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RELATION OF GESTATION TIME TO BRAIN WEIGHT FOR PLACENTAL MAMMALS: IMPLICATIONS FOR THE THEORY OF VERTEBRATE GROWTH*

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The great disparity of development rates among mammalian species is a problem that intersects at least three disciplines. In addition to its obvious relevance for developmental biology, it has important implications for population biology (Cole 1954) and, as will be shown, for gerontology.

Huggett and Widdas (1951) sought to develop a mathematical description of fetal growth that would unify the ontogenetic and phylogenetic aspects of mammalian development. They presented data from several species confirming the existence of a linear relation of the cube root of fetal body weight to the conception age, t, for t greater than a minimum age, t_0,

$$W^{1/3} = \alpha(t - t_0), t > t_0. \quad (1)$$

This relation is now established as the characteristic mammalian fetal growth curve.

Huggett and Widdas then extended the cube root law into the phylogenetic domain. For a number of species from several orders, they plotted the cube root of birth weight against the reduced gestation time, $t_{gj} - t_{0j}$, where t_{gj} is the gestation time from conception for the jth species and t_{0j} is an estimate, for each species, of the intercept, t_0, in equation (1), which they calculated from a relation of t_0 to t_g based on data from seven species for which the fetal growth curves had been determined. They concluded that there is a linear relation of cube root of birth weight to $t_g - t_0$ within orders and that the slope of the relation, α in equation (1), varies between orders. However, the very large differences in growth rates, α, between orders, with a range of variation in rate of mass growth on the order of 1,000, remained unexplained.

Another testable hypothesis is that the differences in fetal growth rates are due to differences in genetically determined limits on the rates of cell proliferation between species. Although this hypothesis has not been put to direct test, the assembled data on the generation cycles of mammalian

* Preliminary accounts of this work were given at meetings of the Zoological Society of London, November 1967, and of the American Society of Zoologists, Dallas, December 1968 (Sacher 1968).

cells in vivo and in vitro (Fry and Reiskin 1972) indicate that the maximum rates of somatic cell proliferation do not vary enough between species to account for the observed differences in rates of fetal mass growth.

This paper examines the hypothesis that rates of fetal growth in mammals are governed by a common limiting factor, the rate of growth of neural tissue. The investigations reported here were undertaken as part of a continuing evaluation of the role of the nervous system in mammalian development and aging (Sacher 1959, 1974). The specific hypothesis to be examined is that the gestation times of eutherian mammals depend principally on brain weight at birth. The existence of a wide range of relative brain sizes in mammals (Bonin 1937; Count 1947) suggests that the hypothesis could be tested by an investigation of the multivariate allometry relations between the reproductive and anatomical parameters of a representative set of placental mammals.

The inquiry is confined to two reproductive parameters, gestation time and litter size. These two parameters are examined in relation to neonatal and adult brain weight and body weight for 91 species. The estimation of the development times to sexual, reproductive, and physical maturity presents special problems which justify a separate investigation.

Since the model proposed by Huggett and Widdas is widely used at present, it is important to show how the model proposed here is an improvement on it. The order of presentation is, therefore, first to examine the Huggett and Widdas relation graphically in the way that they did originally, then to look at the relation of gestation time to neonatal brain weight in the same fashion, and finally to present the multivariate analysis that is the principal content of the paper.

The multivariate analysis shows that the data on mammalian gestation time are accounted for remarkably well in terms of the weight of the brain at birth; this finding is made the basis for a unified theory of fetal growth.

MATERIAL AND METHODS

Estimates of gestation times and litter sizes used here were drawn from the extensive published literature. Tabulations of Kenneth and Ritchie (1953), Asdell (1964), and the International Zoo Year Book (1959) were especially valuable and provided more than 80% of the data on gestation time and litter size. References to sources for specific taxa are given in the Appendix.

Some cervid, mustelid, and pinniped species have delayed implantation, and some microchiropterans have delayed fertilization (Asdell 1964). Data for such species are not included unless the duration of active fetal development has been experimentally determined. Species were also excluded from the analysis if they were known to be heterothermic or hypothermic during pregnancy.

Neonatal brain and body weights were measured for 39 species of mammals at Argonne National Laboratory, Brookfield Zoo, and the Zoological

Society of London in the period 1966–1970. The zoo material consisted of animals that were stillborn or that died shortly after birth. The Argonne specimens were live births from breeding populations in the laboratory. These data were combined with a number of published records and with unpublished data from sources acknowledged below.

Adult brain and body weights for most of the 91 species came from the literature and were supplemented by measurements made by the authors. There were 91 species for which these six variables were tabulated and which satisfied the other conditions listed above. The sample size is 92 because *Macaca mulatta* is represented by two independent sets of data. The values of the six original and two derived variables are listed in the Appendix, arranged taxonomically according to the classification of Simpson (1945), except that the Tupaiidae are included in the Insectivora.

The gestation time data are first examined in relation to the cube root of neonatal body and brain weight, in order to reexamine the findings of Huggett and Widdas (1951) for neonatal body weight. The remainder of the paper is concerned with a multivariate allometric analysis of the relations among the six variables. The analysis is based on four of the original variables and two derived variables. The four original variables are gestation time, T_n, litter size, N, neonatal brain weight, E_n, and neonatal body weight, S_n. The two derived variables are the *advancement factors* for brain size and body size at birth, denoted A_e and A_s, respectively, and defined by $A_e = E_n/E_a$ and $A_s = S_n/S_a$, where E_a and S_a are the adult brain and body weights for the species. The advancement factor for brain size, A_e, corresponds to the *Vermehrungsfaktor* for brain development at birth defined by Portmann (1962) and Mangold-Wirz (1966), except that their parameter is the reciprocal of that defined here. The computed values of the two derived variables are listed in the Appendix, along with data for the six original variables.

All eight variables were transformed to their common logarithms for simple and multiple linear regression analysis. This was done because of the allometric relations among these variables.

The type of placenta for each taxon is recorded in the Appendix. The classification of Grosser is used as amended by Amoroso (1952), Luckett (1969), and Wimsatt (1958). The taxa are classified into Grosser's four major groups, epitheliochorial, syndesmochorial, endotheliochorial, and haemochorial, the latter subdivided into villous haemochorial and labyrinthine haemochorial. Some orders have two types of placentation, but available information does not permit an exhaustive classification in those cases.

