Chapter 2
Pediatric Development: Physiology. Enzymes, Drug Metabolism, Pharmacokinetics and Pharmacodynamics

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Abstract Growth and development consists of a continuum of biologic events that includes somatic growth, neurobehavioral maturation, and eventual reproduction, and has tremendous impact on the pharmacology of drugs in children. This impact is related to changes in body composition, development of organs and organ systems and change in these organs' functions. Ontogeny is the science that studies the origin and development of an organism. Pharmacokinetics of drugs (what the body does to a drug) is summarized in the acronym ADME, which stands for absorption, distribution, metabolism, and elimination.

Abbreviations

ADME	Absorption, distribution, metabolism, elimination
BMI	Body mass index
BSA	Body surface area
CYP	Cytochrome P450
ECW	Extracellular water
FFM	Fat-free mass
FM	Fat mass
GFR	Glomerular filtration rate
HAPMAP	Haplotype map
ICW	Intracellular water
PD	Pharmacodynamics
P-gp	P-glycoprotein

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PGx	Pharmacogenomics
PK	Pharmacokinetics
TBW	Total body weight

2.1 Introduction

Many of the development changes in body composition and organ function influence pharmacokinetics. A better understanding of the various physiologic variables regulating and determining the fate of drugs in the body and their pharmacologic effects has dramatically improved both the safety and the efficacy of drug therapy for neonates, infants, children, and adolescents [17]. During childhood, these changes are dynamic and can be nonlinear and discordant making standardized dosing an inadequate means of effective drug dosing across the span of childhood. The impact of these changes is largely related to function of organs important in metabolism (e.g. the liver) and excretion (e.g. the kidney) and changes in body composition (e.g. body water content, plasma protein concentrations) (see Fig. 2.1).

The first subsection will discuss the anatomical changes in body size and composition. Subsequently, the ontogeny of the developing human and its organs, and the impact on pharmacokinetic of drugs will be discussed.

2.2 Body Size and Composition

Physical growth after birth is a continuum from the extraordinary growth and development that take place in utero. Growth and development is not completed at birth, and maturation is reached much later. Important changes in response to and biodisposition of drugs occur during infancy and childhood. These changes influence the response to drugs and their toxicity and dosing regimens. The first 2–3 years of postnatal life is a period of particularly rapid growth and development. Most of the changes in body composition take place in this period. Puberty is a second period of change, relevant for pharmacokinetic. However, implications for pharmacotherapy are more extensive in the first few years. Figure 2.2a–d shows that both height and weight increase most during these years. Body weight doubles by 5 months and triples by 1 year. Body length increases by 50 % during the first year, and doubles by 4 years. Body surface area (BSA) doubles by the first birthday and triples by 4 years (Fig. 2.3a–d). Growth velocity decreases rapidly from 25 % per month at birth to 4 % at 1 year, and down to 1 % for most of the rest of childhood. Relative body surface is greatest at birth, as compared to body size (Fig. 2.3d). Caloric expenditure increases threefold to fourfold during the first year. Substantial changes in body proportions and composition accompany growth and development, as is shown in the BMI curve (Fig. 2.3e). Major organ systems differentiate, grow, and mature throughout infancy and childhood. Although growth and development are
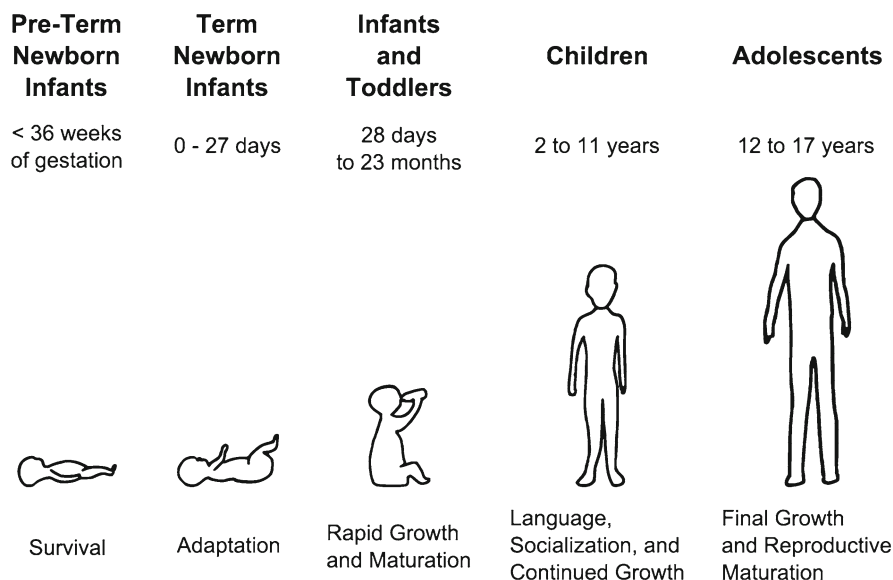
Pre-Term Newborn Infants	Term Newborn Infants	Infants and Toddlers	Children	Adolescents
< 36 weeks of gestation	0 - 27 days	28 days to 23 months	2 to 11 years	12 to 17 years
Survival	Adaptation	Rapid Growth and Maturation	Language, Socialization, and Continued Growth	Final Growth and Reproductive Maturation

