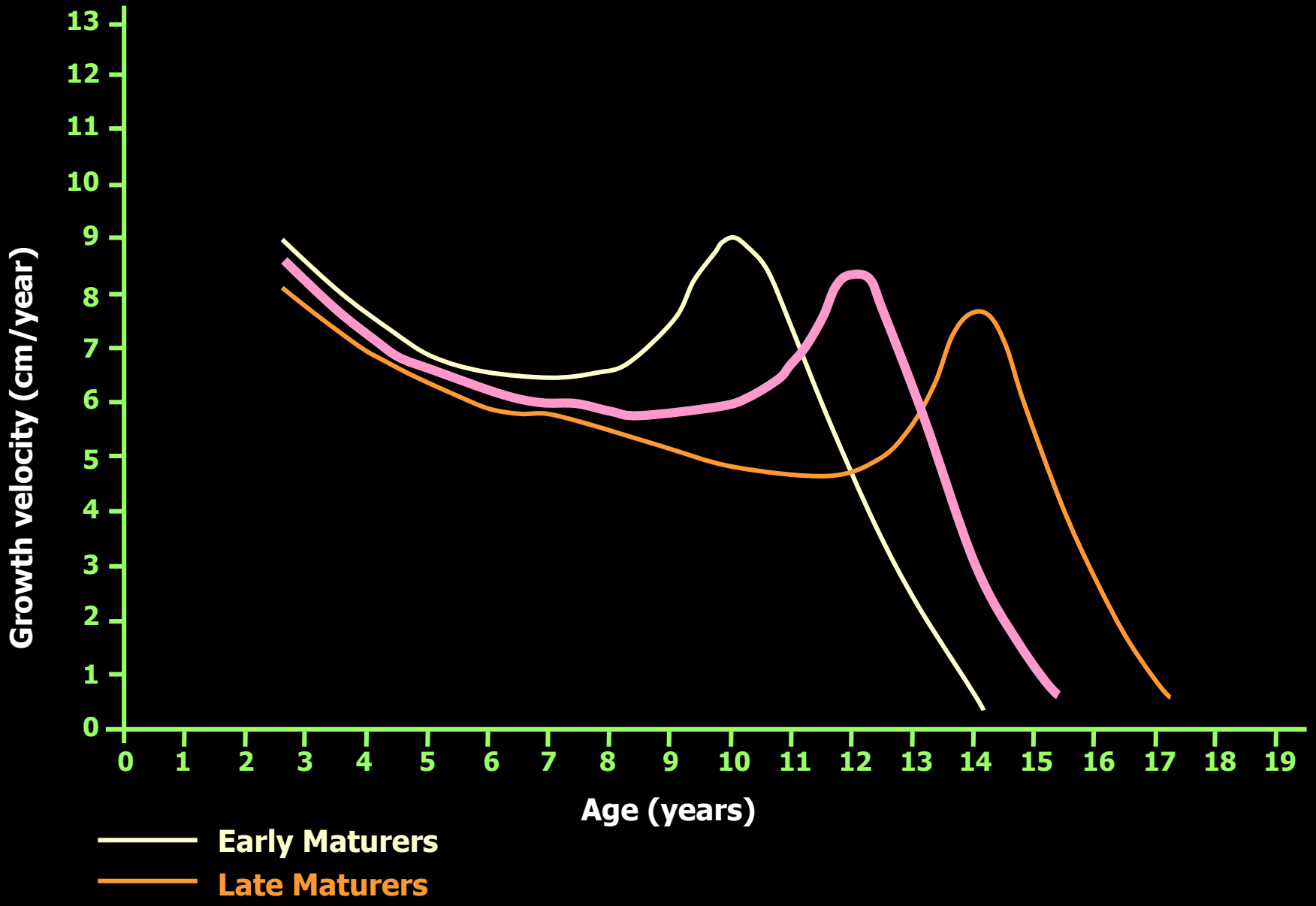
Tanner stage	Testicular volume (cm^3)	
	Left testis	Right testis
1	4,8 ± 2,8	5,2 ± 3,9
2	6,4 ± 3,2	7,1 ± 3,9
3	14,6 ± 6,5	14,8 ± 6,1
4	19,8 ± 6,2	20,4 ± 6,8
5	28,3 ± 8,5	30,2 ± 9,6