RESULTS

Figure 1 is a plot of the cube root of birth weight against the gestation time, in the fashion of Huggett and Widdas, from the data in the Appendix. The t_0 term in equation (1) is omitted, however, because it is numerically unimportant, it has no theoretical justification for the phylogenetic analysis, and it is for most species an estimated rather than an observed quantity. The

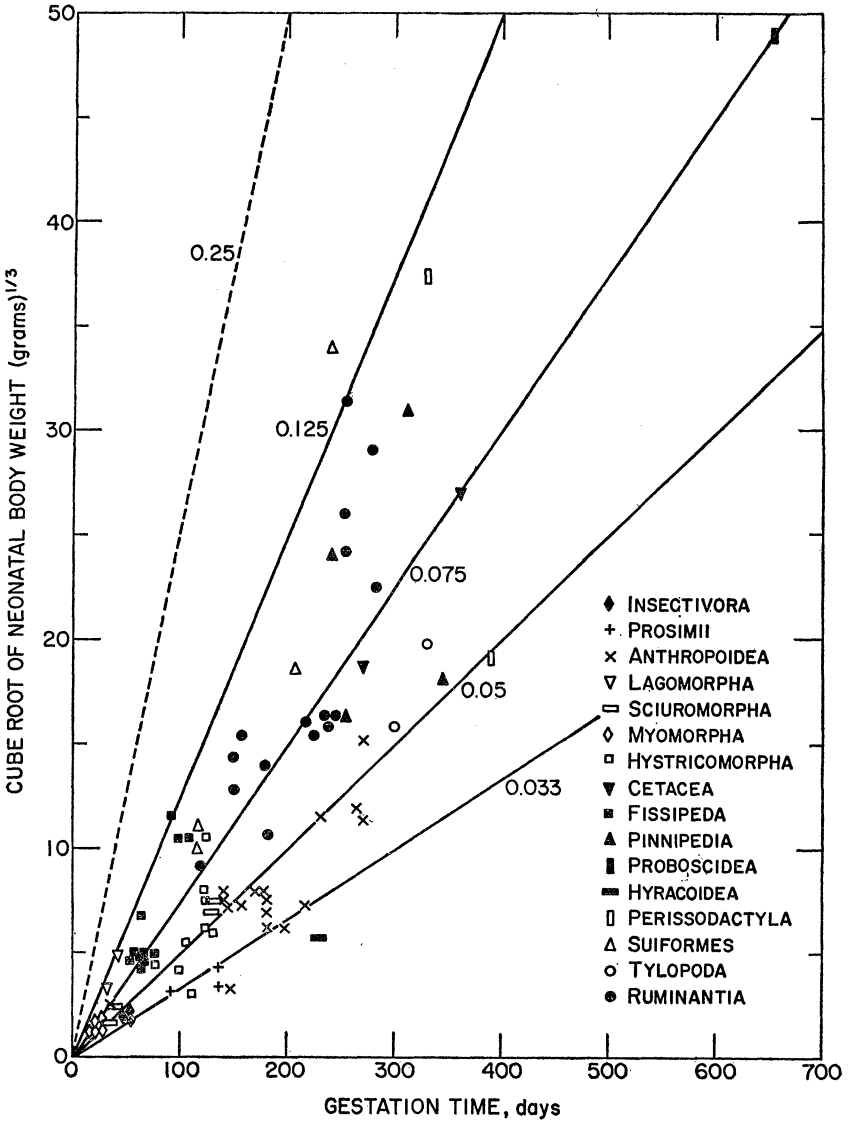

FIG. 1.—Cube root of neonatal body weight on the ordinate, against gestation time on the abscissa. Lines are drawn for visual guidance to the range of growth rates observed. Estimates for great whales are off the top of the scale and lie above the dashed line with slope 0.25.

omission has no appreciable effect on the overall pattern of the data points. The fan of lines through the origin is included as a visual aid to indicate the range of fetal growth rates seen in placental mammals. The Prosimii and some anthropoids have rates as low as 0.033 $g^{1/3}$/day, while some lagomorphs, carnivores, and ruminants have rates of 0.125 $g^{1/3}$/day. The dashed line of slope 0.25 $g^{1/3}$/day is a conservative estimate of the growth rates of the large

mysticete whales, for the blue whale, *Balaenoptera physalus,* is estimated to have a gestation time of about 11 months and a birth weight of 2,000 kg (Slijper 1961), yielding a rate of 0.40 $g^{1/3}$/day.

Figure 2 gives the relation between cube root of neonatal brain weight and gestation time for the same set of species. There is a good linear relation

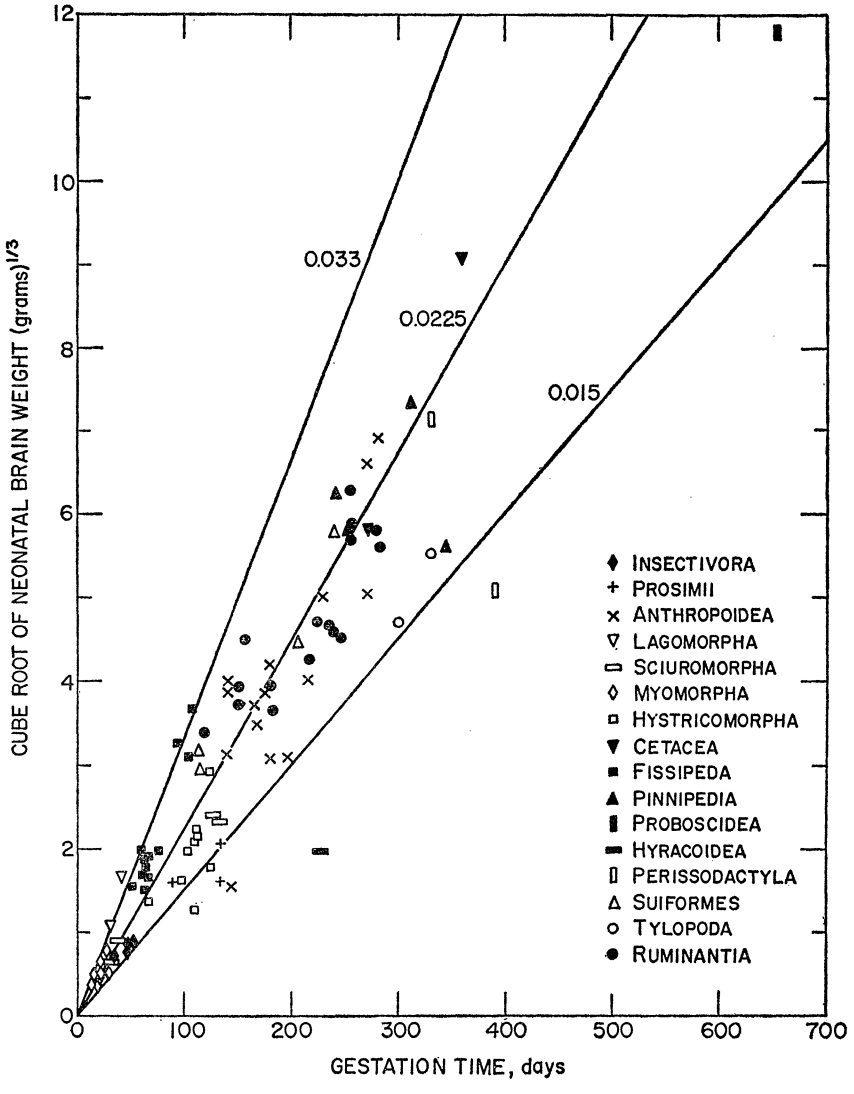

FIG. 2.—Cube root of neonatal brain weight as ordinate, against gestation time on the abscissa. Lines are drawn for visual guidance to the range of growth rates observed. The E_n values for the great whales are estimated to lie in the range 11–12.5 $g^{1/3}$, while T_n are known to range from 330 to 480 days, so great whales fall within the upper limit of brain growth rates for terrestrial mammals.