Fig. 2.1 Five stages of development. The pediatric population extends from the preterm and term newborn infant through childhood, and adolescence, or even to young adulthood. Each period of development has its own very specific characteristics, such as period of survival, period of adaptation, period of rapid growth and physiological maturation, period of language, socialization, and continued growth, and period of final growth and reproductive maturation [22]

most rapid during the first several years of life, maturation continues at a slower pace throughout middle and late childhood. This dynamic process of growth, differentiation, and maturation is what sets the infant and child apart from adults, both physically and pharmacologically.

The proportions of body weight contributed by fat, protein, and intracellular water change significantly during infancy and childhood (Fig. 2.4 and Table 2.1) [1, 11, 12]. Total body water (TBW = ICW + ECW) constitutes 85 % of body weight in the preterm neonate and 70–75 % in term neonates. This decreases to approximately 60 % at 4 months and remains relatively constant from this age onwards. Extracellular water decreases all through childhood (Table 2.1). The percentage of body weight contributed by fat is 3 % in a 1.5 kg premature neonate compared with 12 % in a term neonate; this proportion doubles by 4–5 months of age. "Baby fat" is lost when the infant starts walking and protein mass increases from 20 % in the term neonate to 50 % in the adult.

Puberty is an important phase in physical development. The age of onset of puberty varies as a function of ethnicity, health status, genetics, nutrition, and activity level. Generally, puberty begins between 8 and 14 years and occurs almost 2 years earlier in females than males. A pubertal growth spurt is accompanied by remodeling of the body over a relative short period of time with sexual maturation; feminization with more fat content in females and masculinization with more muscular mass in males (Fig. 2.5).