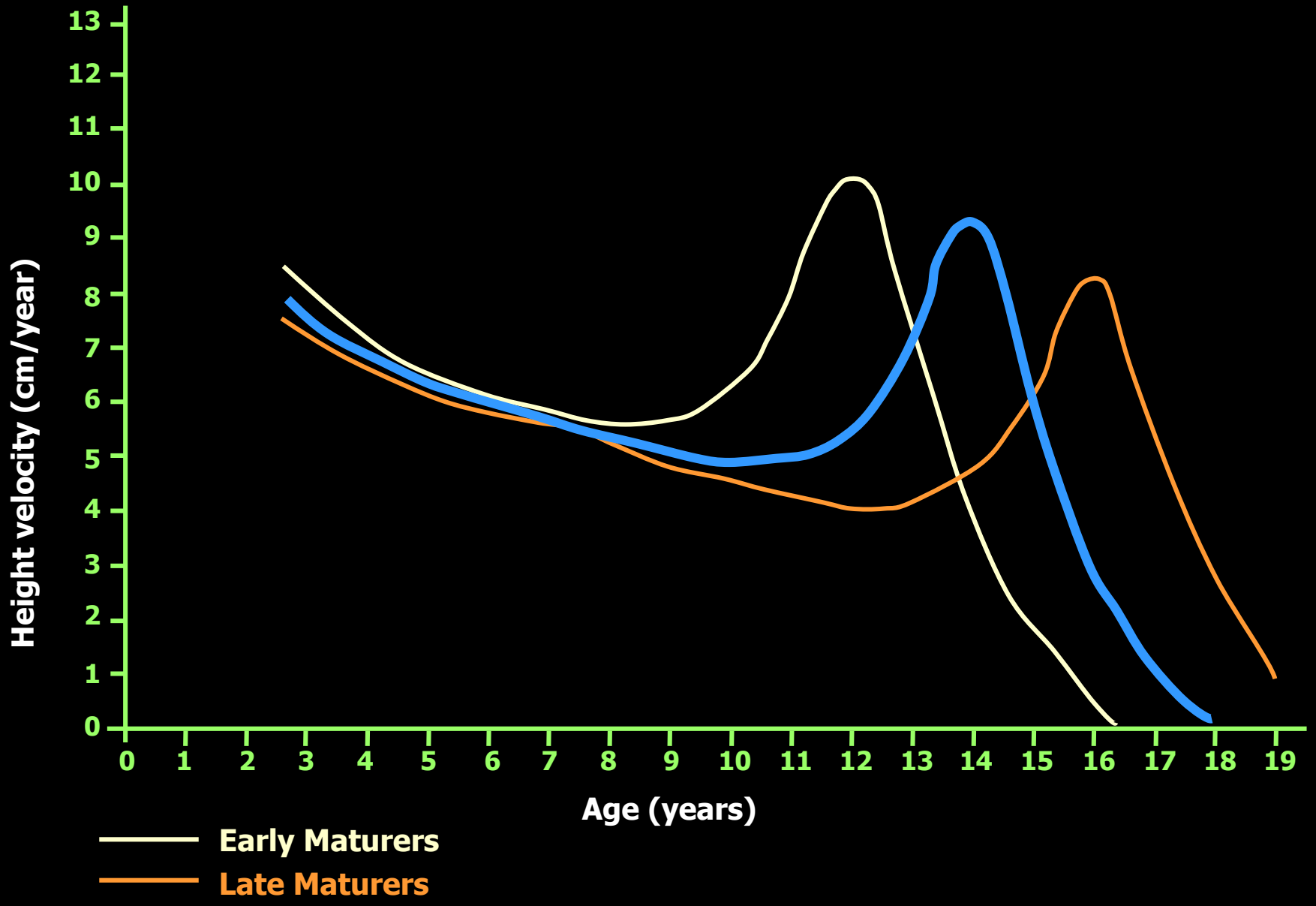
Testicular volume by sexual maturity rating (*J Pediatr* 1982;101:1010)



Prader orchidometer


Growth velocity (cm/year)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Age (years)
2
3
4
2
3
4
Girls
Boys