between these variables, both overall and within orders. The variability is greatly reduced in comparison to the neonatal body weight relationship, for the majority of species now lie within a twofold range of variation. Although data on the neonatal brain weights of the great whales do not exist, rough estimates can be made of the rates of fetal brain growth based on adult brain weights and on the assumption that the brain size advancement factor, A_e, is about 0.30–0.40. The rates so estimated are in the range of 0.025–0.033 $g^{1/3}$/day, i.e., within the upper limit for terrestrial mammals, so that the range of variation of linear brain growth rates for all mammals, including whales, is a factor of about 2.5, compared with a factor of about 10 for body growth. This fourfold decrease in the range of linear growth rates corresponds to a decrease on the order of 50-fold in the variation of mass growth.

Table 1 gives the slopes and intercepts of the structural linear relationships of gestation time and litter size to each of the other variables in logarithmic coordinates (Kendall and Stuart 1967; Sacher 1970). The slopes are estimates of the exponent coefficient, α, in the allometric equation $\log y = \alpha \log x + \log k$, and all but one are different from zero at a 95% confidence level. Gestation time varies as the 0.334 power of brain weight, so the plot of gestation time against cube root of neonatal brain weight in figure 2 is, fortuitously, a best-fit relationship. However, the principal axis slope for gestation time on neonatal body weight is 0.282, which is appreciably lower than the cube root of neonatal body weight used by Huggett and Widdas (1951), and is used in figure 1 to illustrate their model. Note that litter size has a negative slope with every one of the constitutional variables, while gestation time has a positive slope with all six.

Two multiple regression relations were computed in which gestation time and litter size, respectively, are examined in their dependence on the other five variables. The multiple regression relation for gestation time is given in table 2. The first column gives the coefficients of partial regression for gestation time on each variable with the other four held constant. Three partial regression coefficients, for brain weight, brain advancement, and litter size, are significant. The squared multiple correlation, R^2, which measures the fraction of the gestation time variance accounted for, is .925.

In column 1, two independent variables, neonatal body weight, S_n, and body size advancement, A_s, which make no significant contribution to the multiple regression based on all variables, were removed and the analysis was repeated with the remaining three independent variables. The result is shown in column 2. The partial regression coefficients change only slightly, but their standard errors are considerably decreased. The R^2 for the three variables is .926, so there has been no loss of precision. Dropping any of the remaining three variables results in a significant decrease in R^2.

The outcome of the multiple regression analysis, therefore, is that gestation time increases with neonatal brain size and with advancement of brain weight at birth and decreases with increase of litter size.

The multiple regression analysis for litter size is given in table 3. Only

TABLE 1

STRUCTURAL RELATIONS OF LOGARITHM OF GESTATION TIME AND LOGARITHM OF LITTER SIZE TO THE LOGARITHMS OF EACH OF THE OTHER VARIABLES (INTERCEPTS, SLOPES, AND 95% CONFIDENCE LIMITS OF SLOPES ARE RECORDED; $N = 91$)

	GESTATION TIME (DAYS)				LITTER SIZE			
	Intercept	Slope	Lower C.L.	Upper C.L.	Intercept	Slope	Lower C.L.	Upper C.L.
Gestation time, T_n	...	...	...	...	1.770	−0.739	−0.865	−0.627
Litter size, N	2.395	−1.353	−1.595	−1.156	...	...	...	...
Neonatal brain wt., E_n	1.665	0.334	0.297	0.371	0.499	−0.212	−0.307	−0.120
Neonatal body wt., S_n	1.329	0.282	0.232	0.334	0.678	−0.166	−0.284	−0.051
Adult brain wt., E_a	1.437	0.365	0.309	0.424	0.617	−0.216	−0.341	−0.097
Adult body wt., S_a	1.041	0.258	0.191	0.327	0.786	−0.136	−0.291	0.014
Brain advancement, A_e	2.914	1.652	1.289	2.187	−0.344	−1.145	−1.412	−0.934
Body advancement, A_s	6.172	3.034	*	*	−0.765	−0.751	−1.416	−0.346

NOTE.—Computed on assumption of equal sampling errors in x and y ($\lambda = 1$). Formulas from Kendall and Stuart (1967), in Argonne National Laboratory SPEAKEZ program library.

* Limits very wide, cannot be computed.

TABLE 2
PARTIAL REGRESSION COEFFICIENTS AND THEIR STANDARD ERRORS FOR THE REGRESSION OF LOGARITHM OF GESTATION TIME ON ALL OR SOME OF THE FIVE VARIABLES LISTED

	Partial Regression Coefficients (1)	(2)
Neonatal brain weight, log E_n	0.294 ± 0.054	0.274 ± 0.015
Neonatal body weight, log S_n	0.022 ± 0.039	...
Litter size, log N	−0.181 ± 0.071	−0.173 ± 0.065
Brain size advancement, log A_e	0.143 ± 0.075	0.144 ± 0.058
Body size advancement, log A_s	0.006 ± 0.050	...
Intercept, k	1.837 ± 0.066	1.853 ± 0.039
Squared multiple correlation, R^2	.925	.926
Degrees of freedom, df	86	88

NOTE.—The multiple regression in column 2 omits the variables that have nonsignificant coefficients in column 1. Calculated using descending stepwise multiple regression program written by M. Dipert, Argonne National Laboratory.

one partial regression coefficient, for the brain size advancement factor, is not significant. Neonatal brain weight, the body size advancement factor, and gestation time have negative relations to litter size, while the partial coefficient for neonatal body weight is strongly positive, although the bivariate structural coefficient for litter size on neonatal body weight (table 1) is negative.

