



UniversityHospital Heidelberg

Special Considerations for Clinical Trials in the Paediatric Population

Psychosocial, Medicinal, Scientific, and Organizational Challenges



Reinhard Feneberg
Paediatric Unit
KKS Heidelberg



- Psychosocial
Obtaining informed consent and educating motivated patients
- Medicinal
Development and growth
- Scientific
Small and diverse populations
- Organizational
Large, multinational, long running studies

- **Psychosocial**
Obtaining informed consent and educating motivated patients
- Medicinal
Development and growth
- Scientific
Small and diverse populations
- Organizational
Large, multinational, long running studies

The best way
to give advice to your children is
to find out what they want and
then advise them to do it

(H. S. Truman)

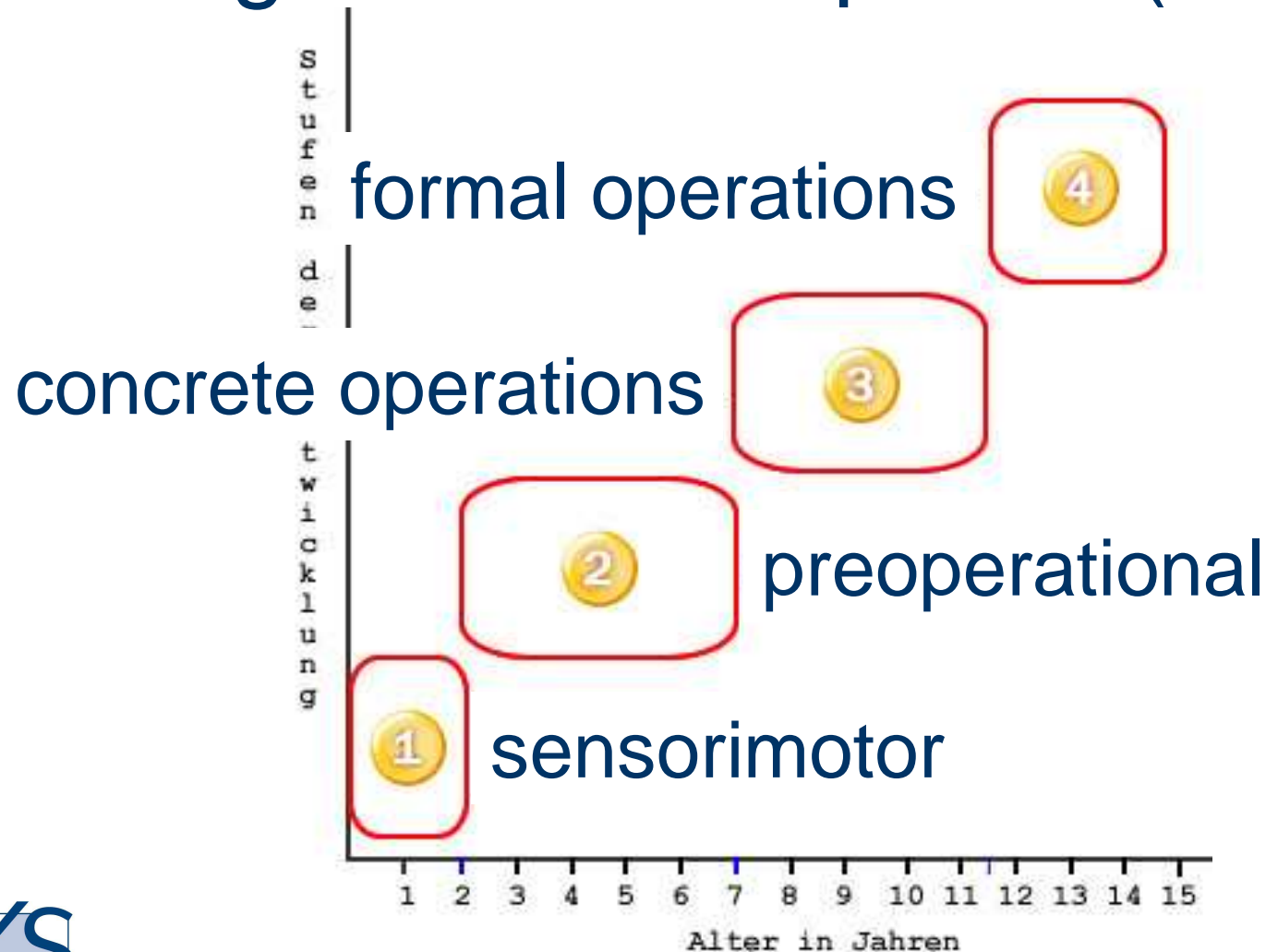


- Psychological
- Legal
- Ethical
- ... Child's perspective

Development of Children

- School age: Ability to understand explanations regarding own body, medication, studies (immense increase of understanding in the first years in school)
- Different theoretical approaches:
 - Theory of cognitive development (Piaget)
 - Information psychology

Cognitive development (Piaget)



Aspects of information psychology

- Piaget:
rough classification, but:
- Children develop
knowledge in conjunction
with their experiences
- Example: Chronically ill
children
- Development depends as
well on available
information!



Influences on Development

- Social rank
- Intelligence
- Previous experience (e.g., history of illness)
- Relationship with parents
- Information
- Diseases
- Peer group
- etc.

Aspects of Capability for Consent

- Criteria according to Coester
 - Maturity
 - Power of judgement
 - Critical faculties
 - Freedom of choice
- Situational aspects (Fegert 2000)
 - Psychopathology
 - Experience of chronically ill children

Aspects of Capability for Consent

- Effects on capability for consent
 - Adapted approach for checking capability for consent
 - Information adapted to stage of disease
- Effects on compliance
 - Without informed consent:
 - little compliance, cooperation, and collaboration
 - little chances for reliable and valid data

The Need to Participate

- Need to participate increases with age
- < 14 yrs: others should decide most frequent
- > 14 yrs: desire to participate most frequent
- Participation is important – not the actual decision
- Consideration of participation needs has positive long term effects on therapy motivation
- (Wiethoff et al. 2002)

Voice effect

- Opportunity to participate in decision making process raises the perceived fairness, even if there is no control of the final decision
- The right to a say leads to higher acceptance and commitment to consequences of the decision

Asymmetries

- Gradient of knowledge: physician, parents, child
- Considerable responsibility of parents
 - Attention after separation and joint custody: (Informed consent MUST be signed by both legal custodians)
- Role conflict of physician: „objective researcher“ vs. „considerate caretaker“
- And: Dependencies in hospital hierarchy

Conflicts of interest

- Parents are interested in the very best treatment of their child and do not want to endanger a trustful relationship with their physician
- Children are often anxious and need specific information about the course of the study and age adapted information concerning fundamental questions
- Conflict of interest between parents and children possible (e.g., maladjustment)

A little bit exaggerated ...

- Parents seem to be becoming increasingly reluctant to enroll their children in basic research with no perceivable immediate benefit (Appelbaum et al. ACT 2003)
- Informed Consent, ein kinderfeindliches Konzept? (Rothärmel et al. Medizinrecht 2000)



Consent and Assent

- Consent of parents always along with assent of child
- Specific information for children:
 - development
 - requirements of study
 - specific for disease („expert“ knowledge of chronically ill children)
 - Legal and ethical aspects, in particular veto

Mac CAT Interview

- Grisso and Applebaum 1998
- Qualitative interview to assess ability for consent and assent
- Ethical: helpful for the decision about inclusion of patient
- Legal: documentation of capability for decision of patient

General Problems

- General ethical obligation to protect minors
- Fundamental problem:

In contrast to adults, minors may not provide legally binding consent

Right to a say of the child?

- Therefore:
Consent of parents or legal guardians necessary
- Consent (or non-consent) has to consider the child's presumed will
- The minor has to receive information according to his/her developmental status by persons with pedagogical experience

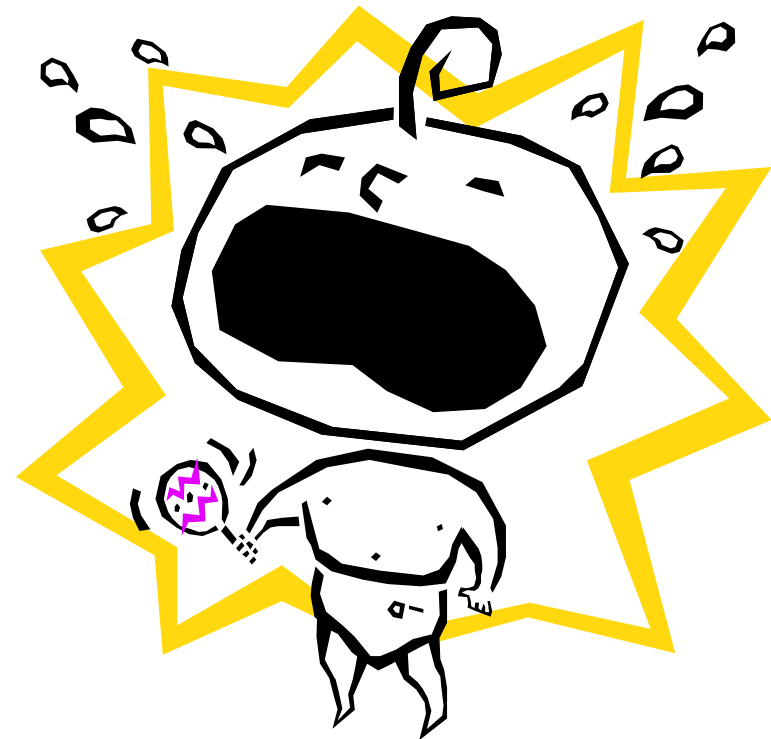
„Legal“ Age Groups

- Consent
 - > 18 yrs. (full legal age)
 - > 12 - 15 yrs. ability to decide independently
- Assent
 - EU: defined by EC
 - AAP: > 7 yrs.
- Dissent
 - 5 - 7 yrs.

Documentation Problems ...

- Documentation of assent?
- Participants of appropriate intellectual maturity should personally sign and date either a separately designed written assent form or the written informed consent ...
- (ICH Topic E11: Clinical Investigation of Medicinal Products in the Paediatric Population)

How to to interprete and document?





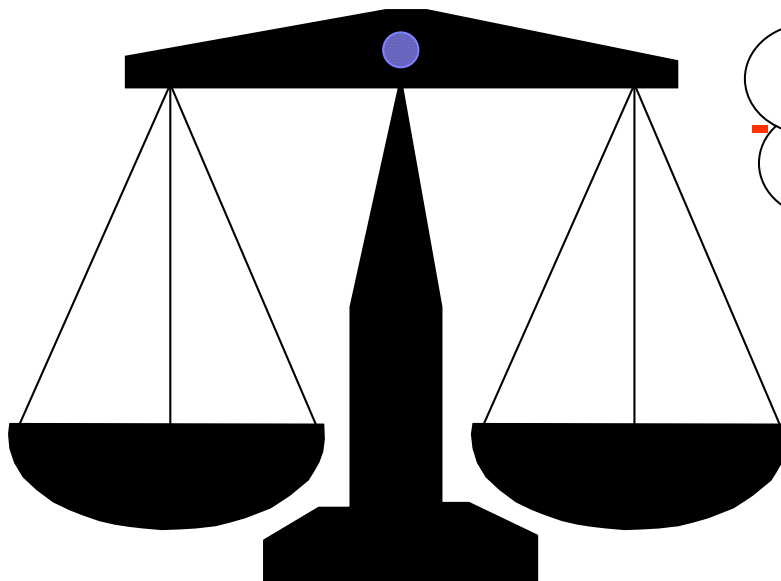
ICH E 11, 2.6.3.

- Although a participant's wish to withdraw from a study must be respected, there may be circumstances in therapeutic studies for serious or life-threatening diseases in which, in the opinion of the investigator and parents(s)/legal guardian, the welfare of a pediatric patient would be jeopardized by his or her failing to participate in the study.



ICH E 11, 2.6.3.

- In this situation, continued parental (legal guardian) consent should be sufficient to allow participation in the study.