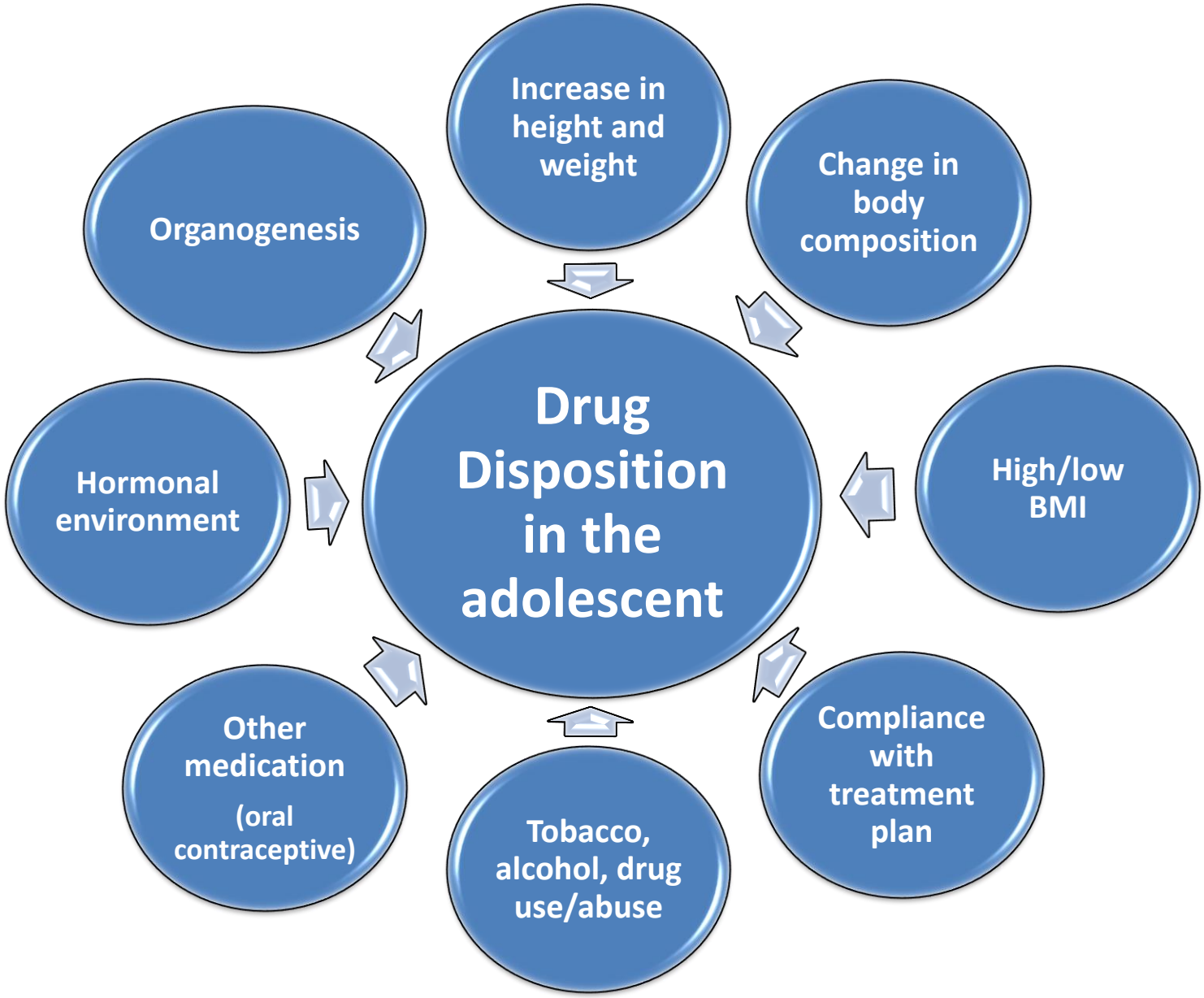

Growth velocity (cm/year)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Age (years)
Early Maturers
Late Maturers


Height velocity (cm/year)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Age (years)
Early Maturers
Late Maturers