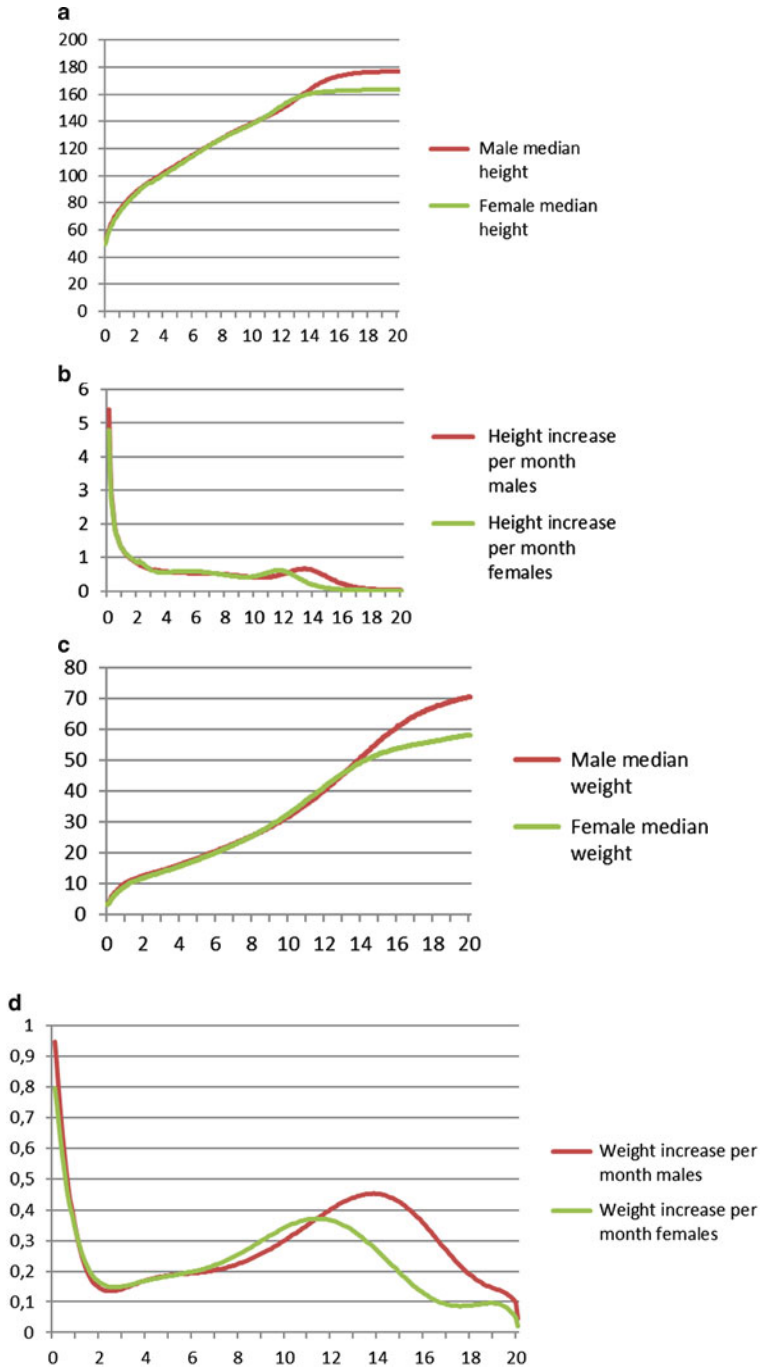
Fig. 2.2 Growth in humans; height and weight [Data: Center for Disease Control and Prevention (CDC) and World Health Organisation (WHO)]. (**a**) Growth chart with median (P50) height in centimeters (cm) in males and females 0–20 years of age. (**b**) Increase in height per month as percentage of height (cm) in males and females 0–20 years of age (calculated for the median height). (**c**) Growth chart with median (P50) weights in kilograms (kg) in males and females 0–20 years of age. (**d**) Increase in weight per month in kilograms in males and females 0–20 years of age (calculated for the median weight)
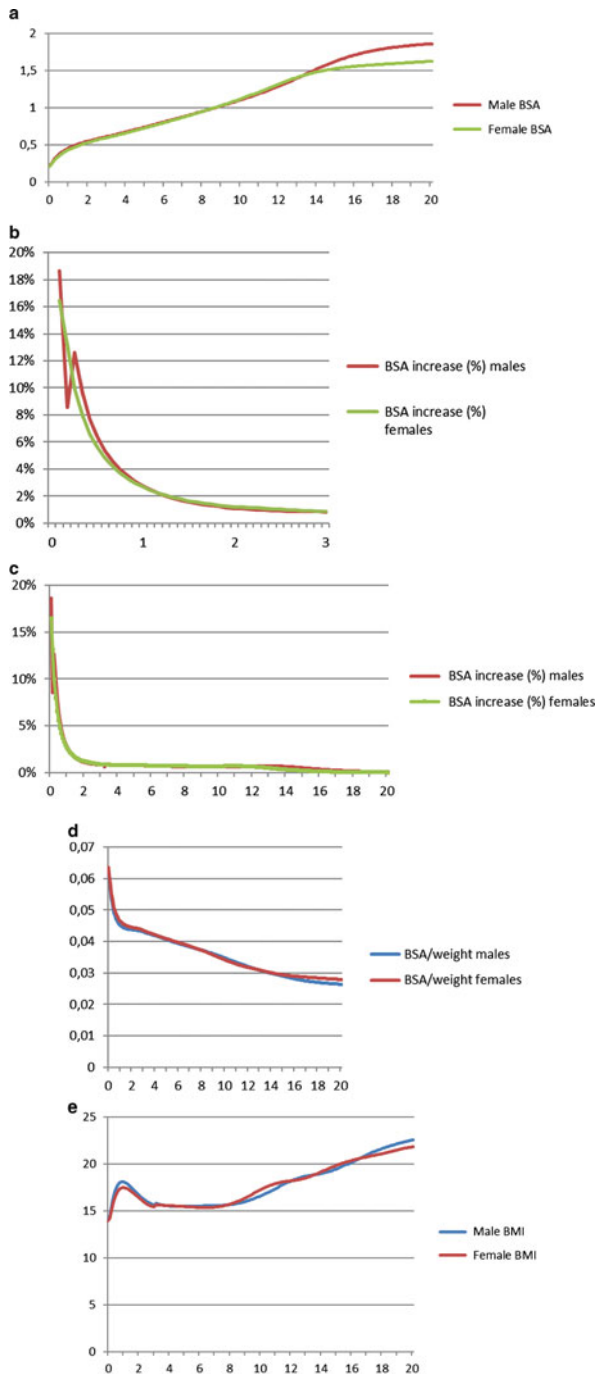
Fig. 2.3 Growth in humans; BSA and body mass index (BMI) [Data: CDC and World Health Organisation (WHO); BMI=weight (kg)/(height (m))^2; BSA calculation based on the Mosteller formula (BSA=($W \times H$/3600)$^{1/2}$)]. (**a**) BSA curve for males and females 0–20 years of age. (**b**) BSA increase as percentage of BSA in males and females 0–3 years of age. (**c**) BSA increase as percentage of BSA in males and females 0–20 years of age. (**d**) BSA corrected for total body weight (BSA/TBW (m^2/kg)) curve for males and females 0–20 years of age (indicating relative BSA to be highest when compared to weight in neonates). (**e**) BMI curve for males and females 0–20 years of age
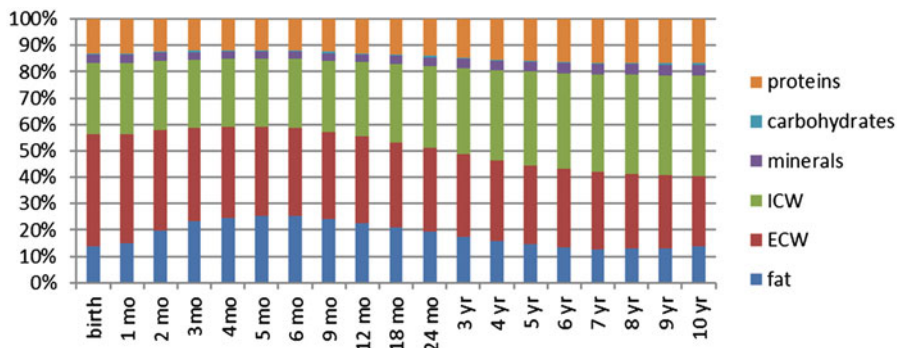
Fig. 2.4 Change in body composition proportions during childhood. *yr* year, *mo* month, *ICW* intracellular water, *ECW* extracellular water