**Adults and minors
- double standards???**

Verständnis und Consent

- Does informed consent to research require comprehension? (Sreenivasan G, Lancet 2003, 362:2016-2018)



The View of the Persons Concerned

- Why do children participate in clinical studies?
- Hope to receive improved treatment (52%)
- Altruism (38%)
- Financial incentives (51%)
- Recommendation of others (44%)
- (Niles, ACT 2003)

The View of the Persons Concerned

Satisfaction		Again?	
„much better than expected“	63%	„definitely consider“	49%
„somewhat better than exp.“	6%	„maybe consider“	25%
„as good as expected“	20%	„definitely not consider“	19%
„somewhat worse as exp.“	0%	„don't know“	7%
„don't know“	11%		

Niles, ACT 2003

- Psychosocial
Obtaining informed consent and educating motivated patients
- Medicinal
Development and growth
- Scientific
Small and diverse populations
- Organizational
Large, multinational, long running studies

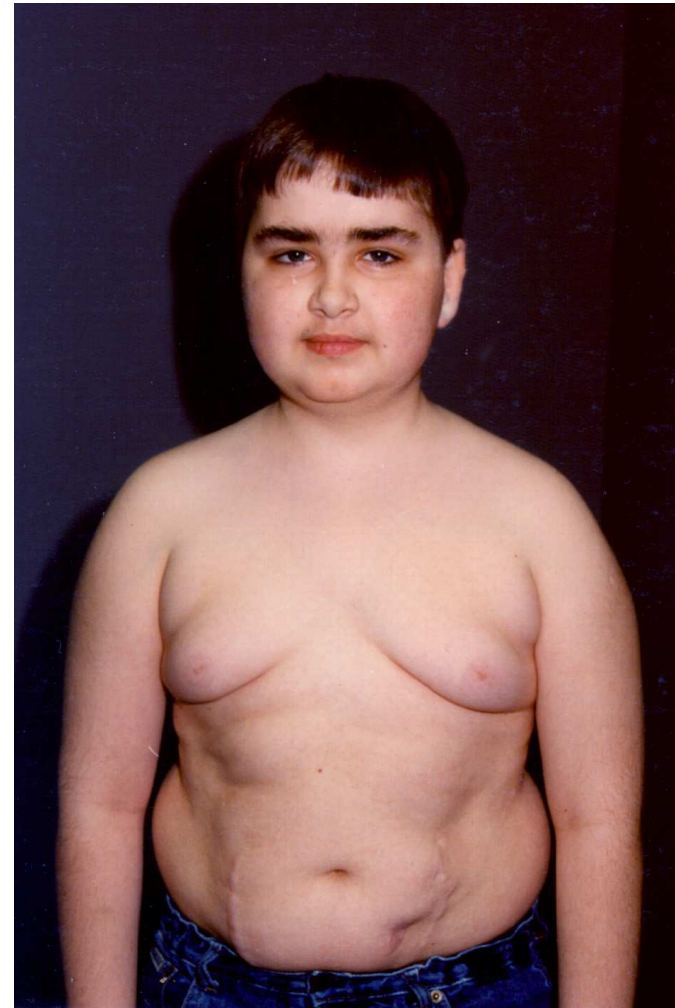
If you bungle raising your children,
I don't think
whatever else you do well
matters very much

(Anonymous)

Efficacy of drugs is influenced by different developmental stages:

- anatomical
- physiological
- biochemical
- behavioural

charakteristics





Physiology (I)

- Maturation of brain, persistent fetal circulation
- (Relatively) large body surface area
- High percentage of body water
- Immature blood brain barrier
- Narrow respiratory tract
- Immune system

Physiology (II)

GI tract

Lower motility

Prolonged gastric passage

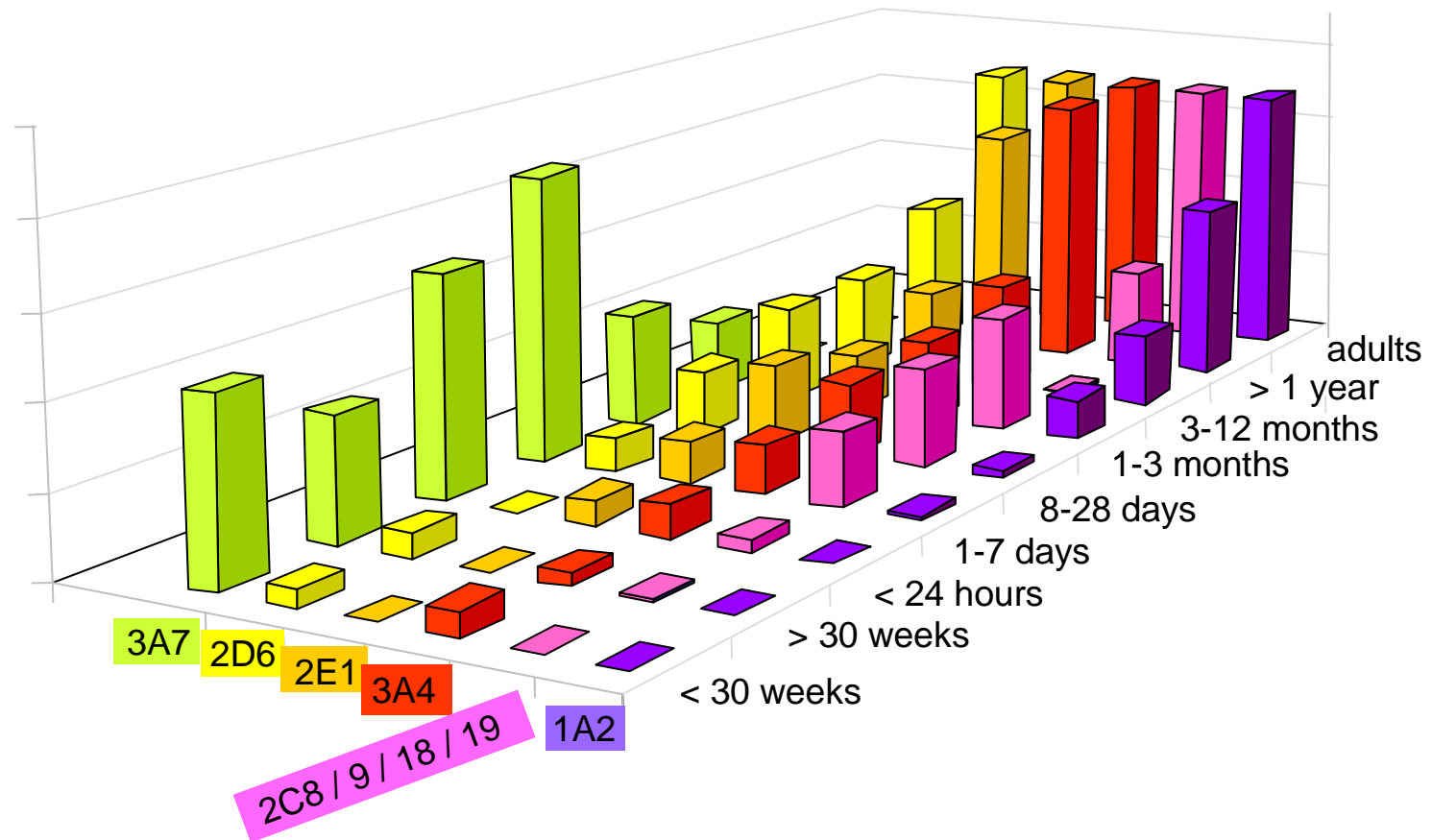
higher gastric pH

Plasma proteins

fetal albumin

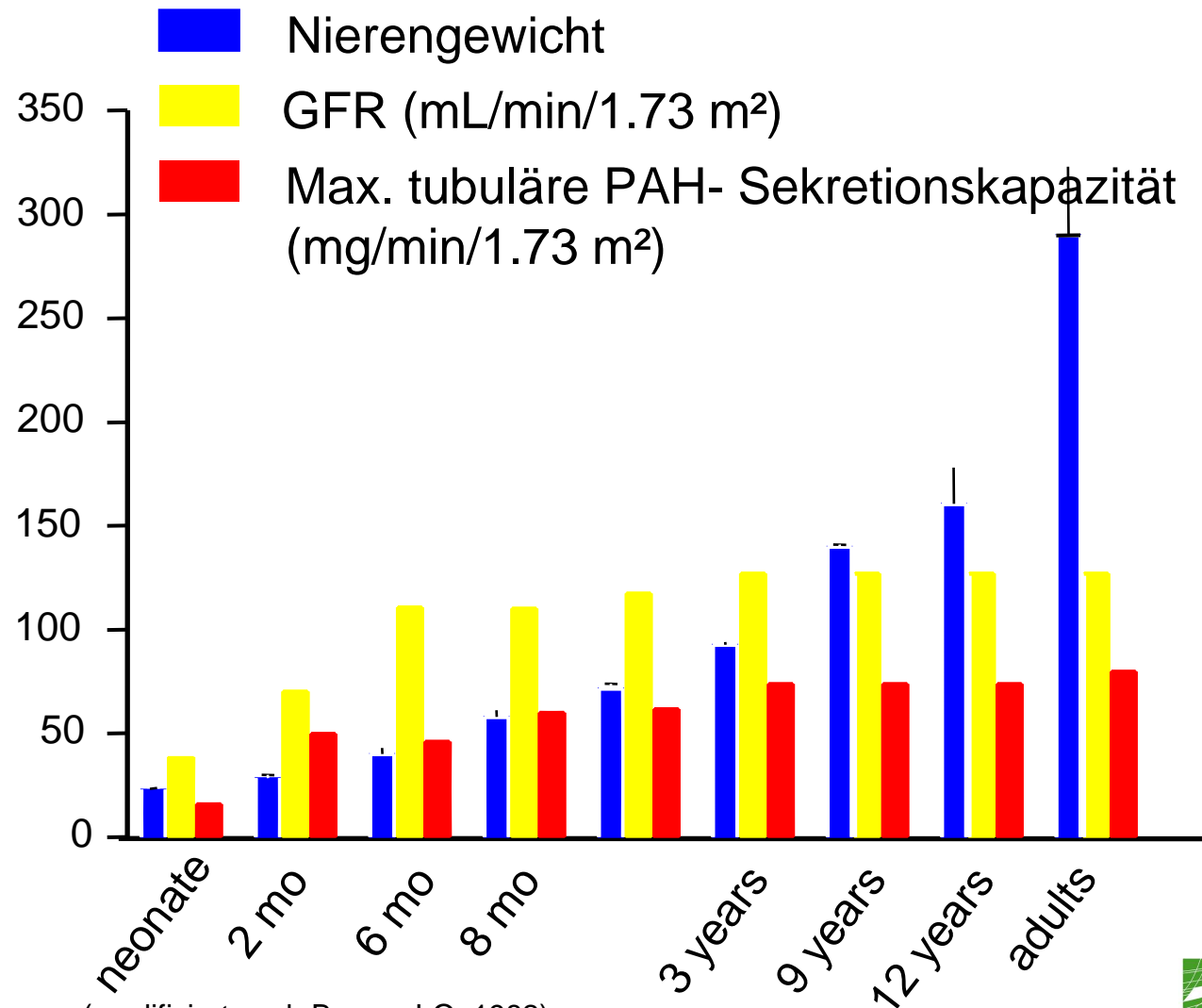
higher percentage of body water
(> 75% in children, 50-55% in adults)