DISCUSSION

The Relation of Birth Weight and Gestation Time Reexamined

Data in figure 1 are consistent with the conclusions of Huggett and Widdas, but relationships are weak. The trend of the data for all orders combined shows a noticeable departure from linearity, and this upward curvilinear trend would have been much stronger had we included available data on the blue whale and other large mysticetes and odontocetes (Frazer and Huggett 1973). The scatter within orders is large, so that it cannot be decided whether the trends for individual orders are linear or not, although

TABLE 3
PARTIAL REGRESSION COEFFICIENTS AND THEIR STANDARD ERRORS FOR THE REGRESSION OF LOGARITHM OF LITTER SIZE ON ALL OR SOME OF THE FIVE VARIABLES LISTED

	Partial Regression Coefficients (1)	(2)
Neonatal brain weight, log E_n	−0.262 ± 0.083	−0.281 ± 0.079
Neonatal body weight, log S_n	0.180 ± 0.053	0.194 ± 0.050
Gestation time, log T_n	−0.386 ± 0.152	−0.412 ± 0.147
Brain size advancement, log A_e	−0.084 ± 0.111	...
Body size advancement, log A_s	−0.209 ± 0.069	−0.244 ± 0.052
Intercept, k	0.349 ± 0.307	0.599 ± 0.294
Squared multiple correlation, R^2	.740	.741
Degrees of freedom, df	86	87

NOTE.—See note to table 2.

data suggest upward curvature for ruminants. This upward curvature is, however, quite evident in the data of Frazer and Huggett (1973) on the relation of body length to gestation time. They found a ninefold range of linear growth rates, from 0.3 cm/day for the smallest species, the harbor porpoise, to 2.7 cm/day for the largest, the blue whale. This trend is consistent with the curvature in terrestrial mammals (fig. 1) and is additional evidence against the conclusion of Huggett and Widdas that the linear growth rate is constant within orders. The relation of the cube root of the birth weight to the gestation time is, in fact, curvilinear within as well as between orders (Sacher, in preparation).

In short, critical reexamination of data on the relationship between gestation time and cube root of birth weight reveals a large variance of rates both between and within orders. Therefore, the mass growth of the fetus is not the controlling factor in fetal growth, and the rate-governing factor or factors must be sought elsewhere.

The Relation of Gestation Time to Cube Root of Neonatal Brain Weight

The residual variation in the plot of cube root of neonatal brain weight against gestation time (fig. 2) is comparatively small, and a considerable fraction of that residual must be attributed to the comparatively large uncertainty in the estimation of gestation times. This small residual also means that differences in growth rate of fetal brain between orders are correspondingly small.

Differences in rates of fetal body growth in figure 1 are clarified by reference to figure 2, for if rate of brain growth is nearly constant between species, as shown in figure 2, then different rates of growth of fetal body weight are inversely related to the brain/body weight ratios. This can be confirmed by inspection of figure 1, for the growth rates increase from primates to the great whales, while brain/body ratios decrease. A more detailed discussion of these relations will appear subsequently (Sacher, in preparation).

Taxonomic Patterns of Fetal Development

The advancement factor for brain growth, A_e, in the Appendix is a useful diagnostic measure, for it successfully discriminates between altricial species, whose young are extremely dependent at birth, and precocial species, whose young are born in an advanced stage of morphological and behavior maturation. The advancement factor for body growth, A_s, has no power of discrimination between altricial and precocial schedules. Evolution of mammalian gestation schedules was analyzed by Portmann (1962), who distinguished between a primitive altricial pattern (see also Hopson 1973) and an evolved precocial pattern, with intermediate grades and some secondary reversions. His paper, and one by Mangold-Wirz (1966), contains information about the advancement of the major brain regions in newborn mammals.

Typically, an entire order displays one habit or the other, but there are occasional cleavages within orders or families. The suborder Myomorpha is almost entirely altricial, while the suborder Hystricomorpha is uniformly precocial. Fissipeda are invariably altricial, whereas Pinnipedia are uniformly precocial. Change of gestation schedule can occur in a single genus, as in the cotton rat, *Sigmodon hispidus,* family Cricetidae, which has a higher A_e value than the other myomorph rodents (see Appendix). This high A_e is consonant with the ecology of the species, for its young can leave the nest at 1 week of age (Odum 1955). Brain advancement at birth differs strikingly between rabbits and hares of the family Leporidae in accord with their ecological situations.

Comparison of the placental type (Appendix) with the brain advancement factor reveals that ruminants with syndesmochorial placentas all have precocial gestation schedules, but this is the only placental type that has an invariable association with one gestation schedule. Carnivores have endotheliochorial placentation, but they include altricial fissipeds and precocial pinnipeds. The labyrinthine haemochorial placental type includes altricial groups, such as squirrels and mice, and precocial groups, such as hystricomorph rodents, and monkeys. The insectivorous bats are precocial; yet they have endotheliochorial placentas (Wimsatt 1958), as do the altricial fissipeds.

These complex relationships suggest commensurately complex evolutionary histories (Luckett 1969) and do not support any simple relation between placental type and gestation schedule. Kihlström (1972) suggested such a relationship, on the basis of some data on the relation of gestation time to maternal body weight, but he failed to include in his tabulation any of the above nonconforming groups. In short, there is no evidence that placental type plays a determinative role in the kind of gestation schedule possessed by a taxon, nor is there any indication that it has a significant influence on rate of fetal growth.

The Allometry of Gestation Time

The nature of the relationships of reproductive parameters to anatomical dimensions cannot be inferred from table 1 alone, because there are high intercorrelations among most variables. The multiple regression analyses, in tables 2 and 3, enable us to estimate the independent contribution that each anatomical variable makes toward the determination of the reproductive variable.

Figure 3 plots observed gestation time (abscissa) against the multiple regression function from column 2 of table 2, which allows us to compare prediction with observation for individual species or taxa. The standard error of estimate is 0.102 common log units, equivalent to $\pm$ 26% variation for individual estimates. The two pairs of dashed lines above and below the regression line are the 90% and 99% confidence intervals for individual observations. The distribution of discrepancies is positively skewed, for only

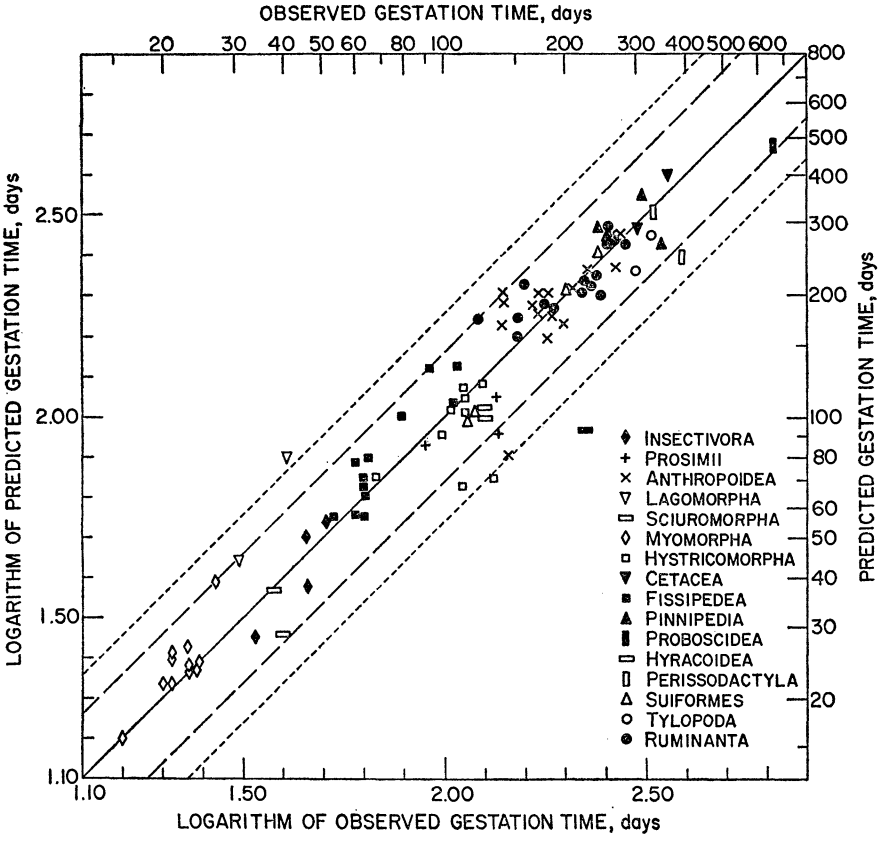

FIG. 3.—Plot of observed gestation time as abscissa, against the gestation time predicted by the multivariate relation. The prediction line has unit slope. Dashed lines above and below prediction line are the 90% and 99% confidence limits for single observations.