Table 2.1 Body composition

Age	Fat	ECW	ICW	Minerals	Carbohydrates	Proteins
Birth	13.7	42.5	27.0	3.2	0.5	12.9
1 month	15.1	41.1	27.3	3.2	0.5	12.9
2 months	19.9	38.0	26.3	3.0	0.5	12.3
3 months	23.2	35.7	25.8	2.9	0.5	12.0
4 months	24.7	34.5	25.7	2.8	0.4	11.9
5 months	25.3	33.8	25.8	2.8	0.4	11.9
6 months	25.4	33.4	26.0	2.8	0.4	12.0
9 months	24.0	33.0	27.2	2.9	0.5	12.4
12 months	22.5	32.9	28.3	2.9	0.5	12.9
18 months	20.8	32.3	29.9	3.1	0.5	13.5
24 months	19.5	31.9	31.0	3.2	0.5	14.0
3 years	17.5	31.1	32.8	3.4	0.5	14.7
4 years	15.9	30.5	34.2	3.5	0.5	15.3
5 years	14.6	30.0	35.4	3.7	0.5	15.8
6 years	13.5	29.6	36.4	3.8	0.5	16.2
7 years	12.8	29.1	37.1	3.9	0.5	16.5
8 years	13.0	28.3	37.5	4.0	0.5	16.6
9 years	13.2	27.6	37.8	4.1	0.5	16.8
10 years	13.7	26.7	38.0	4.1	0.5	16.8

2.3 Pharmacokinetic

Significant efforts over recent years have been directed at research on pharmacokinetic and pharmacodynamics, but there is still a lack of information about the impact of ontogeny on the activity of drug-metabolizing enzymes, transporters, and other targets [22–24, 26].

Physiological processes that influence pharmacokinetic variables in the infant change significantly in the first years of life, particularly in the first few months.
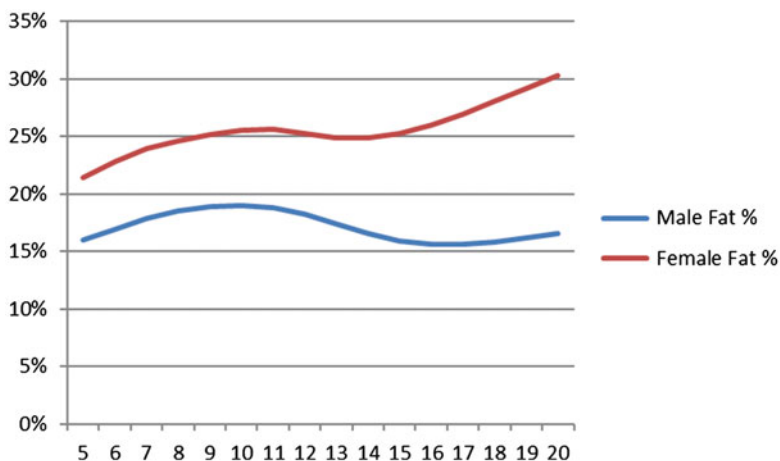
Fig. 2.5 Changes in fat mass (FM) as percentage of total body weight in adolescence (data from [28])

Drug metabolism is divided into absorption, distribution, metabolism, and elimination (ADME), and specific changes to each of these mechanisms will be further discussed. There is a clear distinction in regard to pharmacokinetic between children ≥2 years of age and infants <2 years of (postnatal) age. In children ≥2 years, pharmacokinetic parameters can be predicted from adult data using size differences in pharmacokinetic models. Children are mature and differ from adults only in size—children are small adults, from a pharmacokinetic perspective [15]. Infants <2 years are, of course, even smaller in size than children. When young infants—especially neonates—are being considered, although size is still an important factor, the maturation processes and status are even more important. Age then becomes essential for defining pharmacokinetic in infants compared with children [15] (see Fig. 2.6).