Maturation of CYP in Liver



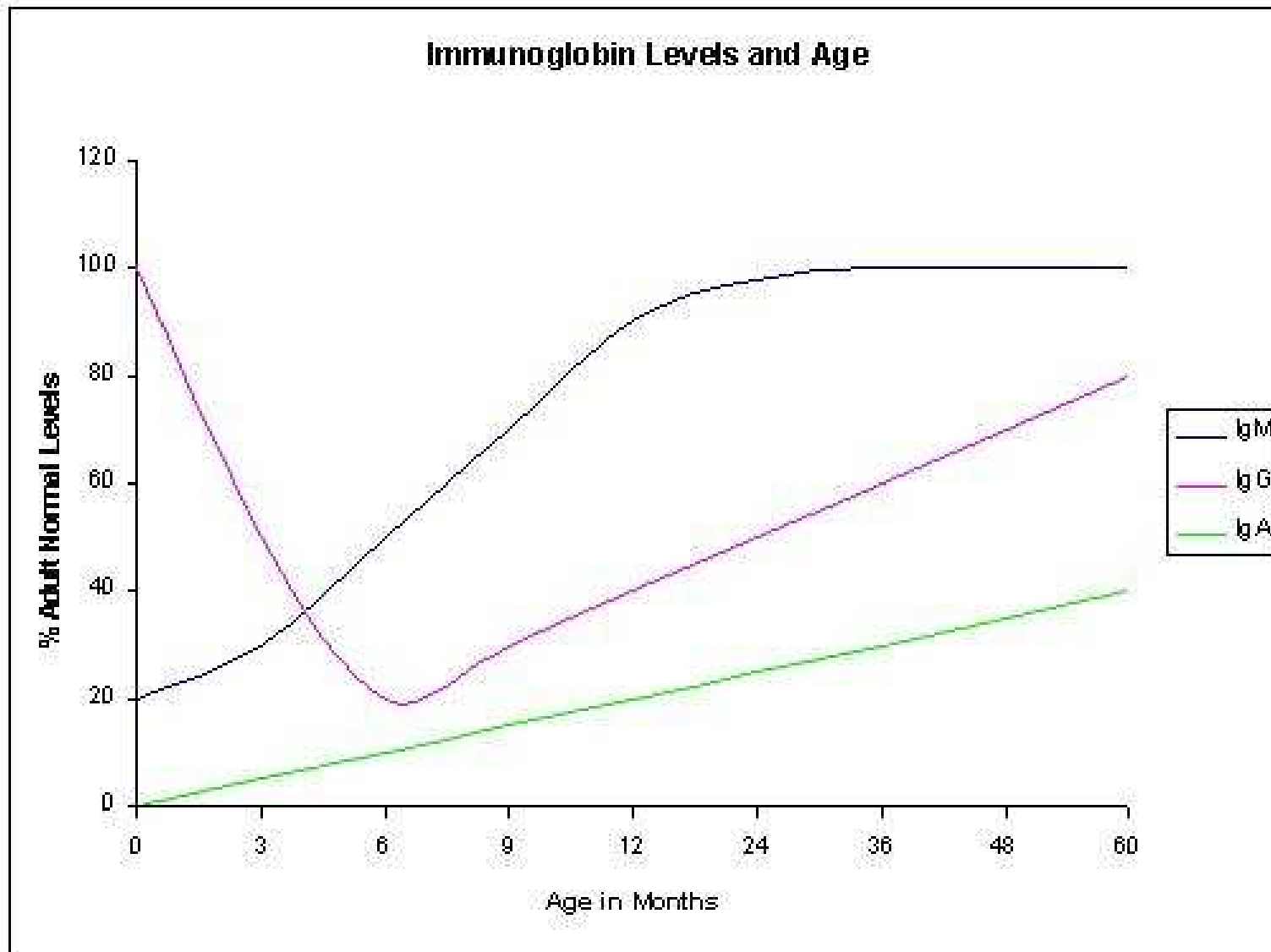
(Cresteil T.; Food Addit Contam 1998)

Maturation of Renal Function



(modifiziert nach Boreus LO; 1982)

Reinhard Feneberg – DGRA 2007 Bonn



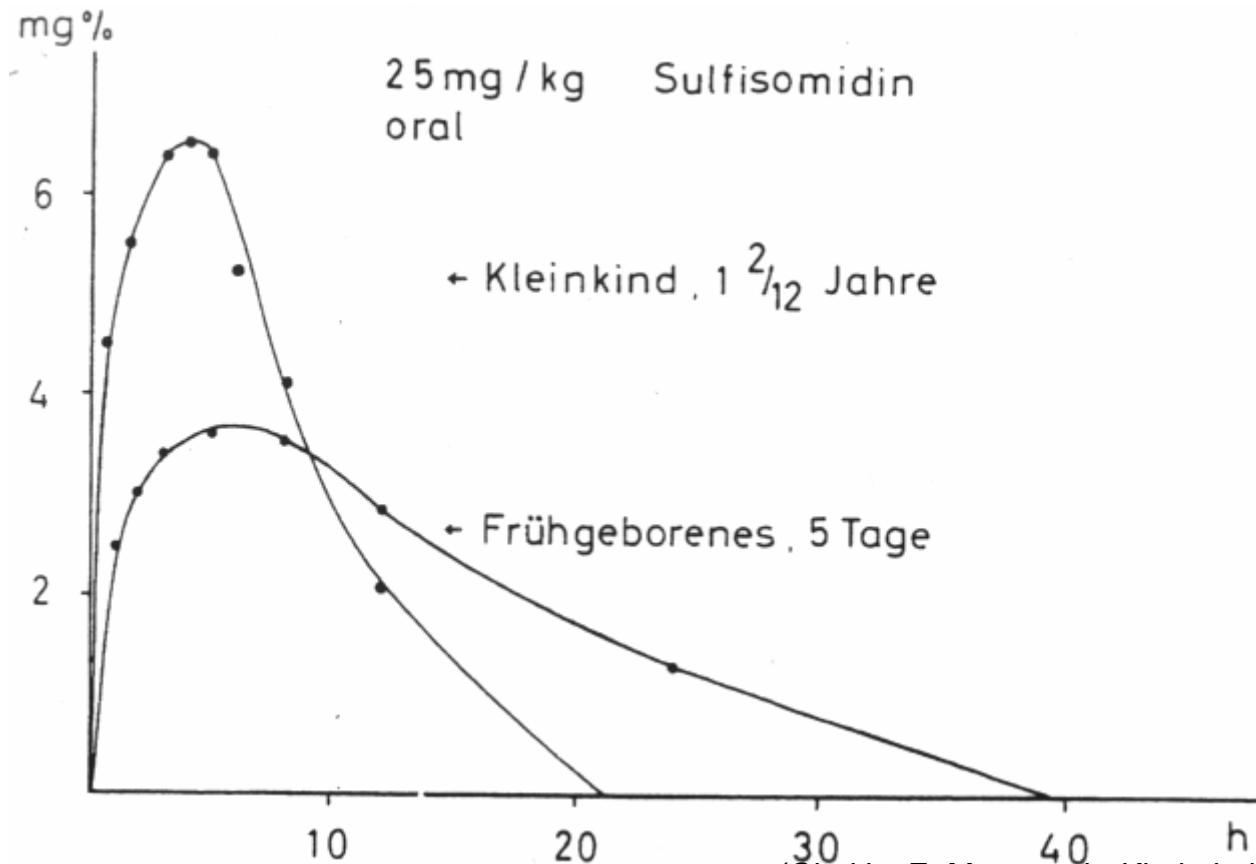
Pharmacokinetics Liberation (LADME)



Pharmacokinetics

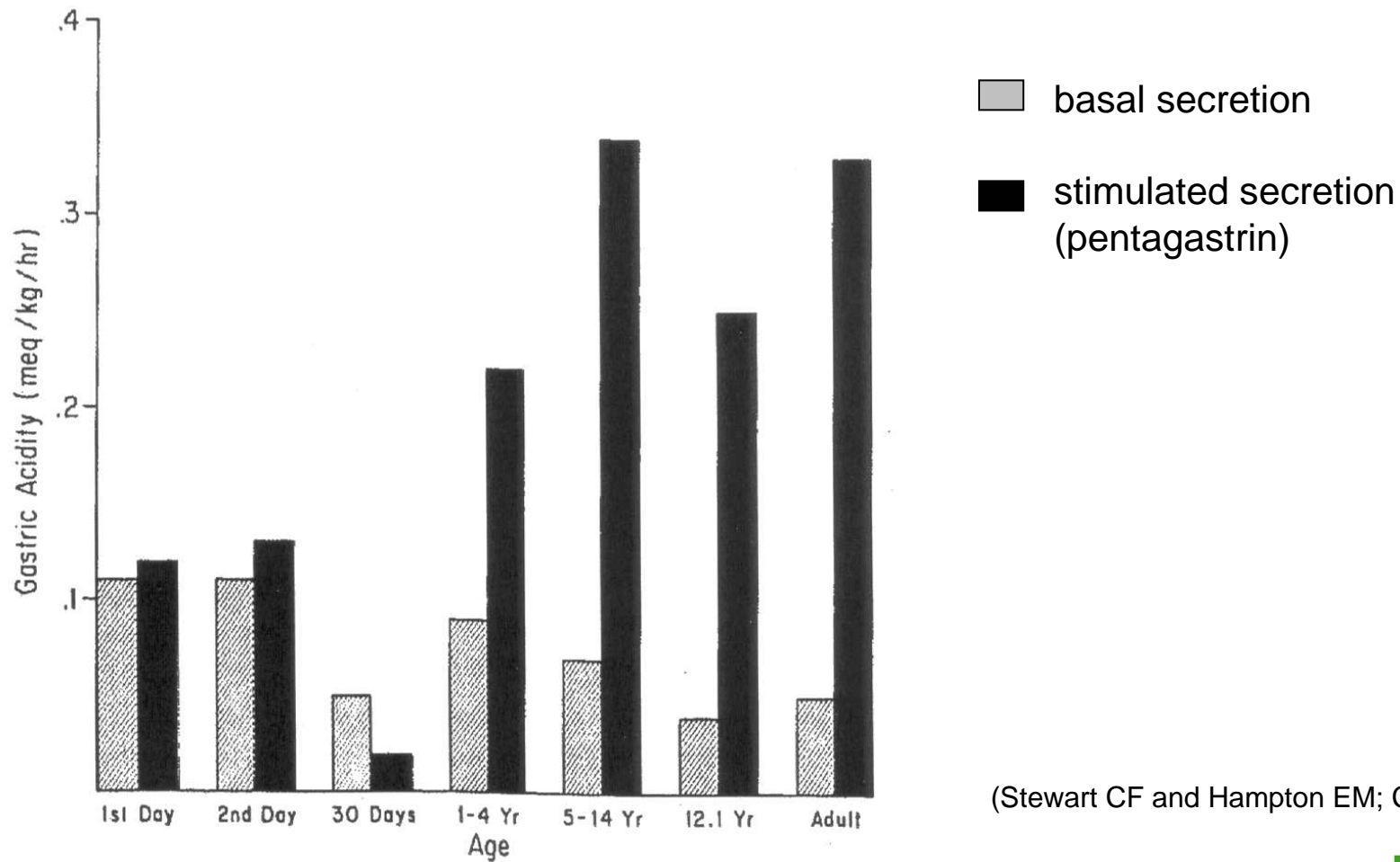
Absorption (LADME)

Sulfisomidin - concentration vs time



(Gladtke E; Monatsschr Kinderheilkd 1979)

Basal and stimulated secretion of gastric acid

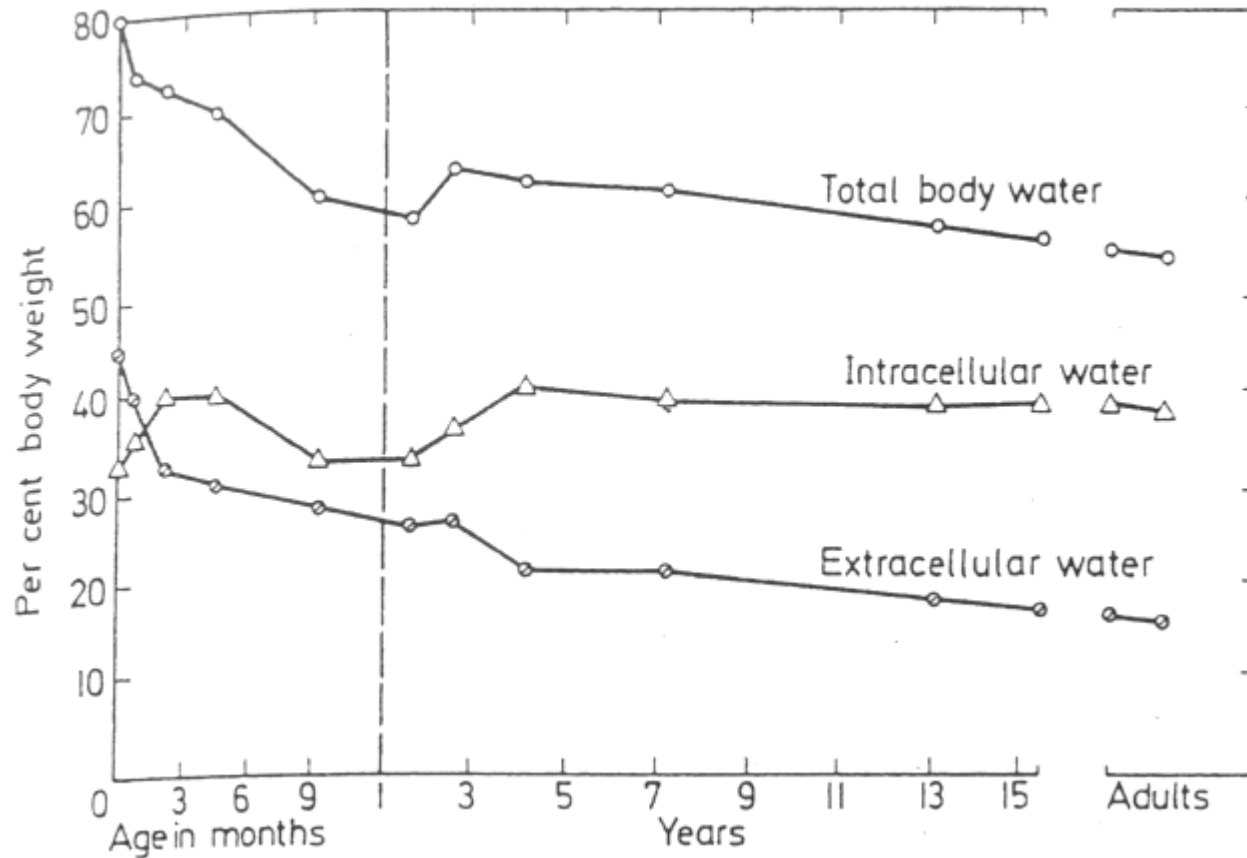


(Stewart CF and Hampton EM; Clin Pharm 1987)

