Physiologic Changes during Growth and Development

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To express growth-related changes in physiologic or other functions in forms usable for kinetic modeling, we are interested in identifying regular relationships that take the form of simple mathematical expressions. Many anatomic and physiologic functions scale within or across species in accordance with the allometric relationship, \( y = ax^b \). These include many organ weights, the glomerular filtration rate, respiration rate, oxygen consumption, or basal metabolic rate. The allometric lines may display discontinuities in slope associated with critical growth periods such as transitions from one growth phase to another. On the other hand, many other kinetically important processes depend on the physicochemical characteristics of the agent and of the sites in the body with which it interacts. Their rates of development are determined by the age-dependence of these physicochemical characteristics and of their interactions. Examples of different types of age-dependence are given, and their combined impact on the age-dependence of lead-kinetic behavior is examined. — Environ Health Perspect 102(Suppl 11):103-106 (1994)

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McCance and Widdowson (1) discussed Minot’s (2) observation that from conception to maturity, guinea pigs grow at an average rate of 1.8 g/day, rabbits at a rate of 6.3 g/day, and humans at a rate of 6.7 g/day. Therefore, humans are bigger than rabbits because they continue to grow for a longer time, while rabbits are bigger than guinea pigs because they grow faster. These are the two basic strategies for attaining a large size: to grow fast or to grow for a long time. McCance and Widdowson classified species into three groups on the basis of their rate of growth from conception to birth (1). Interestingly, membership in these classes did not correlate with mature body size. The intermediate and best documented group included the fox, domestic cat, lion, porpoise, hippopotamus, and horse, with mature body weights ranging from about 2 kg to about 100 kg. The primates, including humans, fell into the slowly growing group. There is generally not a sharp break in growth rate at birth, so humans are also among the more slowly growing animals after birth. In fact, the human male takes 18 years to multiply his birth weight 20 times, while the rat does so in a few weeks. Humans, however, continue to grow at significant rates for as much as one-quarter of their life-span, while smaller animals tend to achieve both sexual maturity and final body size earlier relative to their total life-spans. Thus, humans use a slow but extended growth strategy to achieve adult size.

Humans and the other primates also differ from many other species in the pattern of growth from birth to maturity (1). The growth of many animals can be visualized as taking place in three phases: a fetal/neonatal/infancy phase, in some species essentially complete by birth, a juvenile phase, and an adolescent phase. In humans, the early phase extends well into childhood and the juvenile phase is replaced by a period of steady growth to adolescence. A second distinction is the timing of sexual maturity. The peak rate of growth in adolescence coincides approximately with sexual maturation in many species. This is usually well before the animal is fully grown. The female rat, for example, is sexually mature at about 30% of her mature weight and 50% of her mature length. In humans, however, sexual maturity generally does not occur until the individual has reached at least 90% of his or her adult height. Thus, human growth is characterized by a clearly defined early phase followed by a period of steady growth to adolescence continuing to achievement of adult weight.

To express growth-related changes in physiologic or other functions in forms usable for kinetic modeling, we seek regular relationships that can be expressed in reasonably simple mathematical terms. The forms these relationships take will be determined by the level of organization at which the modeling is carried out: cellular, tissue, organ system, or whole body. At the level of the whole body, we would like to be able to scale physiologic functions with either body weight or age. One class of relationships that has proven generally useful in scaling biologic measures of many kinds is the allometric relationship: \( y = ax^b \), or \( \ln(y) = \ln(a) + b \ln(x) \). The word allometric means “by a different measure” and refers to dependence of the ratio \( y/x \) on the value of \( x \). For example, the weights of most organs are allometrically related to body weight. If the fraction does not change with body size (if, for example, the weight of an organ is a constant fraction of body weight), then the exponent \( b = 1 \) and the variables are isometrically related (“by the same measure”): \( y = ax \) and \( \ln(y) = \ln(a) + \ln(x) \).

Apart from its convenience, the allometric relationship has been found to be descriptive of the way in which many anatomic and physiologic functions depend on body size either between or within species. It is important to point out that allometry is a convenient descriptive tool. It furnishes no insight into the biological basis of a relationship. While many allometric plots give straight lines or approximations to straight lines, not all do. Sometimes a log–log plot gives a smooth curve, in which case the allometric plot is not especially useful. Sometimes two or more straight line segments are indicated, which suggests a rather abrupt transition from one developmental stage to another, such as occurs at puberty. Indeed, it might be expected that rates of development of physiologic functions would display discontinuities at critical developmental times.

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such as at cessation of the rapid growth period in early childhood or at the time of maximum growth rate.

Figure 1 (3) illustrates the allometric relationship between arm length and height in humans. In the infant up to about 1 year of age, arm length increases more rapidly than height and the allometric slope is greater than 1. At later ages, arm length and height are proportional and isometry is therefore observed, with the slope of the isometric line being 1.