two of 92 cases lie below the 90% confidence limit on the short side, whereas six lie above the 90% limit on the long side. Gestation time therefore appears to be prolonged by various influences, but it cannot be shortened to any considerable extent. However, the exceptionally short gestation time for the hare should be noted.

Dependence of gestation time on maternal body temperature and metabolic rate has not yet been examined, but such dependence probably exists. A few species, such as denning boreal bears and hibernating insectivorous bats (Appendix), were excluded from the analysis because of their known departures from homoiothermy, but even within the remaining sample of presumed homoiotherms there is significant variance of temperature and metabolic rate (Altman and Dittmer 1968), which undoubtedly contributes to the residual variance of gestation times in figure 3.

A few species with inordinately long gestation times remain that cannot be explained in terms of hypothermia or delayed implantation. One is the

Cape hyrax, *Procavia capensis,* and another is the Indian tapir, *Tapirus indicus.* Both forms are extremely precocial, but other precocial groups, such as the Ruminantia, bear young at comparable degrees of behavioral and neuroanatomical advancement without unduly long gestation times.

The multivariate analysis confirms the inference, drawn from the properties of figures 1 and 2, that brain growth is the major determinant of the duration of gestation. Brain weight at birth, E_n, is by far the most important factor, but advancement of brain growth, A_e, is a significant secondary factor which explains, in part, the longer gestation times of the precocial taxa relative to altricial taxa with about equal brain weight at birth. Longer gestation times of the precocial hystricomorph rodents relative to the altricial fissiped carnivores are not entirely accounted for by differences in their A_e and litter size terms (fig. 3); but the remaining discrepancy may be due to a difference in metabolic rates between carnivores and hystricomorph rodents, for one hystricomorph rodent, the chinchilla, has a metabolic rate lower than the norm for mammals of its body size (Drozd and Gorecki 1967).

Gestation times of the great apes (Carmichael 1967), which seem to be inordinately long in relation to their small body sizes at birth, become more reasonable when the pongid pattern of neonatal brain weight and brain advancement (Appendix) is taken into account (Sacher 1974).

Implications for the Theory of Vertebrate Growth

Gestation times of homoiothermic placental mammals are accounted for remarkably well in terms of brain weight at birth. This finding provides a basis for a general phenomenological theory of mammalian growth. The essence of the theory is contained in three hypotheses: (1) the brain is the slowest-growing organ in the mammal; (2) the brain is, furthermore, the pacemaker for growth of all other somatic tissues, which are constrained to grow at its pace; and (3) brain growth proceeds at the maximum rate allowed by its nutrition and its intrinsic growth laws, and if nutrition is not rate limiting, then growth of all mammalian brains is governed by a general law leading to a single functional relation among attained size, advancement, and time. We call this the minimax growth theory because of the two extremum properties of brain growth that it introduces. Detailed discussion of the theory is deferred to a future paper which will examine some additional aspects of fetal and early postnatal growth in mammals.

Although the phenomenological minimax theory has a number of testable implications, these implications do not bear directly on the mechanisms involved. Additional hypotheses are required to specify the nature of the limitation on rate of brain growth and the nature of the growth inhibition exercised over other fetal tissues.

Two general hypotheses about the nature of the rate-limiting factor for brain growth can be distinguished: the trophic and the informational. If there is a systemic trophic limitation on fetal brain growth, it presumably must arise from the relation of the fetus, or fetuses, to the dam and be

mediated by the rate of nutrient transfer across the placenta. Zamenhof et al. (1972) show that brain weight of the fetal rabbit at term is correlated with placenta weight and that surgical removal of some fetuses in the rat results in higher brain DNA and cell number at birth in the remaining ones. These results are interesting but do not have any implication about the existence of a trophic limit on the rate of brain growth across orders of mammals.

Another possible trophic mechanism for the rate limitation arises from the consideration that the brain consists in great part of axons and dendrites, which presumably elongate at a nearly constant rate. This constant rate of elongation is perhaps the basis for the cube root kinetics of the growth of brain mass, because the cube root of the mass is proportional to length. The metabolism of axons is supported by axoplasmic flow from the cell body; Weiss (1968*a*) and his colleagues show that this flow advances at the rate of a few millimeters a day. The mean linear growth of the brain is about 0.23 mm/day (fig. 2), but elongation of axons in the spinal tracts must proceed at as much as 10 times this rate.

The alternative hypothesis about the nature of growth limitation is that it arises from an essential molecular-genetic constraint on the rate at which morphological specificity, or information, can be generated. An upper limit on the rate at which genetic instructions for development can be read out would certainly be manifest in brain development because of the unique complexity and specificity of brain structure. Weiss (1968*b*) describes and analyzes brain development and gives a good basis for an information-theoretic analysis of brain growth. For the moment, we can only say that it seems intuitively plausible that growth of all mammalian brains will proceed at or near the maximum rate of information flow, if such a maximum exists, because under these conditions reproductive efficiency is maximal and natural selection will maintain the extreme condition in each species as part of the maximization of its reproductive fitness. When temperature is nearly constant and nutrition is not limiting, this hypothesis can account for the major facts of mammalian brain growth adduced here.

Even if brain growth is the rate-limiting process in organismic growth, the actual information-limited process may not be the growth of anatomical order within the brain but, rather, the ramification of a set of regulator molecules that control the growth of the whole organism, including the brain. Burnet (1971) speculates that regulation of morphogenesis may be accomplished by a kind of specific interaction between tissues with properties of antigen-antibody reactions. Weiss and Kavanau (1957) earlier developed a mathematical theory of growth based on a formally equivalent postulate of templates and antitemplates. With the new conception of fetal growth provided by the present study, it may be possible to arrive at experimental conditions that will allow a decision about the locus of the ultimate rate-controlling process in organismic growth.