Pharmacokinetics

Distribution (LADME)

Extracellular fluid compartments



(Friis-Hansen B; Pediatrics 1961)

Pharmacokinetics

Metabolismus (LADME)

reduced hepatic metabolic capacity

- Enzymes of oxidative metabolism:
t_{1/2} of diazepam
preterm: 80-400 h, children: ~ 12 h
- Glucuronisation

alternative metabolic pathways

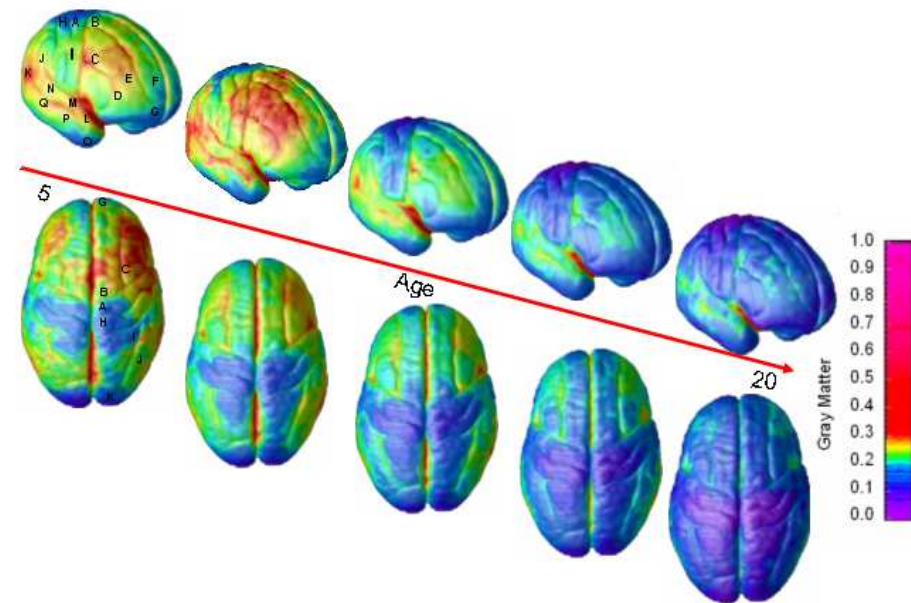
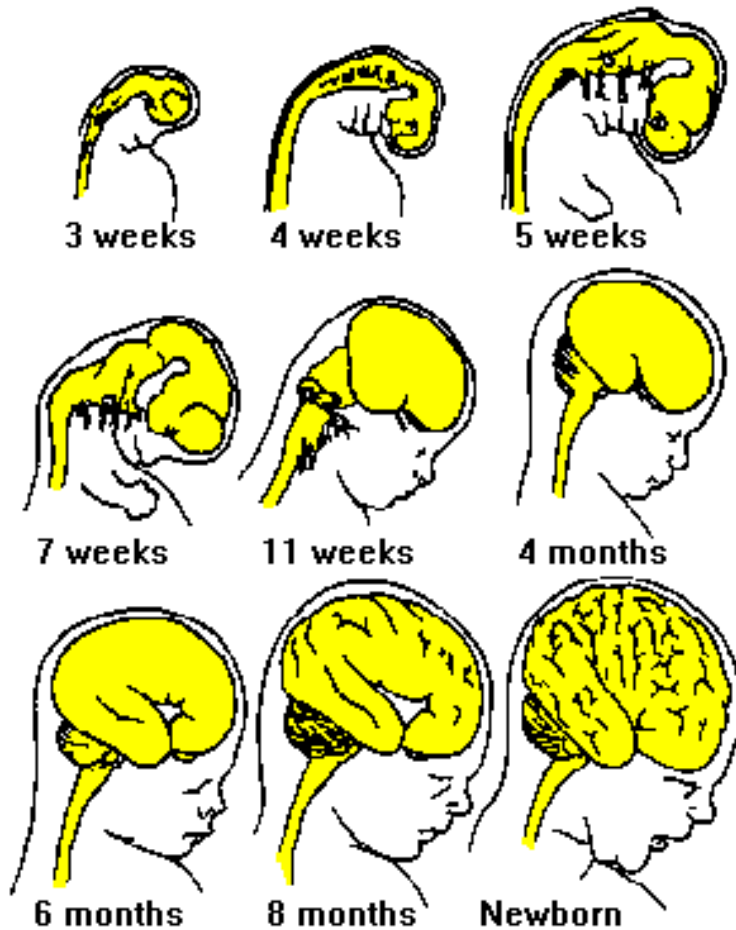
Pharmacokinetics

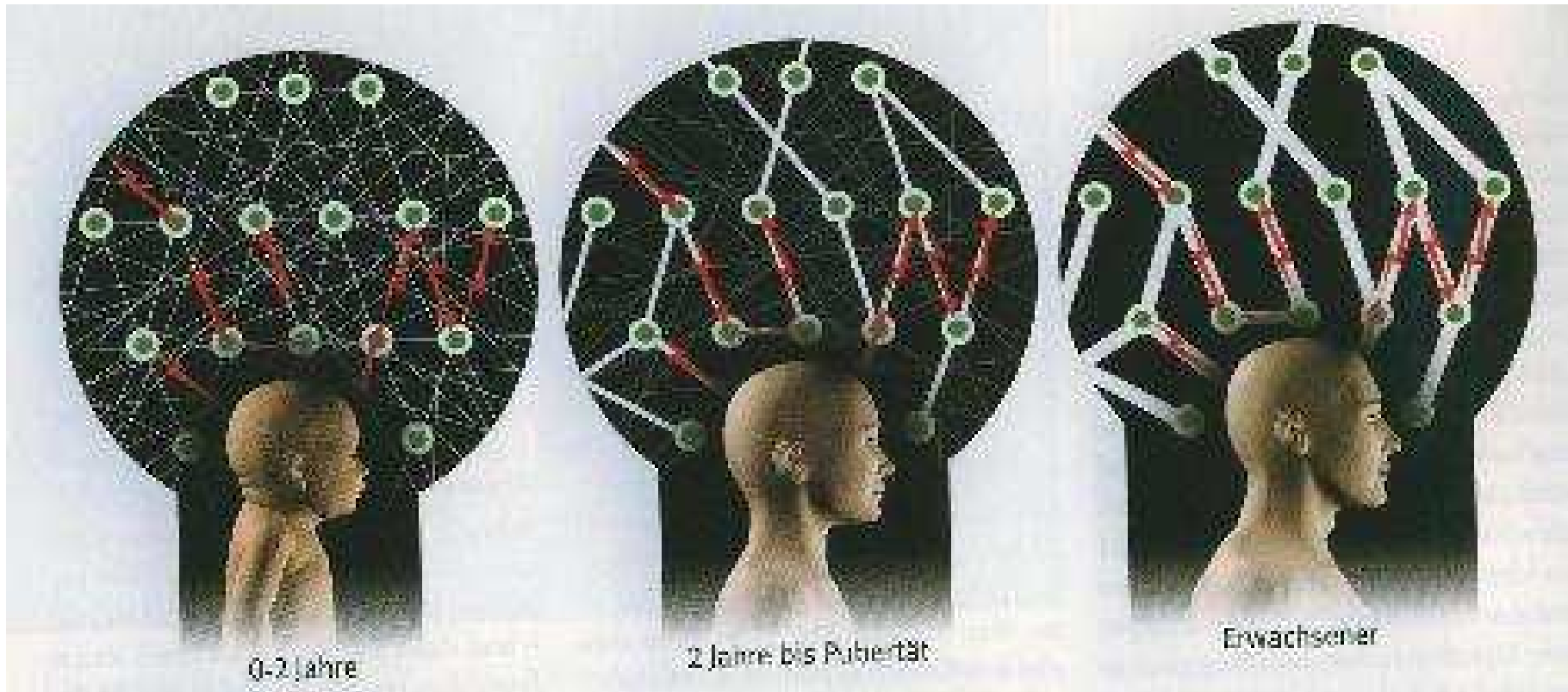
Exkretion (LADME)