2.3.1   Absorption

Drug absorption in infants and children follows the same general principles as in adults. Drug absorption for therapeutic agents administered by oral, topical, or any other route that involves absorption (intrathecal and intraosseal excluded) depends on both the physicochemical properties of the drug and a variety of patient-related factors (e.g. reduced gastric acidity, reduced emptying time, motility, intestinal immaturity of mucosa leading to increased permeability, high levels of intestinal b-glucuronidase activity, reduced first-pass metabolism, maturation of carrier mechanisms, intestinal colonization, perfusion, reduced bile acid excretion in the case of oral administration). Unique factors that influence drug absorption include blood flow at the site of administration, as determined by the physiologic status of the
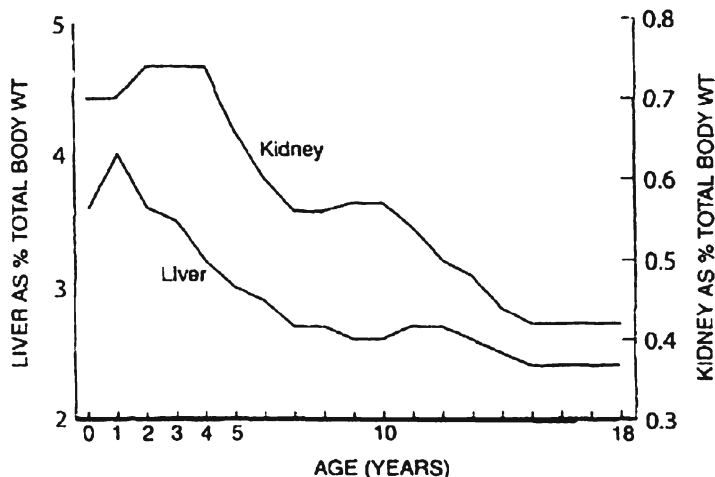
Fig. 2.6 Change in relative liver and kidney mass expressed as percentage of body weight from infancy to young adulthood [26]

infant or child, gastrointestinal function for orally administered drugs, which changes rapidly during the first few days after birth, and skin permeability in topical drugs.

The gut, with its large, folded surface, is our biggest interface to the outside world and is the most common route of administration. Absorption is strongly affected by several changes in physiology that take place during development. As in general growth, the most significant changes take place during infancy and the early years of childhood. In the first hours and days after birth, the intestinal weight and the mucosal mass almost double to accommodate the change from umbilical cord to oral feeding, which is similar to the change from parenteral to oral feeding [9]. Table 2.2 summarizes the age-dependent anatomical and physiological factors that may influence the rate and/or the extent of gastrointestinal absorption [2]. The gastric acid production is lower during infancy than in adults, and results in a higher gastric pH. Significant biochemical and physiologic changes occur in the neonatal gastrointestinal tract shortly after birth. In full-term infants, gastric acid secretion begins soon after birth and increases gradually over several hours. In preterm infants, the secretion of gastric acid occurs more slowly, with the highest concentrations appearing on the fourth day of life. Therefore, drugs that are usually partially or totally inactivated by the low pH of gastric contents should not be administered orally.

Gastric emptying time is prolonged (up to 6 or 8 h) in the first day or so after delivery, and is irregular and erratic in the first year, approaching adult patterns by 6–8 months of age. Therefore, drugs that are absorbed primarily in the stomach may be absorbed more completely than anticipated. In the case of drugs absorbed in the small intestine, therapeutic effect may be delayed. Gut motility is irregular, with a pattern of peristaltic activity different from adults [6], resulting in longer transit times before 6 months of age. Transit times range from 8 to 96 h. Small gut surface area is larger in infants and young children relative to body mass than in adults (as is BSA).