If the developing brain indeed exercises inhibitory control over other tissues, understanding the mechanism becomes a high-priority matter. Evidence for such inhibitory control was reported by Orts-Llorca (1965), who

ablated the brain tissue from one- to seven-somite chick embryos and observed them at the 14- to 20-somite stage. In the absence of the brain, the heart grew to much greater than normal size. This result suggests that control of early fetal growth could be achieved in part by specific regulation of growth of the heart and vascular system; regulation of the growth of this system would, by the resultant control of nutrient flow, serve as a pacemaker for the growth of the entire fetus.

Evidence for the existence of chalones, tissue-specific mitotic inhibitors (Bullough 1971), makes a generalized chalone model attractive as a mechanism of growth limitation. Chalone research has up to now been confined to the self-regulation of adult proliferative tissues, but there is no reason why similar molecular mechanisms of growth control cannot apply to regulations between tissues and to developing as well as adult organisms.

Implications for Population Biology and Gerontology

Identification of factors governing gestation time clarifies a basic issue in mammalian population biology, for it provides well-defined rules about the possible extent and direction of modification of gestation time under selective forces. The evidence strongly suggests that genomes of Recent mammals have little or no potential for speeding up the fetal growth rate so as to deliver, in a reduced period of time, a newborn of a given neurobehavioral advancement. Laws (1961; but see also Frazer and Hugget 1973) suggests that this may occur in the fetal growth of the large mysticete whales. However, his data bear only on accelerated body growth, and there is no indication that brain growth in the fetal mysticete whales is accelerated above the characteristic mammalian rate.

The disadvantage of a reduced rate of fetal growth in homoiotherms must be severe, for in the ecological situations that require postponement of birth, this requirement is almost always met by means of delayed implantation or delayed fertilization. It can be inferred that reduced growth rate is not resorted to because it is a suboptimal method for achieving delay of birth.

Although fetal growth rate can be modified only within narrow limits, the gestation schedule can be modified to alter neurobehavioral advancement at birth, and hence gestation time. Such changes apparently can evolve rapidly, as instanced by the precocial genus *Sigmodon* within the altricial tribe Hesperomyini, and by the marked shift toward altriciality within the brief course of hominid evolution (Sacher 1974).

The incentive for this study arose out of a problem in comparative gerontology. Sacher (1959, 1974) found that life spans of mammalian species are directly related to brain weight. One question raised by this finding is whether those species with larger brains must necessarily live longer because of the need to compensate, by means of a longer reproductive period, for the decreased reproductive rate imposed by the larger brain. The answer to this question is now seen to be affirmative, for a larger fetal brain entails a longer gestation time (table 2) and a decreased litter size (table 3), and

these effects contribute to a reduction of reproductive rate. This relation of reproductive span to brain size raises a fundamental question for gerobiology: does the brain, which by its size determines the reproductive span and life span required for reproductive success, also contribute to securing the requisite length of life by a commensurate stabilization of the internal milieu? Although the answer still eludes us, continued analysis of the relation of development and aging to brain structure may eventually point to the solution.

SUMMARY

Duration of gestation in homoiothermic placental mammals has a much more precise allometric relation to neonatal brain size than to neonatal body size or any of three other neonatal or maternal dimensions. This was shown by a multivariate analysis of data on gestation time, neonatal and adult brain and body weight, and litter size for 91 species. These results can be explained by a theory of kinetics of fetal growth based on three hypotheses: (1) the brain is the slowest-growing organ in the fetal mammal; (2) it is also the pacemaker for growth of other tissues, which are held to its rate of growth; and (3) brain growth proceeds at the maximum rate allowed by its intrinsic growth law, so that the growth of all mammalian brains is governed in great degree by a single functional relation of attained size and time. The invariant rate constant for mammalian brain growth could be due to nutritional limitations or to the existence of an upper limit on rate of information flow during development.

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APPENDIX

Gestation times, litter sizes, neonatal and adult brain and body weights, and advancement factors for brain and body growth at birth, arranged by orders and suborders, are given in the Appendix table. Placental type is in parentheses following the taxon. Gestation times are in days. All weights are in grams. Data on neonatal brain and body weight are given for 105 species. Of these, 13 species are excluded from the statistical analysis because of missing data or for reasons given in the text. These are identified by an asterisk after the species name. Numbered references in the right-hand column are to sources of neonatal brain and body weights. In the citations below, "p.c." means private communication and "auth." refers to measurements by the authors, sometimes with the name of a cooperating individual or institution. References: (1) Shield, p.c.; (2) Mangold-Wirz (1966); (3) auth.; (4) auth., London Zoo; (5) Welker, p.c.; (6) Warncke (1908); (7) Leutenegger (1970); (8) Crile and Quiring (1940); (9) Schultz (1941); (10) Kerr et al. (1969); (11) (citation missing); (12) Kennard and Willner (1941); (13) auth., Brookfield Zoo; (14) Crisp (1865); (15) Schultz (1944); (16) Schultz (1965); (17) Coppoletta and Wolbach (1933); (18) Storrs and Williams (1968); (19) Anthony (1928); (20) King (1965); (21) Müller et al. (1969); (22) Friedenthal (1910); (23) Dobbing and Sands (1970); (24) Pilleri (1959); (25) Rowlands, p.c.; (26) auth., Perrin; (27) Lilly (1967); (28) Andersen, p.c.; (29) Ziehen (1901); (30) Scheffer (1960); (31) auth., San Diego Museum; (32) Øritsland, p.c.; (33) Elsner, p.c.; (34) Laws, p.c.; (35) Fox (1923); (36) Hrdlicka (1905); (37) Treus and Kravchenko (1968).

Gestation times and litter sizes come from the following sources: all orders, Kenneth and Ritchie (1953), International Zoo Yearbook (1959), Asdell (1964); primates, Napier and Napier (1967); Prosimii, Petter-Rousseaux (1962), Manley (1967); *Macaca mulatta,* Kerr et al. (1969); *Gerbillus,* Heyder (1968); *Myoprocta,* Kleiman (1970); *Chinchilla,* Weir (1970); *Myocastor,* Newson (1966); Pinnipedia, King (1964).