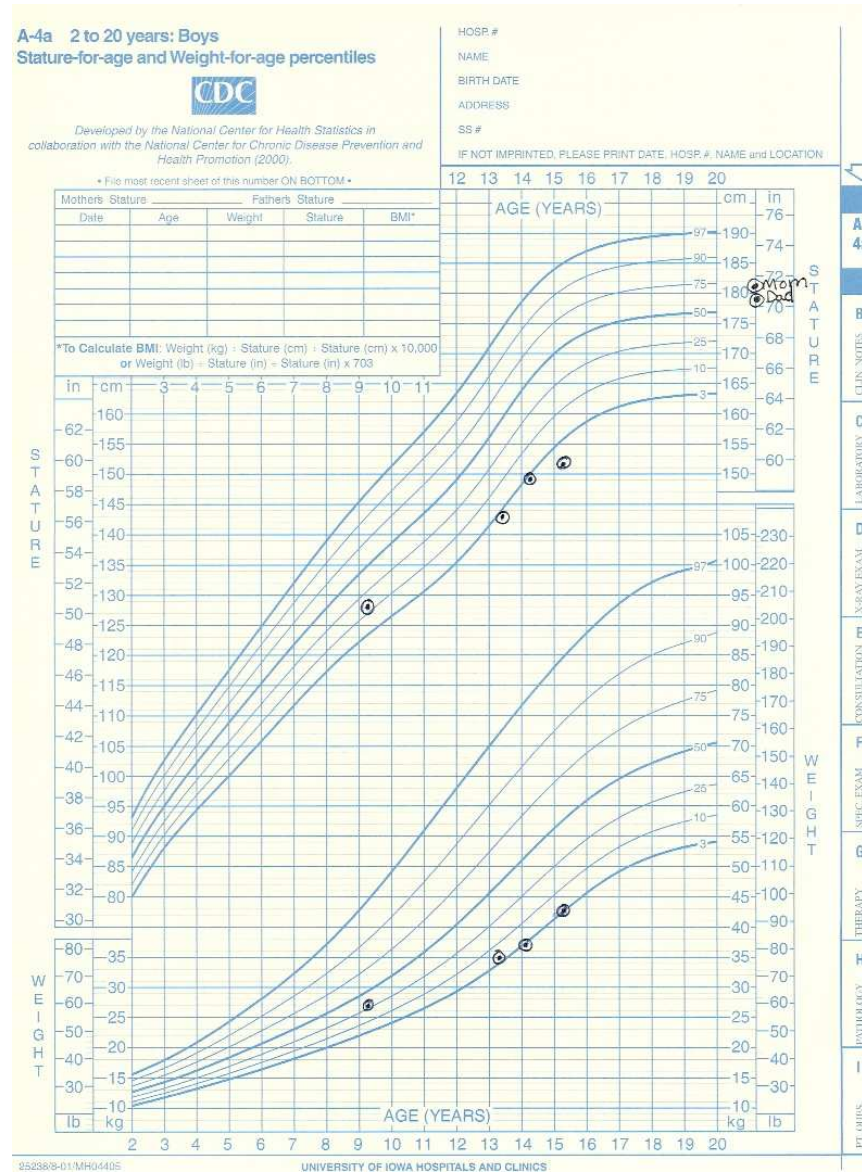
Reduced renal elimination

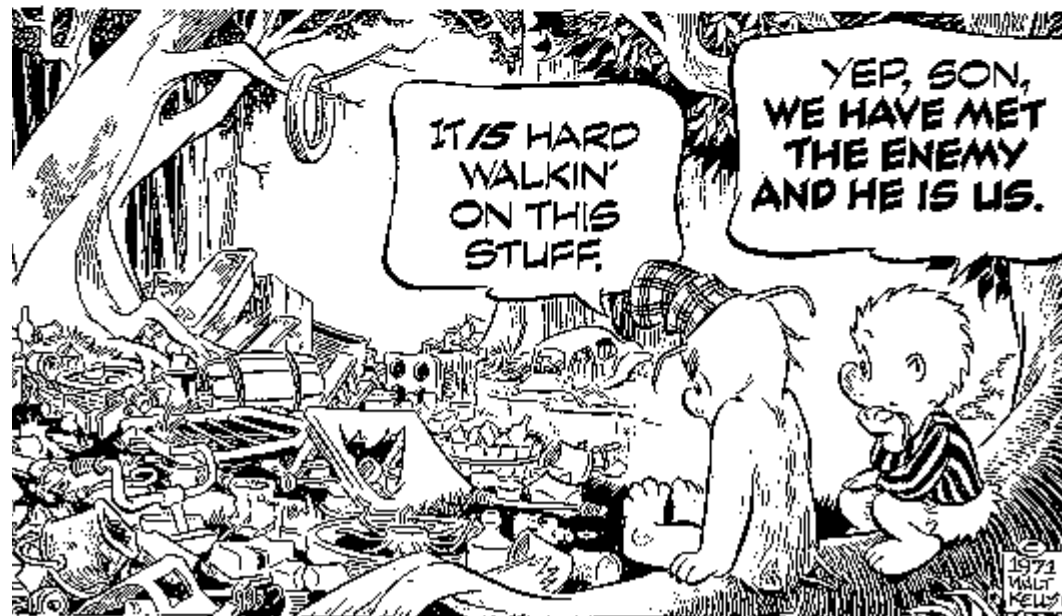
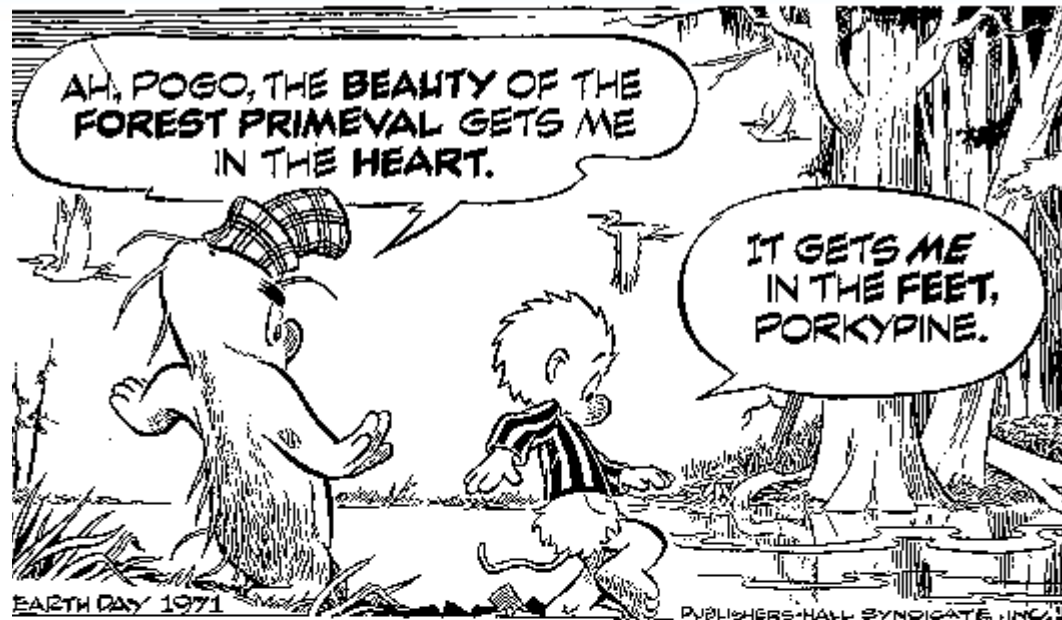
- lower GFR in newborns
- e.g., $t_{1/2}$ of penicillin prolonged
- development of tubular secretion

Endpoints









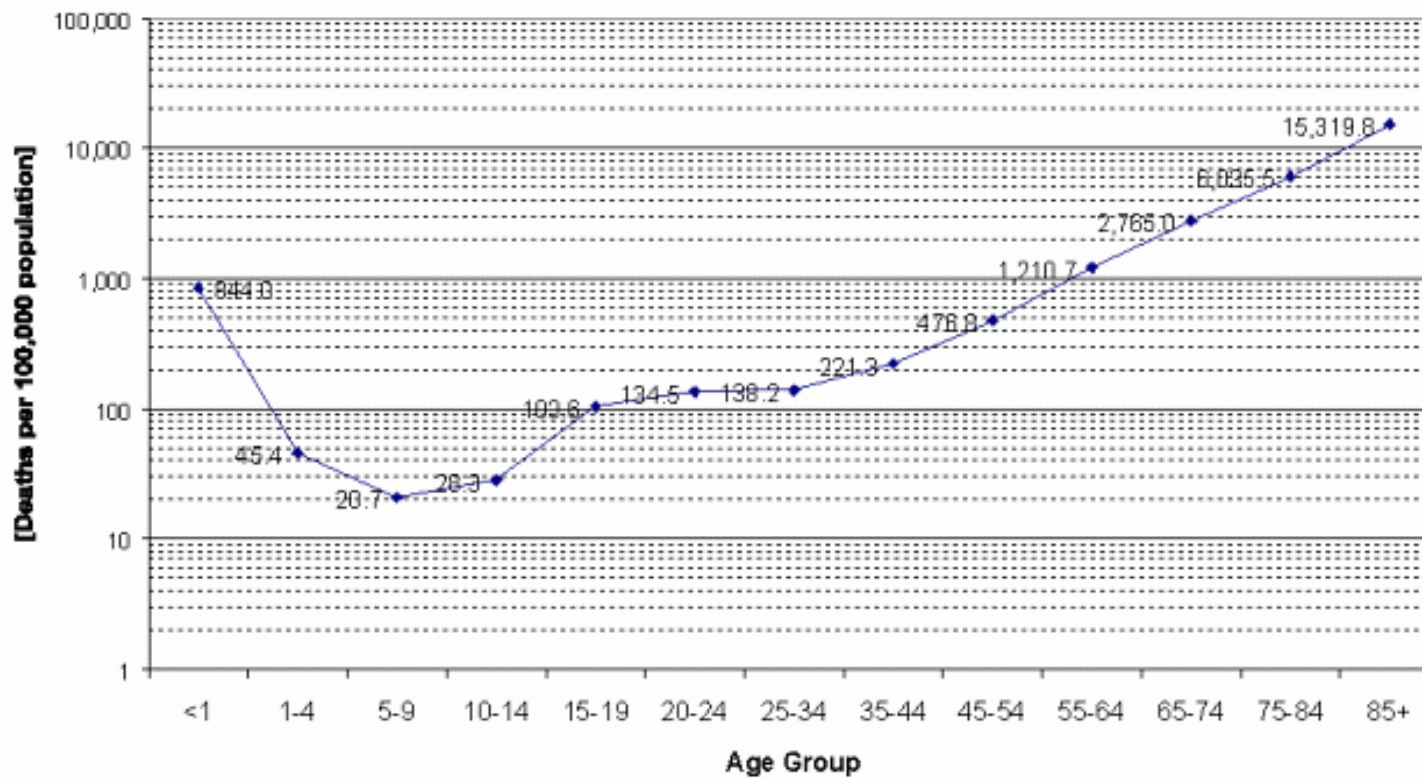
- Psychosocial
Obtaining informed consent and educating motivated patients
- Medicinal
Development and growth
- **Scientific**
Small and diverse populations
- Organizational
Large, multinational, long running studies

Never have ideas about children –
and never have ideas for them

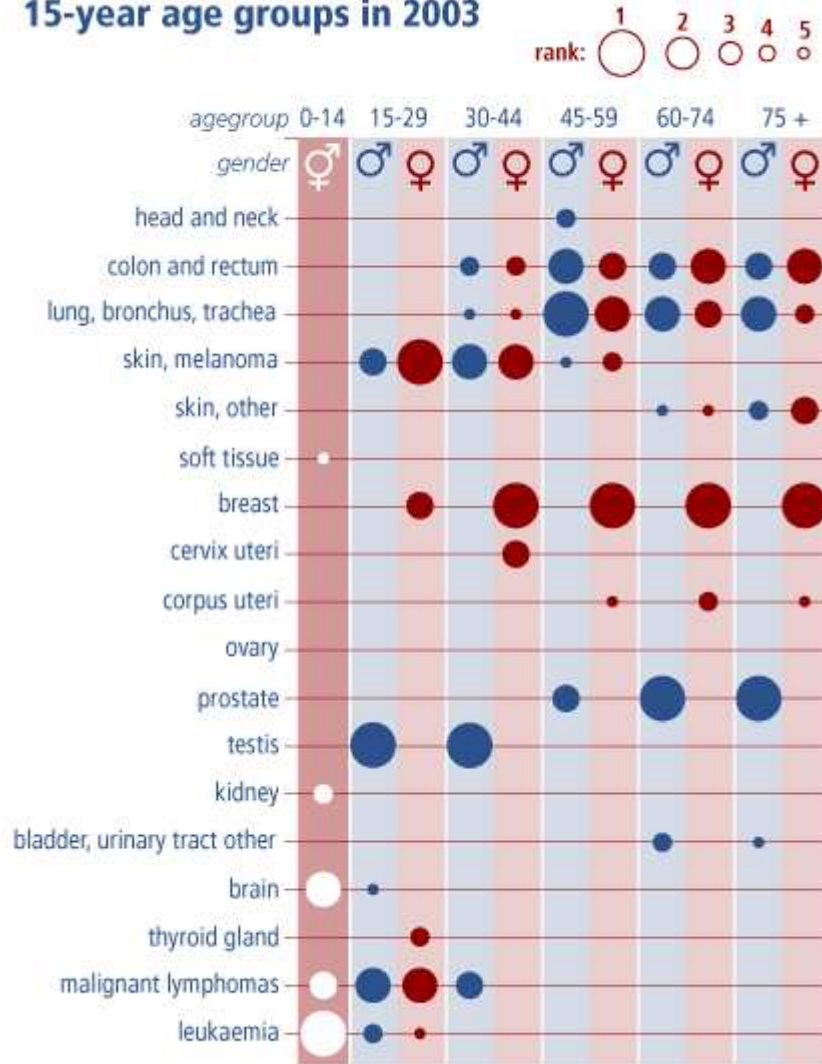
(D. H. Lawrence)

Death Rates by Age

Figure 26
Death Rates by Age Group
San Bernardino County, 1990-1996



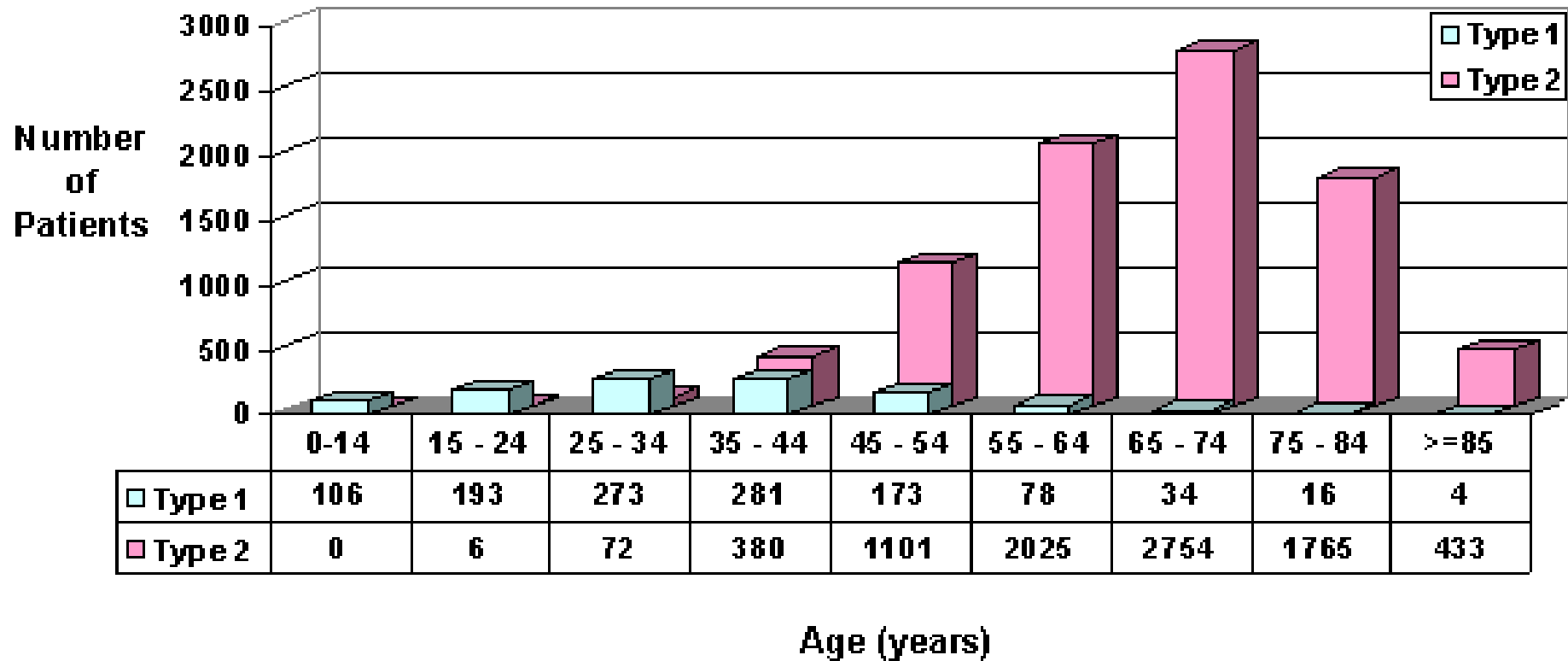
Ranking of the most frequent invasive tumours among males and females according to 15-year age groups in 2003