While the relationship of length to length is interesting, we are more frequently concerned with functions that are likely to be related to mass or surface area. In the simplest model of growth, the surface area (SA) or cross-sectional area of an immature animal whose general body shape is that of the adult of the species should scale as the square of the length (L), or height, \(SA \propto L^2\). The mass (M) scales as the cube of the height, \(M \propto L^3\), and therefore surface areas of either the whole body or of individual organs would be expected to scale as the two-thirds power of the mass, \(SAM^{2/3}\). Weights of individual organs, in this isometric model, would be directly proportional to body weight while the rates of many physiologic functions would be expected to be proportional to the two-thirds power of body weight. Sometimes certain physiologic functions are thought of as being related to body surface area, but this concept should not be over generalized.

Some functions do follow isometric principles. In the most frequently cited example of isometry, oxygen consumption or basal metabolic rate is isometrically related to body mass. Figure 2 (3) shows the basal metabolic rate of resting guinea pigs of various body sizes to be proportional to body mass to the 0.67 power. Knowing nothing about the development of specific physiologic functions or anatomic characteristics during growth we might choose to model them as isometrically related to body mass, which is the most defensible default position. However, isometry usually applies only over a limited size range, within a species, or under other special circumstances.

There are a number of reasons why isometry may not apply to rates of development of physiologic functions. Larger bodies require relatively larger bone cross-sectional areas for support than would be predicted by strict isometry, and other factors related to gravity and inertia will also increase the relative demand placed on physical support mechanisms. Surface to volume ratio, rather than absolute surface area, is an important determinant of rates of gas exchange. Competing requirements often will depend variously on surface area (diffusion, heat loss), cross-sectional area (muscle strength), or volume (body mass, buoyancy, chemical kinetic volumes of distribution).

Data for Figures 3 to 5 are taken from a monograph on growth (4) that contains compilations of information from many sources concerning the dependence of critical anatomic and physiologic measures on age or body size. In Figure 3, the dependence of liver and kidney weight on body weight in children is shown. Each data set has been fit by linear regression to give the allometric slope, which is close to 0.85 in both cases. If the principle of isometry were obeyed, the slopes of these lines would be close to 1. What the observed slope of 0.85 means is that liver and kidney are slightly larger relative to body weight in the human newborn than in the adult. Note also that kidney weight does not precisely follow the allometric line. At the time the child weighs around 7 to 8 kg or is about 1 year old, the kidney displays a rapid increase in weight, after which its weight reverts slowly to that which would be predicted from the average allometric slope.

The glomerular filtration rate (Figure 4) is not related to body weight by such a simple allometric relationship. Immediately after birth, glomerular function increases much more rapidly relative to body weight than kidney weight does. Without the data
point at birth, the allometric slope of the early portion of the glomerular filtration line would be around 1.7, about twice that for kidney weight. When the child weighs around 7 to 8 kg, the glomerular filtration rate line reverts to an allometric relationship with a slope of 0.68, about what would be expected from isometric principles alone. Thus, until the child is roughly 1 year old, kidney function as measured by glomerular filtration rate matures rapidly. From about this age on, however, the kidney is functionally mature with respect to its filtration ability and further increments in glomerular function are what would be expected based on kidney size alone.

The respiration rate (Figure 5) shows a similar kind of relationship to body weight, but the discontinuity occurs later, when the child weighs around 20 kg and is about 6 years old. Thus, respiration rate reaches adult levels (relative to body size) shortly before the child’s period of maximum growth rate begins. (The open data point shown at birth, the mean of two widely disparate measurements, is not considered to be reliable.) The allometric slope of the line from age 6 years to adulthood is 0.62, again close to the value to be expected based on isometric principles.

Many kinetically important processes are not dependent solely on passive physiologic functions like respiration or glomerular filtration but involve more complex physicochemical interactions. Examples of complex kinetic processes include glomerular filtration of an incompletely filterable or plasma protein-bound chemical, renal excretion involving active tubular secretion or reabsorption, and absorption from the gastrointestinal tract by any mechanism other than simple diffusion. Age dependence of such processes also may be expected to be chemically dependent. A good example of dependence of fractional gastrointestinal absorption on age is the behavior of lead. Table 1 gives published estimates of fractional lead absorption from the human gastrointestinal tract, showing that it is markedly higher in children than in adults. The table also illustrates the nature of the published observations on many of the more complex kinetic processes that depend on basic physiologic functions. Information, when it is available, often must be collected from a variety of sources, was obtained by different techniques, and is concentrated in one or two age ranges that have been of particular interest because of toxicity or regulatory considerations. Some of the estimates in Table 1 were obtained from balance studies and some by using lead isotopes. Some involved addition of measured quantities of lead salts to the diet, and some involved measurement of lead present in the natural diet. The results of those studies in which the subjects fasted or in which trace quantities of lead were used are not included because these studies give different (higher) fractional absorption values. The table shows that adults and a rather loosely defined group called children have been studied with little consideration given to the rate at which fractional lead absorption declines during childhood from neonatal to adult values.