APPENDIX TABLE

SPECIES	GEST. TIME	LITTER SIZE	-NEONATAL- BRAIN WEIGHT	-NEONATAL- BODY WEIGHT	-ADULT- BRAIN WEIGHT	-ADULT- BODY WEIGHT	-ADVANCEMENT- BRAIN	-ADVANCEMENT- BODY	REFERENCE NUMBERS	
MARSUPIALIA										
SETONIX BRACHYURUS *	26.	1.0	0.023	0.38	17.50	3500.0	0.0013	0.0001	1	
INSECTIVORA (VILLOUS HAEMOCHORIAL, ENDOTHELIOCHORIAL)										
ERINACEUS EUROPAEUS	34.	4.6	0.313	13.90	3.50	928.0	0.0894	0.0150	2	
TUPAIA GLIS	46.	3.0	0.530	9.20	3.15	150.0	0.1683	0.0613	3	
ELEPHANTULUS INTUFI	51.	1.5	0.673	10.50	1.14	49.0	0.5904	0.2143	4	
ELEPHANTULUS MYURUS	46.	1.5	0.580	9.00	1.37	64.0	0.4234	0.1406	4	
CHIROPTERA (ENDOTHELIOCHORIAL)										
PLECOTUS AURITUS *		1.0	0.098	1.42	0.23	8.0	0.4261	0.1775	4	
PRIMATES - PROSIMII (EPITHELIOCHORIAL, LABYRINTHINE HAEMOCHORIAL)										
LEMUR CATTA	135.	1.0	8.780	78.00	22.00	2100.0	0.3991	0.0371	4	
NYCTICEBUS COUCANG	90.	1.2	4.000	30.50	12.80	1230.0	0.3125	0.0248	5	
GALAGO CRASSICAUDATUS	135.	1.0	4.000	40.00	9.90	700.0	0.4040	0.0571	6	
PRIMATES - ANTHROPOIDEA (LABYRINTHINE HAEMOCHORIAL, VILLOUS HAEMOCHORIAL)										
ALOUATTA PALIATTA	139.	1.0	30.800	440.00	54.00	7670.0	0.5704	0.0574	7	
CEBUS CAPUCINUS	180.	1.0	29.000	250.00	73.00	3700.0	0.3973	0.0676	7	
ATELES DARIENSIS	140.	1.0	58.000	407.00	114.00	9100.0	0.5088	0.0447	8	
ATELES GEOFFROYI	140.	1.0	64.000	512.00	109.00	7640.0	0.5872	0.0670	9	
HAPALE LEUCOCEPHALA	145.	2.0	3.700	35.30	7.80	220.0	0.4744	0.1605	4	
MACACA MULATTA	175.	1.0	58.000	540.00	84.60	5980.0	0.6856	0.0903	10	
MACACA MULATTA	165.	1.0	51.500	394.00	107.00	8700.0	0.4813	0.0453	9	
MACACA MAURUS *		1.0	32.000	390.00	72.00	7400.0	0.4444	0.0527	19	2
PAPIO HAMADRYAS	180.	1.0	75.000	443.00	183.00	20700.0	0.4098	0.0214	12	2
PAPIO PAPIO	180.	1.0	53.000	335.00	179.00	32000.0	0.2961	0.0105	13	
CERCOPITHECUS PYGERYTHRUS	195.	1.0	33.500	227.00	67.00	4600.0	0.5000	0.0493	14	
PRESBYTIS OBSCURUS	168.	1.0	43.000	514.00	65.50	5800.0	0.6565	0.0886	11	
COLOBUS POLYKOMOS *		1.0	38.000	340.00	96.00	6800.0	0.3958	0.0500	13	
HYLOBATES LAR	210.	1.0	65.000	400.00	102.00	5500.0	0.6373	0.0727	15	
PONGO PIGMAEUS	270.	1.0	129.000	1500.00	343.00	36900.0	0.3761	0.0407	9	
PAN TROGLODYTES	230.	1.0	128.000	1560.00	360.00	45000.0	0.3556	0.0347	9	
GORILLA GORILLA	265.	1.0	227.000	1750.00	406.00	140000.0	0.5591	0.0125	16	
HOMO SAPIENS,	270.	1.0	335.000	3660.00	1300.00	65000.0	0.2577	0.0563	17	

APPENDIX TABLE—Continued

SPECIES	GEST. TIME	LITTER SIZE	-NEONATAL- BRAIN WEIGHT	-NEONATAL- BODY WEIGHT	-ADULT- BRAIN WEIGHT	-ADULT- BODY WEIGHT	-ADVANCEMENT- BRAIN	-ADVANCEMENT- BODY	REFERENCE NUMBERS
EDENTATA (VILLOUS HAEMOCHORIAL)									
DASYPUS NOVEMCINCTUS *	120.	4.0	3.500	80.00	12.00	3700.0	0.2917	0.0216	18
LAGOMORPHA (LABYRINTHINE HAEMOCHORIAL)									
ORYCTOLAGUS CUNICULUS	31.	5.0	1.290	38.00	9.60	2200.0	0.1344	0.0173	19
LEPUS EUROPAEUS	41.	2.5	4.490	123.00	13.30	2850.0	0.3376	0.0432	2
RODENTIA - SCIUROMORPHA (LABYRINTHINE HAEMOCHORIAL, VILLOUS HAEMOCHORIAL)									
SCIURUS VULGARIS	38.	3.0	0.623	11.50	6.23	327.0	0.1000	0.0352	2
GLAUCOMYS VOLANS	40.	3.1	0.234	3.80	1.89	52.0	0.1238	0.0731	3
CASTOR CANADENSIS	128.	2.9	13.900	472.00	40.00	20000.0	0.3475	0.0236	5
CASTOR FIBER	128.	4.0	13.800	340.00	45.00	25000.0	0.3067	0.0136	2
RODENTIA - MYOMORPHA (LABYRINTHINE HAEMOCHORIAL)									
PEROMYSCUS GOSSYPINUS	23.	3.7	0.149	2.45	0.68	27.2	0.2191	0.0901	3
PEROMYSCUS LEUCOPUS	23.	5.0	0.113	2.27	0.63	25.5	0.1794	0.0890	3
PEROMYSCUS MANICULATUS BAIRDII	24.	5.0	0.111	1.86	0.52	17.2	0.2143	0.1081	20
PEROMYSCUS MANICULATUS GAMBELI	24.	5.0	0.126	1.98	0.69	24.0	0.1826	0.0825	20
CRICETULUS GRISEUS	21.	4.6	0.097	1.85	0.67	36.0	0.1448	0.0514	3
MESOCRICETUS AURATUS	16.	6.3	0.060	1.80	1.12	125.0	0.0536	0.0144	3
GERBILLUS PYRAMIDUM	21.	4.0	0.144	2.60	1.04	65.0	0.1385	0.0400	21
RATTUS NATALENSIS	23.	7.3	0.140	2.77	0.72	50.0	0.1944	0.0554	3
RATTUS NORVEGICUS	21.	8.0	0.280	4.92	2.38	339.0	0.1176	0.0145	19
MUS MUSCULUS	19.	5.0	0.090	1.50	0.45	24.0	0.2000	0.0625	22
NOTOMYS ALEXIS *		4.0	0.171	2.15					3
SIGMODON HISPIDUS	27.	5.6	0.510	7.20	1.18	148.0	0.4322	0.0486	3
RODENTIA - HYSTRICOMORPHA (LABYRINTHINE HAEMOCHORIAL)									
HYSTRIX CRISTATA	112.	1.2	11.300	530.00	37.00	11300.0	0.3054	0.0469	19
HYSTRIX HYBRID	112.	1.2	9.200	238.00	37.00	13500.0	0.2486	0.0176	4
ERETHIZON DORSATUM	113.	1.0	10.000	480.00	24.00	6640.0	0.4167	0.0723	4
CAVIA PORCELLUS	67.	2.6	2.520	97.00	4.28	971.0	0.5888	0.0999	23
HYDROCHOERUS HYDROCHAERIS	123.	3.0	24.800	1200.00	76.00	29500.0	0.3263	0.0407	2
DASYPROCTA AGUTI	104.	1.3	7.730	165.00	20.30	2800.0	0.3808	0.0589	24
MYOPROCTA PRATTI	98.	1.2	4.200	72.00	9.90	780.0	0.4242	0.0923	25
CHINCHILLA LANIGER	110.	2.0	2.030	28.00	5.25	432.0	0.3867	0.0648	3