© the Netherlands Cancer Registry

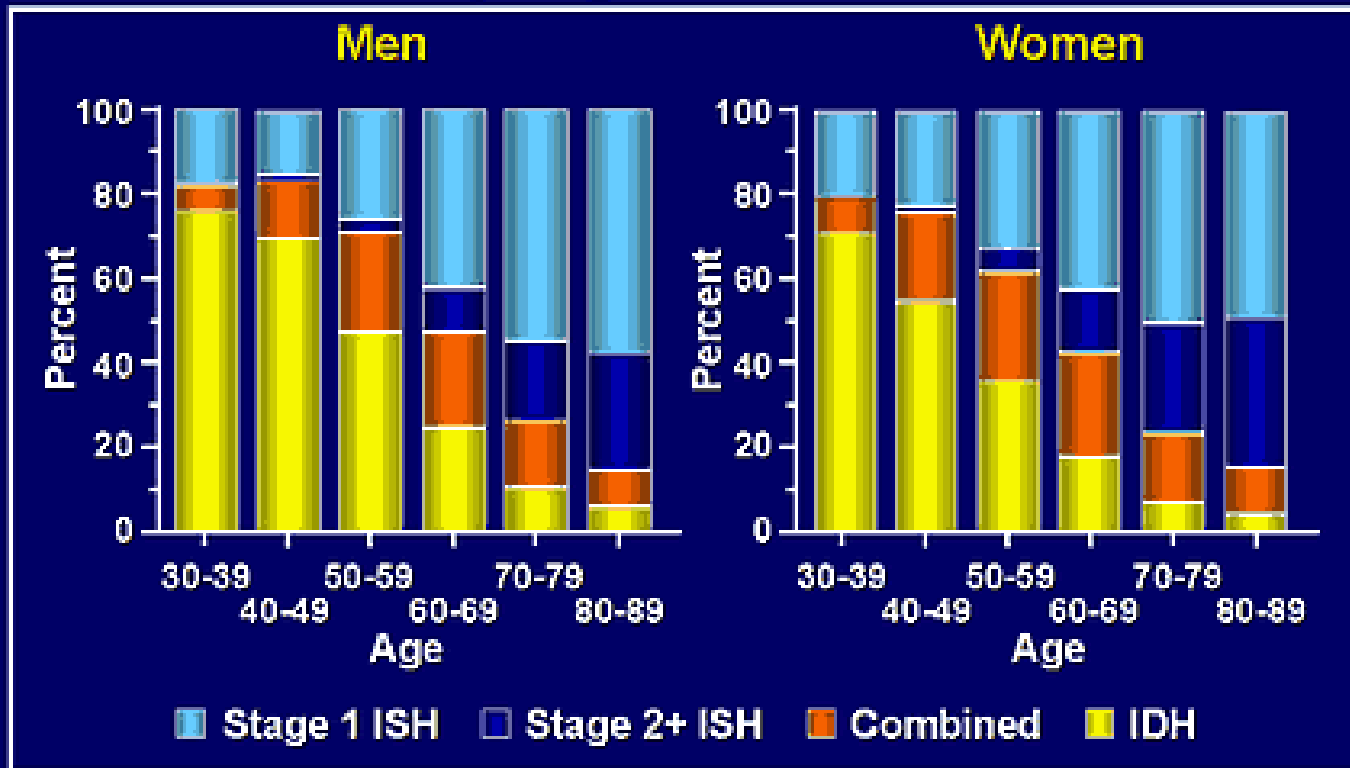
Cancer: Age distribution of deaths

Onset of Diabetes



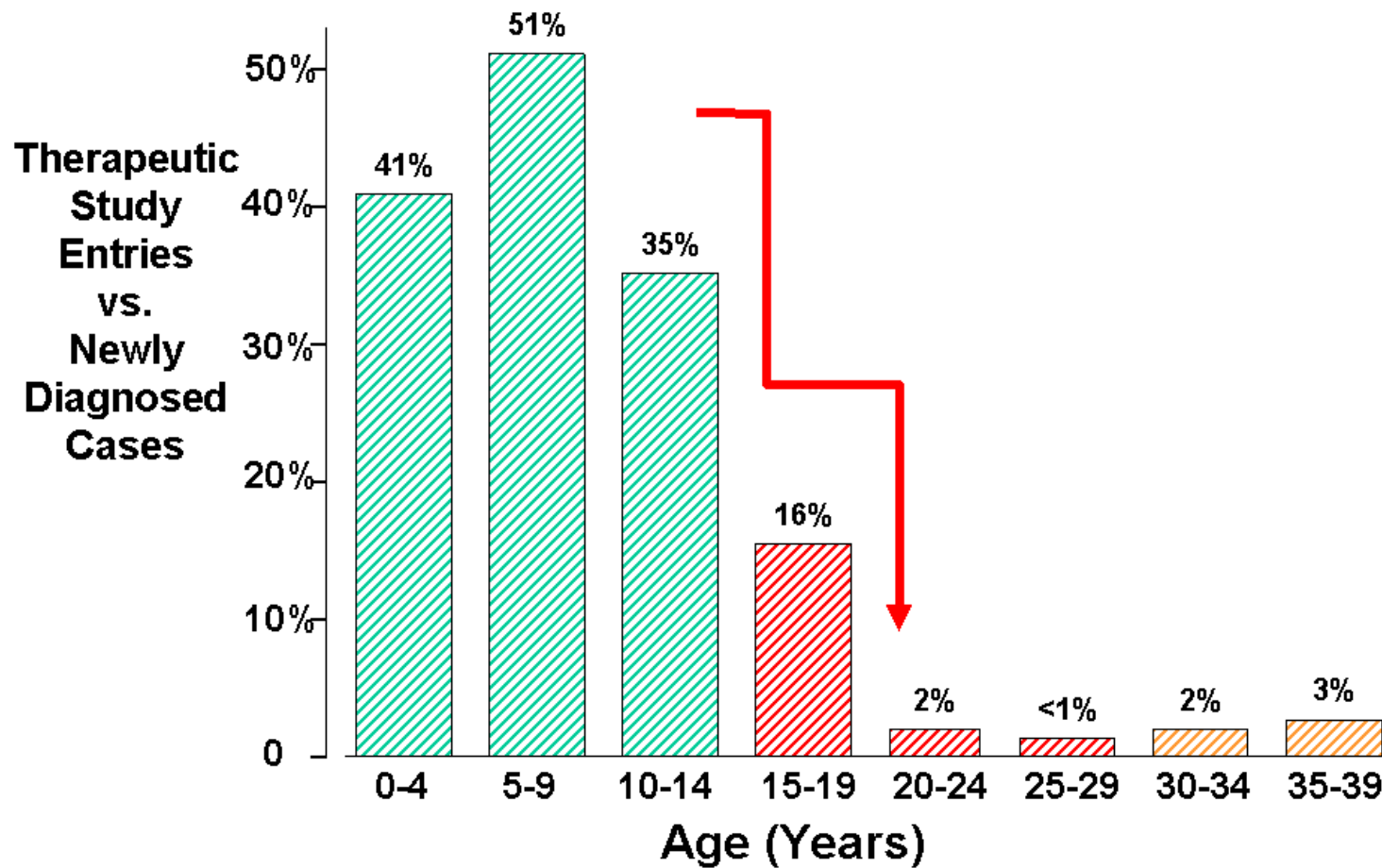
Hypertension by Age What is Missing?

Distribution of Hypertension Categories by Age and Sex

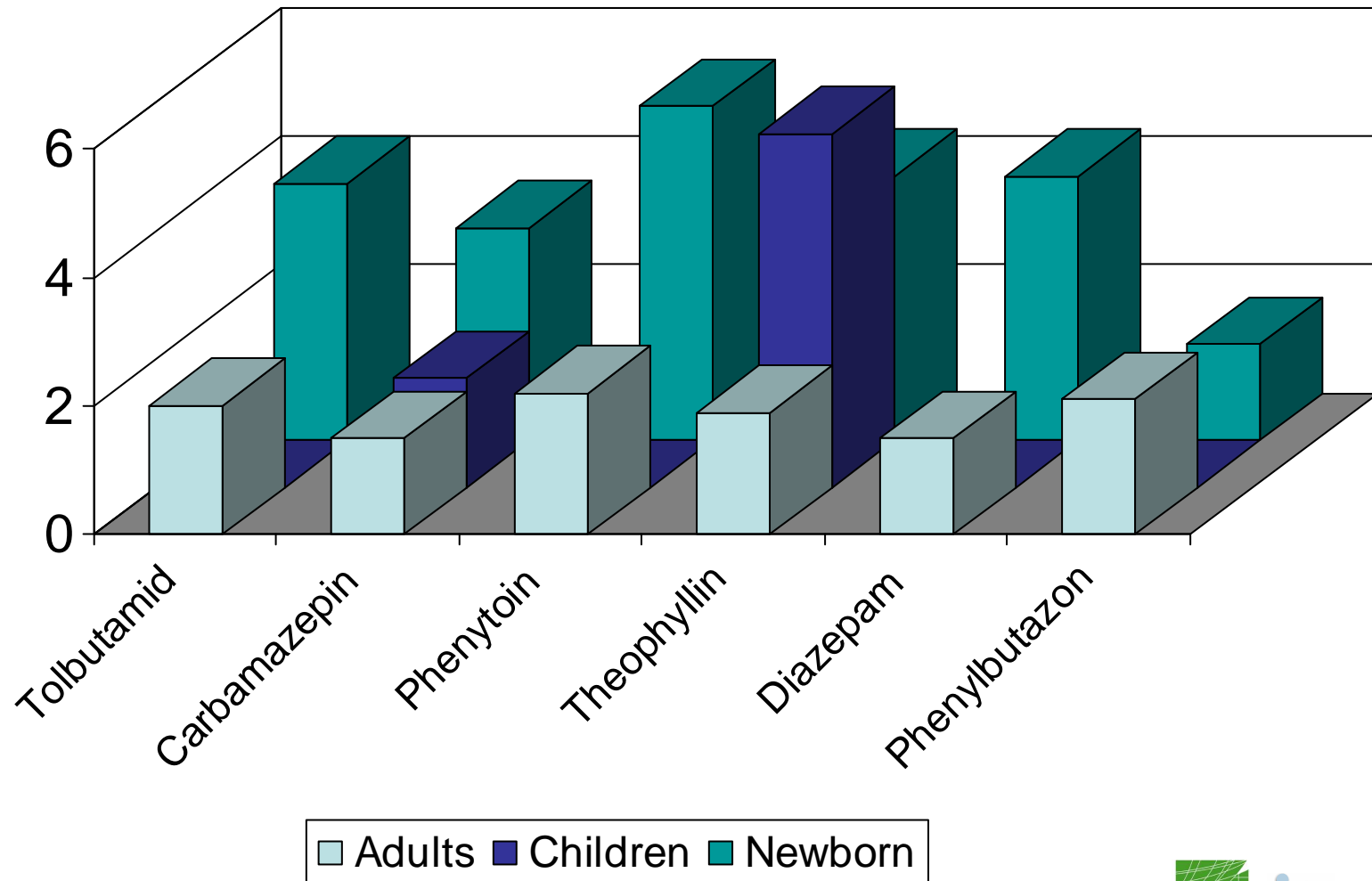


But:

- 1% – 10% of all pediatric patients suffer from high blood pressure
- only 10% of these correctly diagnosed
- Consequences (??)
Up to now, no approval for any antihypertensive agent for children in Germany



Variation of Half Life



Dilemma

- Many pediatric participants for clinical studies required
 - 5 different age groups (ICH E 11)
 - Higher variability
- Fewer patients available

www.paed-net.org

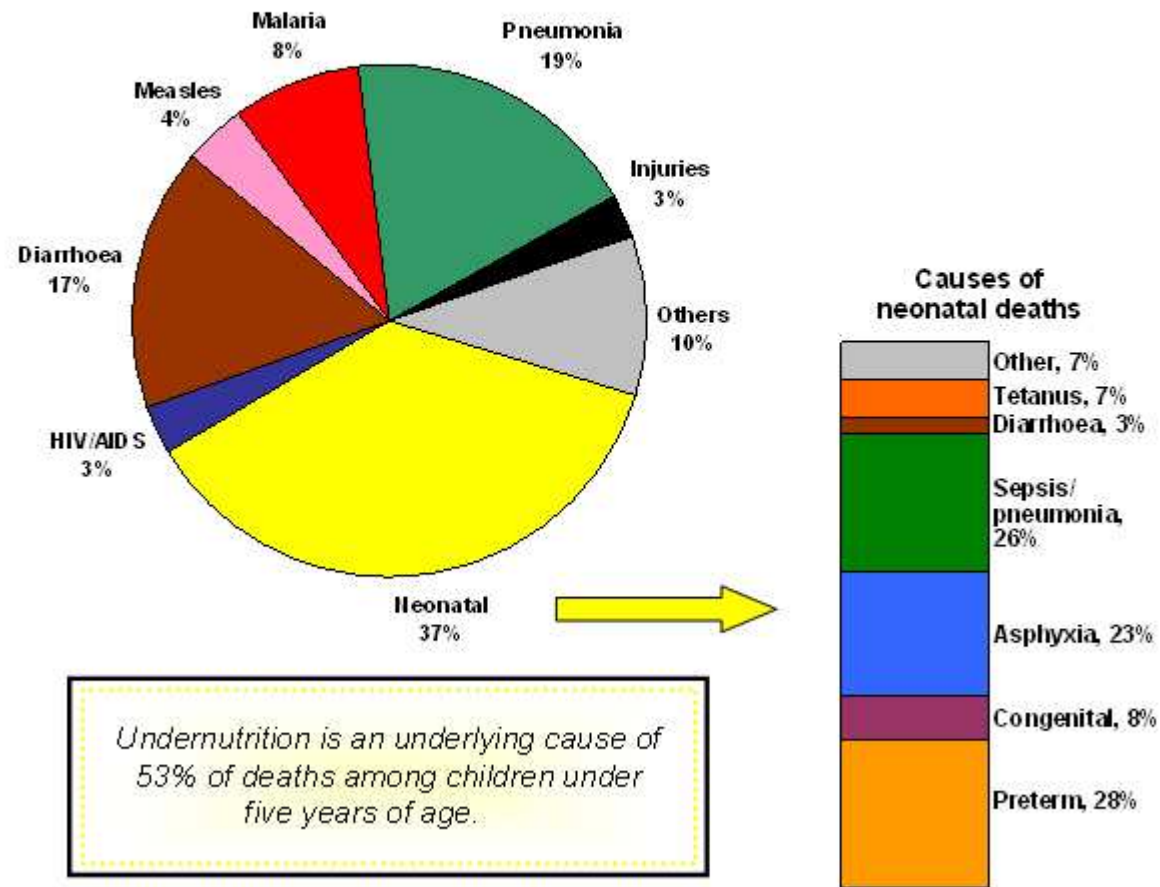


- Psychosocial
Obtaining informed consent and educating motivated patients
- Medicinal
Development and growth
- Scientific
Small and diverse populations
- **Organizational**
Large, multinational, long running studies

Large organization
is loose organization.
Nay, it would be almost as true to say
that organization is
always disorganization.

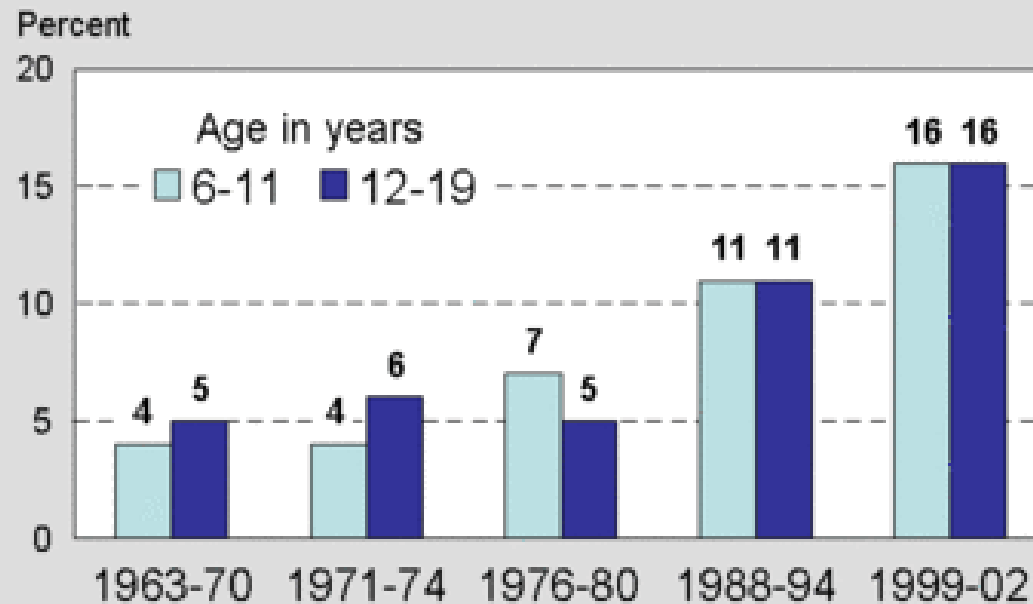
(G. K. Chesterton)

Major causes of death among children under 5 years of age and neonates in the world, 2000-2003



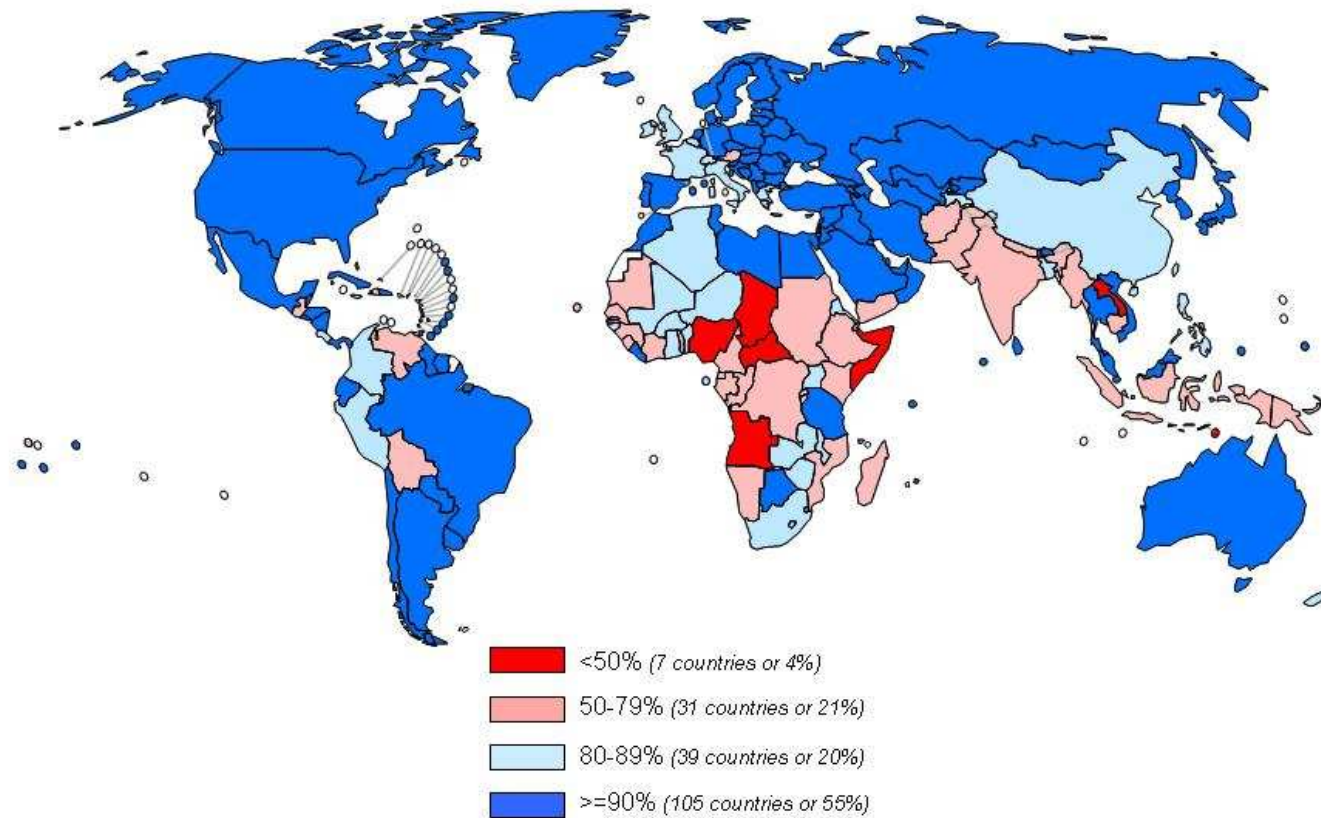
Epidemiology: Overweight

Figure 1. Prevalence of overweight among children and adolescents ages 6-19 years



NOTE: Excludes pregnant women starting with 1971-74. Pregnancy status not available for 1963-65 and 1966-70. Data for 1963-65 are for children 6-11 years of age; data for 1966-70 are for adolescents 12-17 years of age, not 12-19 years.
SOURCE: CDC/NCHS, NHES and NHANES