Biopsychosocial Development of the Adolescent

- **Growth Spurt**
  - Second most important growth spurt:
    - 20-25% of final adult height
    - 50% of final adult weight
    - Bone – optimal mineralization period (40% of adult bone mineral density), growing / growth plate closure (♀ - 16-17y; ♂ - until 21y)
  - Also:
    - **Not age specific**
    - **Gender differences**
      - **timings**
      - **final outcome - height/weight and body composition**

Specific aspects of drug evaluation in adolescents



in Gareth J. Veal, Christine M. Hartford, and Clinton F. Stewart. Clinical Pharmacology in the Adolescent Oncology Patient. *J Clin Oncol 28:1-10*

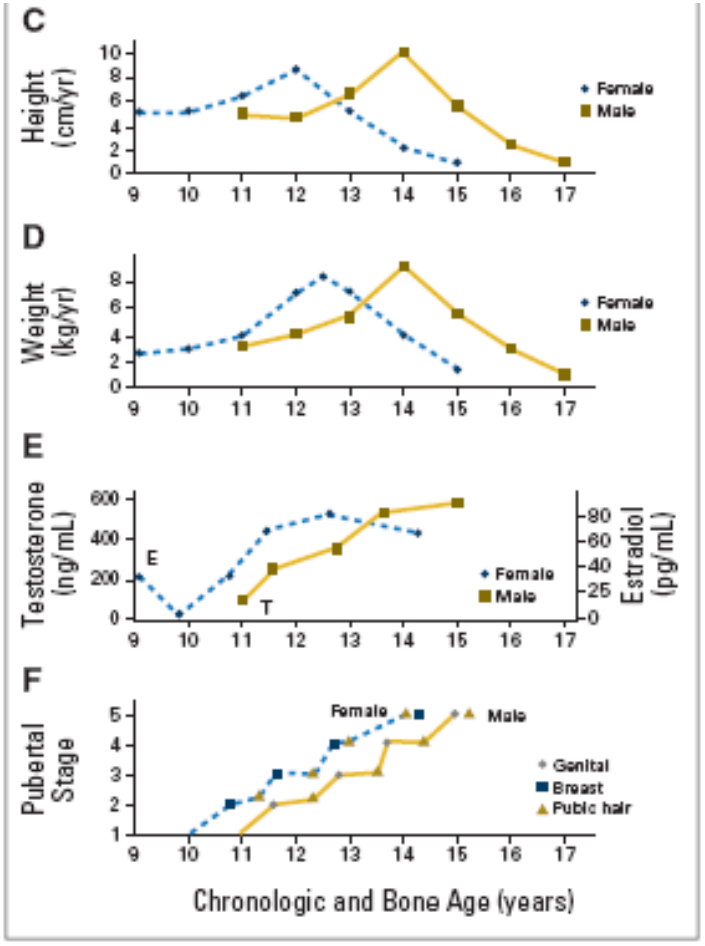
Percentage of Body Fat during Puberty

Stage of Puberty	% Body Fat
Female	
1	15.7
2	18.9
3	21.6
4	26.7
Male	
1	14.3
2	11.2

Percentage of body fat remains unchanged in stages 3, 4, and 5.

Specific aspects of drug evaluation in adolescents

- **Pubertal changes**
  - Which trigger?
    - Genetic and environmental factors (nutritional, activity, hormonal)
    - Not age specific:
      - ♀ → 8-13 y (11 +/- 1 y)
      - ♂ → 9-14 y (12 +/- 1 y)
    - Hypothalamic GH pulse increases (daytime)
    - Hypothalamic GnRh pulse secretion → Increased adrenal androgens → activation of HP-gonadal axis (FSH – LH secretion → gonadal androgen/estrogen production) → 2nd sexual characteristics
  - **Great variability within and between individuals and groups of individuals on onset, duration and final outcome:**
    - **Similar sequence**
    - **Duration of ~50-60 months**



Body Composition

Fat / water distribution

- ♀ - greater increase in fat mass (25% of total weight); 5% decrease in total body water
- ♂ - greater increase in fat-free mass (12% of final weight is fat); 5% increase in total body water

Obesity (increasing prevalence) - affects drug distribution and clearance:

- which dose - Ideal vs Real Weight-based?
- adverse effects / under treatment

Height/Weight

Different timings

Different final height

Organogenesis (size and maturity)

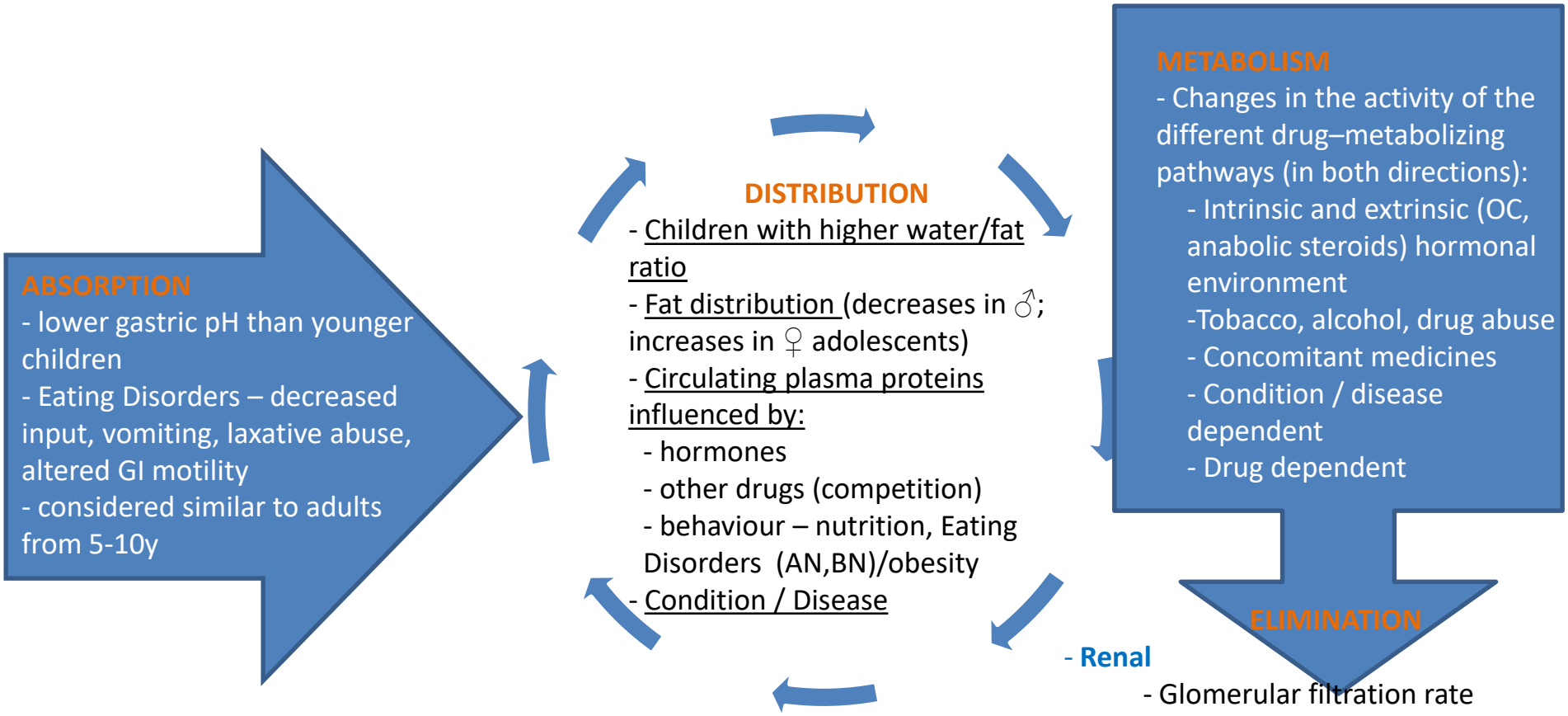
Liver

- increased absolute but decreased proportional size
- influence on drug metabolism dependent on the drug/metabolic pathway