Table 2.2 Age-dependent factors affecting gastrointestinal absorption and the resultant pharmacokinetic outcomes relative to adult levels

	Newborn	Neonate (1 day to 1 month)	Infant (1 month to 2 years)
Physiological factor			
Gastric pH	Neutral → 1	>5	Adult
Gastric emptying	Reduced (variable)	Reduced (variable)	Increased
Intestinal surface area	Reduced	Reduced	Adult
Intestinal transit time	Reduced	Reduced	Increased
Pancreatic and biliary function	Very immature	Immature	Adult
Bacterial flora	Very immature	Immature	Adult
Enzyme/transporter activity	Very immature	Immature	Adult
Pharmacokinetic outcome			
Rate and extension of absorption	Variable	Variable	≥Adult
Gastrointestinal first-pass effect	Very reduced	Reduced	Approaching adult

Ileal active bile salts transport is absent at birth and develops during the first postnatal weeks, and pancreatic exocrine enzymes are less active in newborns and small infants. Human milk has been shown to have a direct impact on the development of the infant's digestive system, which equally impacts the digestion processes of its primary substrate. Intestinal permeability is increased for large molecules, such as proteins and high-molecular-weight drugs. The elimination of drugs through the first-pass effect is decreased due to decreased transporter and enzyme activity in the liver. Because of frequent feeding, and delayed emptying results in nutrients mostly being present in the stomach.

Gastrointestinal enzyme activities tend to be lower in the newborn than in the adult. Activities of α-amylase and other pancreatic enzymes in the duodenum are low in infants up to 4 months of age. Neonates also have low concentrations of bile acids and lipase, which may decrease the absorption of lipid-soluble drugs. Little information regarding the clinical effects of ontogenetic changes of cytochrome P450 enzymes and transporter proteins such as P-glycoprotein (P-gp) in the small bowel is available [16]. Reduced expression of CYP3A and P-pg in newborns and young children can result in increased bioavailability of medicines [10].

Absorption after intramuscular or subcutaneous injection depends mainly, in neonates as in adults, on the rate of blood flow to the muscle or subcutaneous area injected. Physiologic conditions that might reduce blood flow to these areas are cardiovascular shock, vasoconstriction due to sympathomimetic agents, and heart failure. However, sick preterm infants requiring intramuscular injections may have very little muscle mass. This is further complicated by diminished peripheral perfusion to these areas. In such cases, absorption becomes irregular and difficult to predict, because the drug may remain in the muscle and be absorbed more slowly than expected. If perfusion suddenly improves, there can be a sudden and unpredictable increase in the amount of drug entering the circulation, resulting in high and potentially toxic concentrations of drug. Examples of drugs especially hazardous in such situations are cardiac glycosides, aminoglycoside antibiotics, and anticonvulsants.

The skin of the full-term neonate possesses an intact barrier function and is similar to that of an older child or adolescent. However, the ratio of surface area to body weight of the full-term neonate is much higher than that of an adult (Fig. 2.2d). Thus, the infant will be exposed to a relatively greater amount of drug topically than will older infants, children, or adolescents. In contrast, data of human skin from preterm infants indicates an inverse correlation between permeability and gestational age. Permeability rates were 100- to 1,000-fold greater before 30 weeks gestation as compared with full-term neonates, with a three- to fourfold greater permeation rate seen beyond 32 weeks. In vivo studies suggest that this increased dermal permeability in preterm infants is a short-lived phenomenon with the permeability barrier of even the most premature neonates similar to that of full-term neonates by 2 weeks of postnatal life [13]. There are numerous reports in the literature underscoring the importance of skin absorption in neonates primarily showing toxicity after exposure to drugs or chemicals. Therefore, extreme caution needs to be exercised in using topical therapy in neonates and young infants. In contrast, the possibility of turning enhanced skin absorption of drugs to the infant's advantage was explored by using the percutaneous route to administer theophylline or caffeine for apnea in preterm infants [4].

2.3.2 Distribution

As body composition changes with development, the distribution volumes of drugs also change. The neonate has a higher percentage of its body weight in the form of water (70–75 %) than does the adult (50–60 %). Differences can also be observed between the full-term neonate (70 % of body weight as water) and the small preterm neonate (85 % of body weight as water). Similarly, extracellular water is 40 % of body weight in the neonate, compared with 20 % in the adult (Table 2.1, Fig. 2.4). Since many drugs are distributed throughout the extracellular water space, the size (volume) of the extracellular water compartment may be important in determining the concentration of drug at receptor sites. This is especially important for water-soluble drugs (such as aminoglycosides) [20] and less crucial for lipid-soluble agents. Preterm infants have much less fat than full-term infants [1]. Total body fat in preterm infants is about 1 % of total body weight, compared with 15 % in full-term neonates. Therefore, organs that generally accumulate high concentrations of lipid-soluble drugs in adults and older children may accumulate smaller amounts of these agents in less mature infants. Another major factor determining drug distribution is drug binding to plasma proteins. Albumin is the plasma protein with the greatest binding capacity. In general, protein binding of drugs is reduced in the neonate. This has been seen with local anesthetic drugs, diazepam, phenytoin, ampicillin, and phenobarbital. Therefore, the concentration of free (unbound) drug in plasma is increased initially. Because the free drug exerts the pharmacologic effect, this can result in greater drug effect or toxicity despite a normal or even low plasma concentration of total drug (bound plus unbound). Some drugs compete