Immunization coverage with measles containing vaccines in infants, 2005



Source: WHO/UNICEF Coverage estimates 1980-2005, August 2006

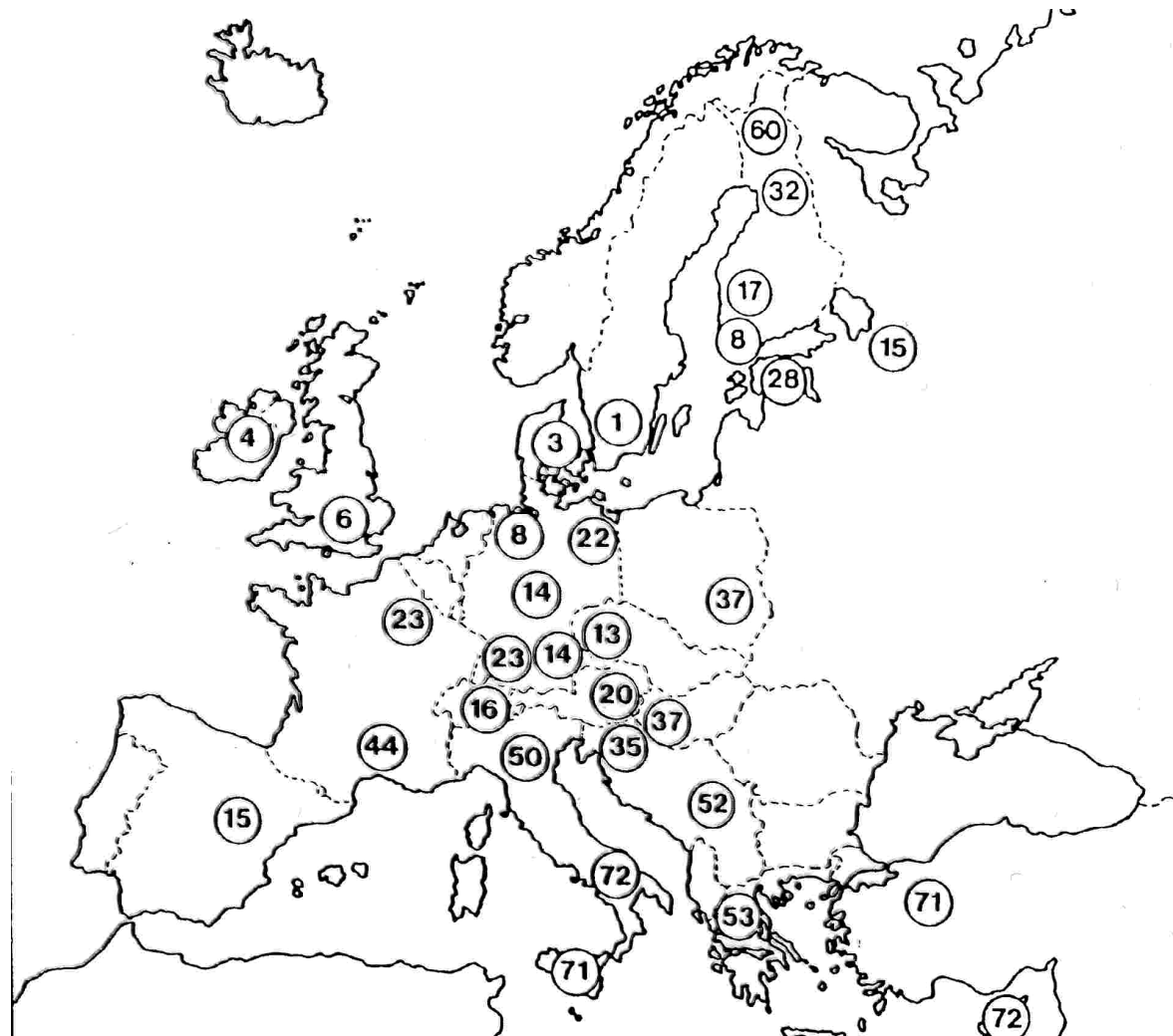
192 WHO Member States

Date of slide: 25 august 2005

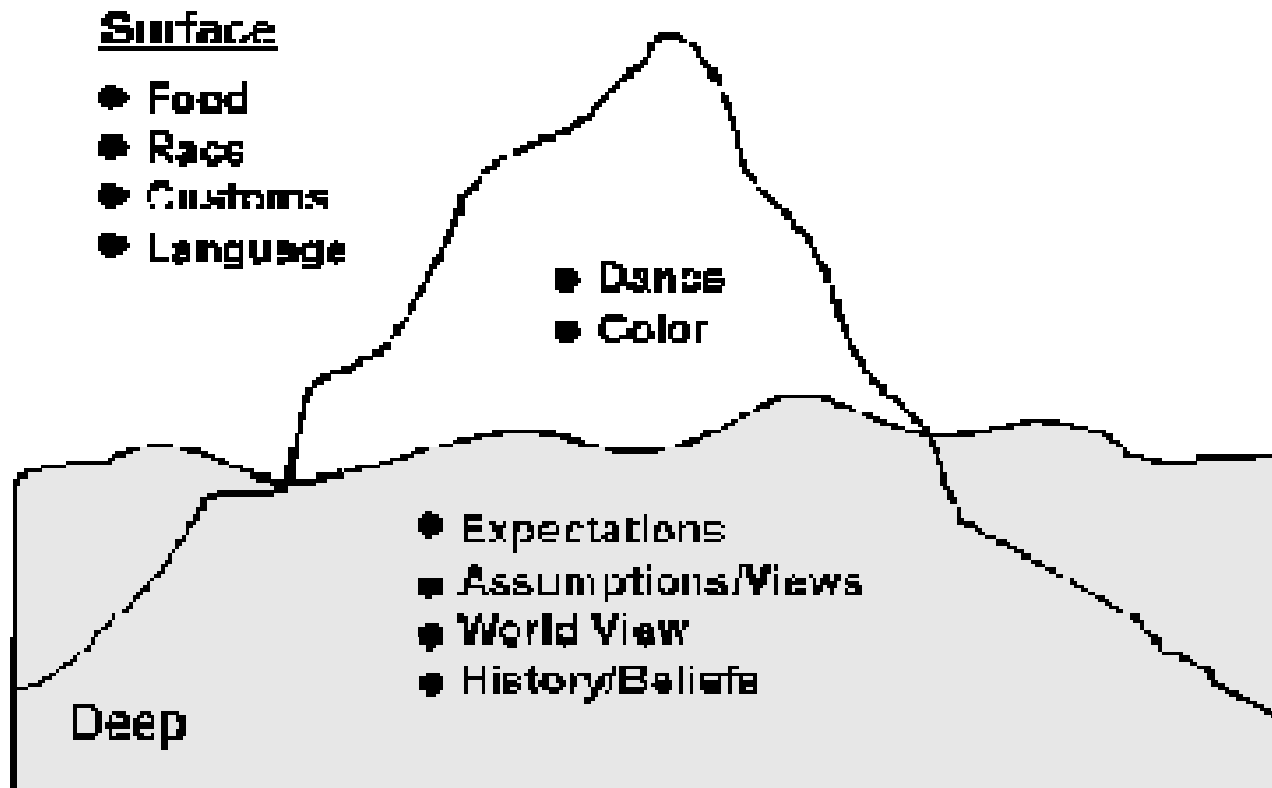
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
© WHO 2006. All rights reserved.



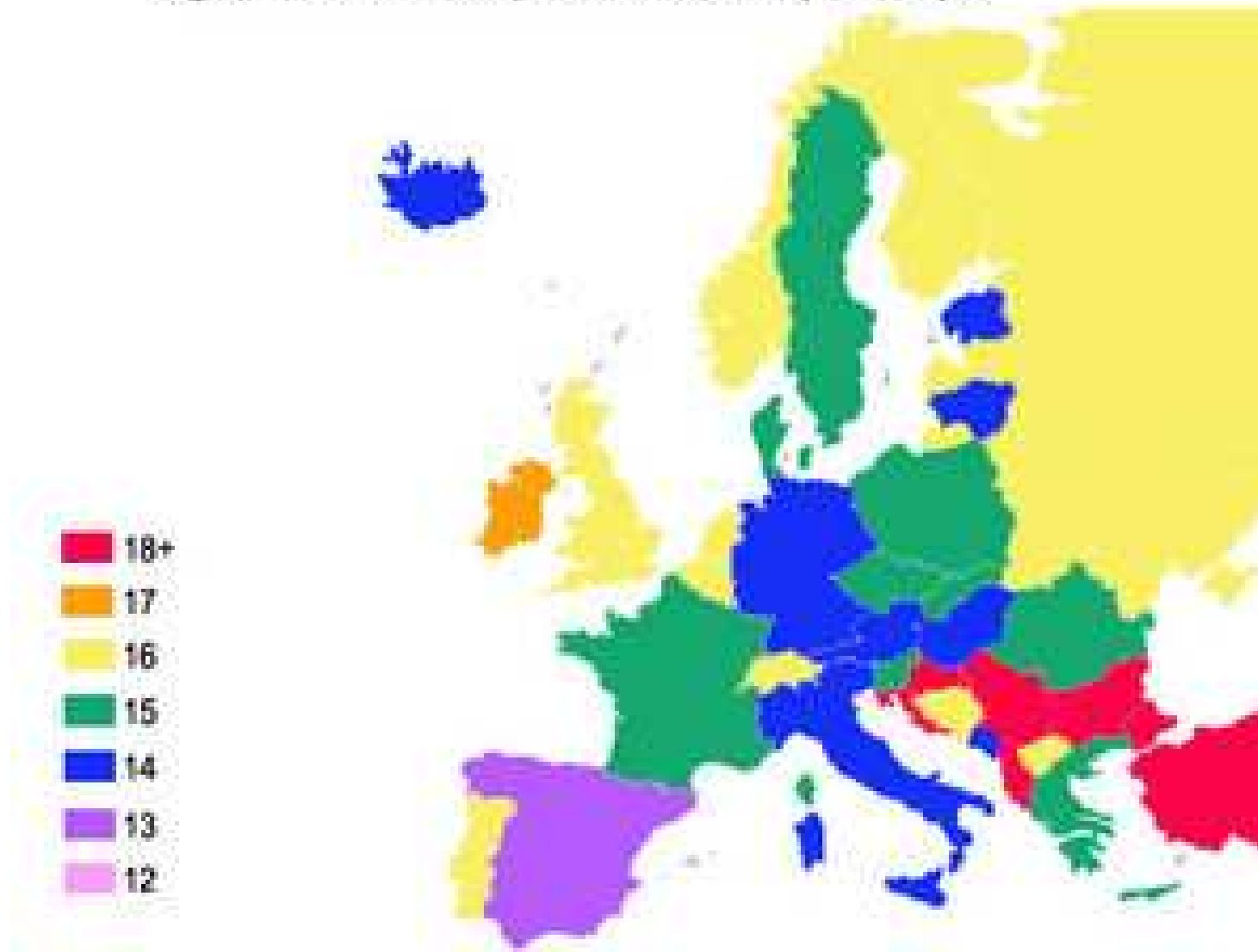
% lactose intolerant



Cultural Iceberg



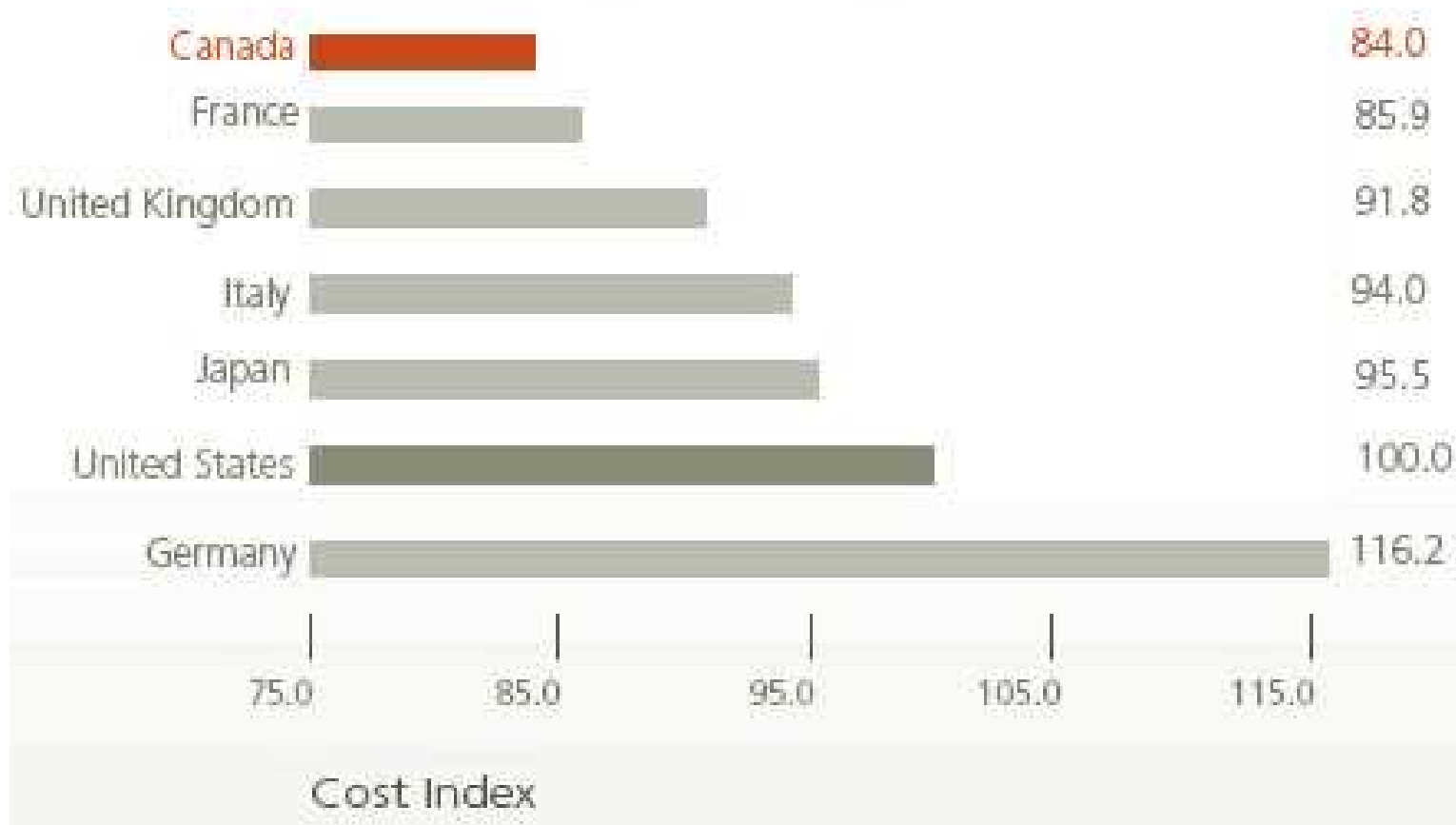
Age of consent for lawful pederastic relationships in Europe





Clinical Trials Management Costs

G7 results (US = 100.0)





Thank you!