Kidney

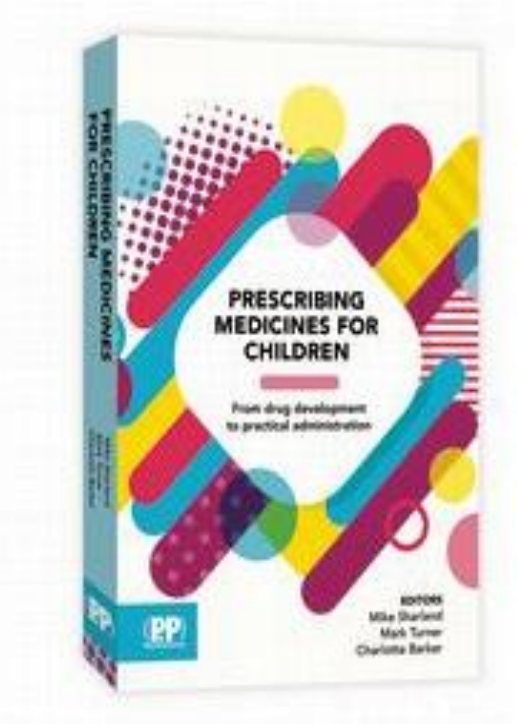
- increased absolute but decreased proportional size
- glomerular function stable since 12 months
- tubular function/secretion matures during adolescence

Drug disposition in adolescents



When does the normal development of adolescents end?

- Usually healthy → low health care resources consumers
- Growth spurt, pubertal changes/ maturation specificities → **not only gender ≠ but also ≠ within same gender**
- **Brain development → only full mature at the age of 25 y** (experimentation/ compliance)
- Ethics → right to be informed and to decide on participation in clinical studies



When does the normal development of adolescents end?

PIP development/assessment – Clinical program

- Safety and/or Efficacy Extrapolation
- **Separate clinical plan *vs* inclusion in adult trials** (need for a specific % of adolescent patients – sample size)
- Patient selection / inclusion-exclusion criteria
  - Adolescents participate in the decision to engage in clinical trials
  - **Use of Tanner stage rather than age to define beginning of puberty**
  - Inclusion criteria may be different depending on the patient age
  - Exclusion criteria e.g. pregnancy risk

When does the normal development of adolescents end?

Paediatric age subsets

- Neonates (0 to 27 days)
- Infants (28 days to 23 months)
- Children (2 to 11 years)
- **Adolescents (… 12 to 18 years …)**

When does the normal development of adolescents end?

- When does adolescence really start? √
  - Is there a specific trigger?
  - How to measure / evaluate it?

- When can we consider adolescents “similar” to adults?
- **When does the normal development of adolescents end?**

  - Tanner stage 5
  - Growth plate closure

  - Brain development ends later

Bibliography

- Barca CC, Vicario MIH, Romero Redondo. Medicina de la adolescencia – Atencion Integral.2004. Ergon (Madrid)
- Kaplan DW MD, Love-Osborne MD. Adolescence. Current Diagnosis a Treatment in Pediatrics. 18th ed. 2007
- Neinstein Lawrence. Adolescent Health Care – a Pratical Guide. 4th Edition. 2004
- Russel Viner. Adolescent development. BMJ 2005;330:301-304
- Gutgesell M, Payne N. Issues of Adolescent Psychological development in the 21 st century. Pediatrics in review. 2004;25(3):79-85
- Patton G, Viner R. Pubertal Transition in health. The Lancet.2007; 369:1130-1139
- Hazen E, Schlozman S, Beresin E. Adolescent Psycological Development: A review. Pediatrics in Review. 2008;29:161-168
- Roxane R. Carr, B.Sc.Pharm, PharmD1,2 and Mary H.H. Ensom, B.Sc.Pharm, PharmD. Drug Disposition and Therapy in Adolescence:The Effects of Puberty. J Pediatr Pharmacol Ther 2003:8;86-96
- Gregory L. Kearns, Pharm.D., Ph.D., Susan M. Abdel-Rahman, Pharm.D., Sarah W. Alander, M.D., Douglas L. Blowey, M.D., J. Steven Leeder, Pharm.D., Ph.D., and Ralph E. Kauffman, M.D. Developmental Pharmacology — Drug Disposition, Action, and Therapy in Infants and Children. N Engl J Med 2003;349:1157-67
- www.euteach.com

  www.ama-assn.org/adolhlth

  www.aap.org

  www.aafp.org

  www.adolescenthealth.org