The dependence on body size of two anatomic measures, liver and kidney size; two physiologic measures, respiration and glomerular filtration; and an agent-specific process, absorption of lead in the gastrointestinal tract, has been examined. It will be interesting to consider several of these together with other aspects of lead kinetics to illustrate the combined effects of a number of age-dependent factors acting together on kinetic behavior.

It is well known that in spite of the much greater fractional absorption of lead from the immature than from the mature gastrointestinal tract, comparable concentrations of lead in diet or drinking water are associated with comparable concentrations of lead in blood of children and adults. It has been suggested that growing bone acts as a “sink” for lead, but this explanation is far too simplistic by itself and a fuller explanation must lie in the balance of all of the cooperating and opposing factors controlling lead disposition in adults and children.

Table 2 gives estimated rates of selected processes of lead disposition in a 5-year-old boy and in a 40-year-old man. Both have been exposed for 2 years to lead in this simulation, without any prior background exposure. While this is not a realistic situation, it allows direct comparison of the handling of current environmental lead during the two age periods uncomplicated by consideration of any additional contribution of accumulated body (bone) lead to blood lead. The simulated lead exposure is low even by contemporary standards and consists only of lead in air, drinking water, and food. The simulation was carried out using a recently developed, physiologically based lead kinetic model (10; O’Flaherty, unpublished data) that is conceptually similar to those used for chemicals such as the volatile halogenated hydrocarbons. However, the lead model is superimposed on a standardized curve for growth of the human male from birth to maturity and
incorporates scaling as illustrated above for tissue volumes, glomerular filtration rate, and respiration rate as functions of body weight. Physiologic functions and tissue volumes are scaled isometrically with body weight when relevant measurements are not available.

Fractional absorption from the gastrointestinal tract is estimated to be about three times greater in the child at this age than in the adult. As noted above, the magnitude of fractional absorption in the child is very uncertain; the value used is no more than a reasonable guess. The efficiency of lead excretion in the child is even less certain. Reported values of plasma lead clearance in adults range from about 4 to 30% of the glomerular filtration rate (J3). Limited evidence suggests (O’Flaherty, unpublished data) that clearance of lead from the blood is only slightly lower in infants and children than in adults. Assuming that clearance actually takes place from the plasma rather than from whole blood, these observations are reconciled in the model by the assumption that all filtered lead is excreted by the child but only a fraction of the filtered lead is excreted by the adult.

Simulated blood lead concentration is low and the same in both the child and the adult. This equivalence is the outcome of a number of cooperating and opposing processes. Although fractional absorption is higher in the child, when lead intake from food and drinking water is isometrically scaled to body size using the two-third power of body weight it is seen (Table 2) that the child would absorb only about 25% more lead per day from the gastrointestinal tract than the adult. With the addition of lead entering the systemic circulation from the lung, the adult’s simulated total daily lead absorption is greater than that of the child (although the child’s total daily absorption is greater on a body weight basis). However, the child excretes lead more efficiently than the adult, so the adult is in more positive lead balance. Of the lead retained, most is accounted for by net uptake into bone. On a per unit body weight basis, the child’s bone is more active in this respect than the adult’s. Although the absolute rate of lead incorporation into bone is about twice as great in the adult as in the child, the relative rates are 6.8 μg/kg bone/day in the child and 2.4 μg/kg bone/day in the adult. Similarly, the absolute rate of return of lead to blood with resorption of bone is somewhat less than twice as great in the adult as in the child but the relative rates are 3.4 μg/kg bone/day in the child and 1.1 μg/kg bone/day in the adult. Thus, while the child’s bone does take up more lead, on a unit bone weight basis, than the adult’s, it is sufficiently more active metabolically that it also returns more lead to the blood on a unit bone weight basis. In both cases, after only 2 year’s exposure, the bone is not near a steady state and there is continuing net transfer of lead into bone. On a unit bone weight basis, the child’s net transfer rate is greater than that of the adult. Nonetheless, this process alone cannot account for the comparability of blood lead concentrations in the child and the adult. It is the combination of greater fractional gastrointestinal absorption with greater excretion and greater net transfer of lead into the child’s bone that results in comparable blood lead concentrations after 2 year’s simulated exposure.

In conclusion, we have seen that developing physiologic functions frequently display discontinuities in their rates of change. These discontinuities may be associated critical periods such as adolescence or with critical time points such as transitions from one growth phase to another. Once the individual is past adolescence or even earlier, the critical physiologic functions examined tend to scale as would be predicted by isometric theory, that is, as the two-thirds power of body weight. Many kinetically important processes, on the other hand, are not purely physiologic. Their rates of development are determined by the age dependence of physicochemical interactions between the agent and the process itself. The age dependence of overall kinetic behavior will be the outcome of the age dependence of all of the cooperating and opposing anatomic, physiologic, and chemical factors that contribute to disposition of the chemical.

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