with serum bilirubin for binding to albumin. Drugs given to a neonate with jaundice can displace bilirubin from albumin. Because of the greater permeability of the neonatal blood–brain barrier [21], substantial amounts of bilirubin may enter the brain and cause kernicterus [3]. This was in fact observed when sulfonamide antibiotics were given to preterm neonates as prophylaxis against sepsis. Conversely, as the serum bilirubin rises for physiologic reasons or because of a blood group incompatibility, bilirubin can displace a drug from albumin and substantially raise the free drug concentration. This may occur without altering the total drug concentration and would result in greater therapeutic effect or toxicity at normal concentrations.

2.3.3 Metabolism

Upon termination of umbilical blood supply, the liver in the newborn takes on many biosynthetic and detoxification functions essential for adaptation to extrauterine life. These include aerobic metabolism, gluconeogenesis, synthesis of coagulation factors, and bile production and transport. Both liver size and volume relative to total body weight body decrease during childhood (Fig. 2.5) [19]. About 80 % of drugs in clinical use undergo metabolic reactions in the body. Eighty percent of these are metabolized by cytochrome P450s (CYPs). P450 isoforms are expressed in an age-dependent manner [14].

The drug-metabolizing activities of the cytochrome P450-dependent mixed-function oxidases and the conjugating enzymes are substantially lower (50–70 % of adult values) in early neonatal life than later [2, 5]. The point in development at which enzymatic activity is maximal depends upon the specific enzyme system in question. Enzymes most commonly involved in drug metabolism are those of the cytochrome P450 (CYP) family (phase I reactions) and the uridine diphosphate glucuronosyltransferase (UGT), sulfotransferase, glutathione-S-transferase, and N-acetyltransferase (NAT) families (phase II reactions). Each of the specific isozymes within a family matures at different rates during the first several years of life. The effect on metabolism of a specific medication depends on the dominant enzymatic pathway(s) responsible for metabolism of the drug [14]. The development of the enzymes involved in human metabolism was classified by Hines [14] in three categories: (1) those expressed during all or part of the fetal period, but silenced or expressed at low levels within 1–2 years after birth; (2) those expressed at relatively constant levels throughout fetal development, but increased to some extent postnatally; and (3) those for which onset of expression can occur in the third trimester, but where a substantial increase is noted in the first 1–2 years after birth. It is for this reason that certain biotransformation pathways, including hydroxylation by the P450 mono-oxygenase system and glucuronidation, demonstrate only limited activity at birth, while other pathways, such as sulfate or glycine conjugation, appear very efficient at birth.

For some genes, such as CYP2D6, longitudinal phenotyping studies in infants and young children have demonstrated that genotype–phenotype concordance is

apparent as early as 2 weeks after birth in term infants [7]. For others, such as CYP2C19, this concordance is mostly absent during infancy, as shown for pantoprazole, and phenotype cannot be predicted from the genotyping in this case [18, 25]. Microbial colonization in newborns also begins at birth, with microbiome composition being affected by mode of delivery, breast vs. formula feeding, hospitalization, antibiotic treatment, and diet [27]. Evidence assimilated from animal studies suggests that factors such as diet also have the potential to modulate the ontogeny of drug biotransformation pathways. Prediction of drug clearance, both on a population basis and at the level of individual patients, is therefore very complex [18].

The process of maturation must be considered when administering drugs to this age group, especially in the case of drugs administered over long periods. Another consideration for the neonate is whether or not the mother was receiving drugs (e.g. phenobarbital) that can induce early maturation of fetal hepatic enzymes. In this case, the ability of the neonate to metabolize certain drugs will be greater than expected, and one may see less therapeutic effect and lower plasma drug concentrations when the usual neonatal dose is given. During toddlerhood (12–36 months), the metabolic rate of many drugs exceeds adult values, often necessitating larger doses per kilogram than later in life. Besides these intrinsic aspects that influence pharmacokinetic during the neonatal period, there are other important events such as inborn or acquired diseases, environment and finally pharmacogenetics and pharmacogenomics.

Pharmacogenetics is the study of the genetically determined variations in an individual's response to drugs. Pharmacogenomics is defined as the influence of DNA sequence variations on the effect of a drug [18]. The goal of this approach should be to identify which group of patients responds positively, which patients are non-responders, and which experience adverse reactions for the same drug and dose. Interindividual variability in response to any drug is mostly dependent on DNA sequence variations across the human genome, the haplotype map (HAPMAP). This should constitute a powerful tool in understanding genetic variants and drug responses (biomarkers). At present, there is still a significant lag between knowledge in genetics and practical application for modeling of drug profiles (molecule, dose regimen, route of administration) on the genetic/genomic profile of the individual patient. Knowledge about drug-metabolizing enzymes, transporters, and receptors and their ontogeny is limited. To develop truly individualized pharmacotherapy, future clinical trials should consider the complex system formed by genotype, pharmacodynamics, pharmacokinetic, and environmental factors.

2.3.4   Elimination

The most prominent observation is that the mass of kidney relative to age is several-fold greater in preschool-age children than in young adults (Fig. 2.4) [8]. Renal clearance is an important route of drug elimination. While during the neonatal period there is minimal glomerular filtration and active tubular secretion of drugs, there is a
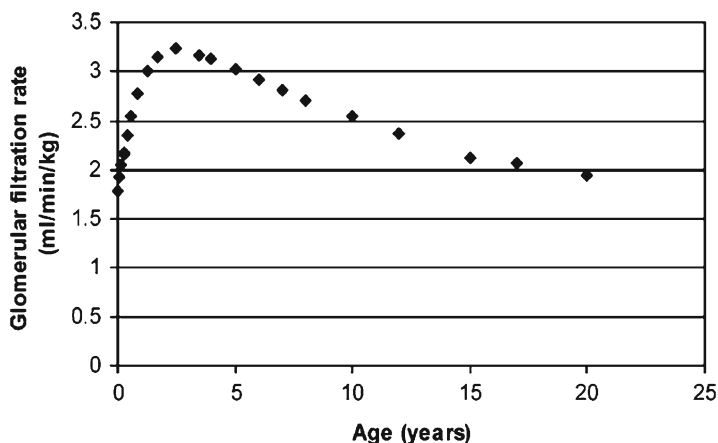
Fig. 2.7 Human GFR vs. age [8]

well-described rapid development in these processes in the post-neonatal period. The glomerular filtration rate (GFR) is much lower in newborns than in older infants, children, or adults, and this limitation persists during the first few days of life. Calculated on the basis of BSA, glomerular filtration in the neonate is only 30–40 % of the adult value. The GFR is even lower in neonates born before 34 weeks of gestation. Function improves substantially during the first week of life. At the end of the first week, the GFR and renal plasma flow have increased 50 % from the first day. By the end of the third week, glomerular filtration is 50–60 % of the adult value; by 6–12 months, it reaches adult values (per unit surface area). Therefore, drugs that depend on renal function for elimination are cleared from the body very slowly in the first weeks of life. A less appreciated fact is that during toddlerhood, there is an "overshoot" of the GFR well above the levels encountered in older children and adults, and there is an early achievement of adult levels in active drug secretion, which stays at a plateau throughout childhood and adulthood. Due to the high GFR in toddlers, dose requirements for renally excreted drugs in this age group are on a per-kilogram basis, much larger than in adults [8]. The need for higher doses of renally cleared drugs during early childhood reflects the enhanced excretory capacity of the kidney in this age group when normalized to body weight. One observes a shorter elimination half-life and faster clearance rate of renally excreted drugs than adult levels (Fig. 2.7). In contrast to animal models, the developmental changes in the human kidney are not linear processes. In particular, GFR in prepubertal children is almost twofold higher compared to adult values, as is the expression and function of the P-glycoprotein transporter. In contrast, no similar "surpass" is seen with organic anionic or cationic transport. Hence, the current adult dosing cannot simply be extrapolated to children. Instead, developmental changes must be taken into account when designing appropriate dosage regimens of renally excreted drugs for

infants and children. In particular, knowledge of the specific drug transporters involved in drug clearance is important to the therapeutic dose adjustment.

Subsequently, during toddlerhood, it exceeds adult values, often necessitating larger doses per kilogram than in adults, as described previously for drug-metabolic rate. Penicillins, for example, are cleared by preterm infants at 17 % of the adult rate based on comparable surface area and 34 % of the adult rate when adjusted for body weight. A decreased rate of renal elimination in the neonate has also been observed with aminoglycoside antibiotics (kanamycin, gentamicin, neomycin, and streptomycin). Since renal function in a sick infant may not improve at the predicted rate during the first weeks and months of life, appropriate adjustments in dosage and dosing schedules may be very difficult. In this situation, adjustments are best made on the basis of plasma drug concentrations determined at intervals throughout the course of therapy. Although great focus is naturally concentrated on the neonate, it is important to remember that toddlers may have shorter elimination half-lives of drugs than older children and adults, due probably to increased renal elimination and metabolism. For example, the dose per kilogram of digoxin is much higher in toddlers than in adults. The mechanisms for these developmental changes are still poorly understood.

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