APPENDIX TABLE—Continued

SPECIES	GEST. TIME	LITTER SIZE	-NEONATAL- BRAIN WEIGHT	-NEONATAL- BODY WEIGHT	-ADULT- BRAIN WEIGHT	-ADULT- BODY WEIGHT	-ADVANCEMENT- BRAIN	-ADVANCEMENT- BODY	REFERENCE NUMBERS
RODENTIA - HYSTRICOMORPHA (LABYRINTHINE HAEMOCHORIAL)									
MYOCASTOR COYPUS	132.	5.5	5.710	230.00	23.00	5000.0	0.2483	0.0460	25
CETACEA (EPITHELIOCHORIAL)									
STENELLA GRAFFMANNI *		1.0	313.000	5350.00	780.00	77000.0	0.4013	0.0695	26
TURSIOPS TRUNCATUS	360.	1.0	770.000	20000.00	1600.00	155000.0	0.4812	0.1290	27
PHOCAENA PHOCOENA	270.	1.0	199.000	6750.00	537.00	55500.0	0.3706	0.1216	19
CARNIVORA - FISSIPEDA (ENDOTHELIOCHORIAL)									
CANIS FAMILIARIS (BEAGLE)	63.	4.0	6.800	312.00	70.20	8480.0	0.0969	0.0368	28
CANIS FAMILIARIS HALLSTROMI *		4.0	5.050	111.00					13
VULPES VULPES	52.	4.0	3.820	105.00	48.00	6000.0	0.0796	0.0175	2
UROCYON LITTORALIS	63.	3.7	3.410	77.10	37.30	3760.0	0.0914	0.0205	13
OTOCYON MEGALOTIS	65.	4.0	7.110	123.00	28.50	3200.0	0.2495	0.0384	13
URSUS ARCTOS *	219.	2.3	7.000	361.00	400.00	245000.0	0.0175	0.0015	19
THALARCTOS MARITIMUS *	240.	1.8	11.100	590.00	500.00	250000.0	0.0222	0.0024	2
PROCYON LOTOR	63.	3.5	4.800	98.00	41.60	5270.0	0.1154	0.0186	19
POTOS FLAVUS	77.	1.1	7.730	117.00	31.20	1970.0	0.2478	0.0594	13
TAXIDEA TAXUS	60.	2.2	3.340	116.00	53.00	6000.0	0.0630	0.0193	5
FELIS CATUS (DOMESTIC)	63.	4.0	5.600	114.00	28.40	2500.0	0.1972	0.0456	19 29
LYNX CANADENSIS	60.	2.5	7.750	138.00	75.00	12000.0	0.1033	0.0115	13
PANTHERA PARDUS	92.	2.5	35.300	1570.00	157.00	46300.0	0.2248	0.0339	6
PANTHERA LEO	108.	3.0	49.500	1300.00	260.00	175000.0	0.1904	0.0074	6
PANTHERA TIGRIS	104.	3.0	30.000	1300.00	302.00	209000.0	0.0993	0.0062	6
CARNIVORA - PINNIPEDIA (ENDOTHELIOCHORIAL)									
CALLORHINUS URSINUS	254.	1.0	198.000	4410.00	355.00	250000.0	0.5577	0.0176	30
ZALOPHUS CALIFORNIANUS	343.	1.0	180.000	6000.00	363.00	100000.0	0.4959	0.0600	31
PAGOPHILUS GROENLANDICUS	240.	1.0	243.000	14000.00	442.00	107000.0	0.5498	0.1308	32
LEPTONYCHOTES WEDDELLI	310.	1.0	400.000	30000.00	550.00	400000.0	0.7273	0.0750	33
CYSTOPHORA CRISTATA *		1.0	250.000	20000.00					32
PROBOSCIDEA (ENDOTHELIOCHORIAL)									
LOXODONTA AFRICANA	655.	1.0	1650.000	120000.00	4480.00	2750000.0	0.3683	0.0436	34
HYRACOIDEA (LABYRINTHINE HAEMOCHORIAL)									
PROCAVIA CAPENSIS	225.	2.4	7.750	200.00	20.50	3800.0	0.3780	0.0526	2

APPENDIX TABLE—Continued

SPECIES	GEST. TIME	LITTER SIZE	-NEONATAL- BRAIN WEIGHT	-NEONATAL- BODY WEIGHT	-ADULT- BRAIN WEIGHT	-ADULT- BODY WEIGHT	-ADVANCEMENT- BRAIN	-ADVANCEMENT- BODY	REFERENCE NUMBERS
PERISSODACTYLA (EPITHELIOCHORIAL)									
EQUUS CABALLUS	330.	1.0	368.000	53000.00	712.00	484000.0	0.5169	0.1095	8
TAPIRUS INDICUS	390.	1.0	131.000	7000.00	250.00	225000.0	0.5240	0.0311	2
ARTIODACTYLA - SUIFORMES (EPITHELIOCHORIAL)									
SUS SCROFA (WILD)	120.	4.0	26.600	1030.00	185.00	147000.0	0.1438	0.0070	4
SUS SCROFA (DOM.)	115.	8.0	30.000	1400.00	180.00	192000.0	0.1667	0.0073	8 19
HIPPOPOTAMUS AMPHIBIUS	240.	1.0	195.000	40000.00	590.00	1400000.0	0.3305	0.0286	35
CHOEROPSIS LIBERIENSIS	205.	1.0	90.000	6600.00	260.00	150000.0	0.3462	0.0440	13
ARTIODACTYLA - TYLOPODA (EPITHELIOCHORIAL)									
LAMA GLAMA	330.	1.0	170.000	8000.00	225.00	93000.0	0.7556	0.0860	6
VICUGNA VICUGNA	300.	1.1	104.000	4000.00	198.00	45000.0	0.5253	0.0889	25
ARTIODACTYLA - RUMINANTIA (EPITHELIOCHORIAL, SYNDESMOCHORIAL)									
MUNTIACUS MUNTJAC	183.	1.1	50.000	1240.00	124.00	16000.0	0.4032	0.0775	2
DAMA DAMA	240.	1.0	97.300	4080.00	223.00	80000.0	0.4363	0.0510	2
AXIS AXIS	218.	1.0	78.600	4170.00	219.00	88500.0	0.3589	0.0471	13
CERVUS CANADENSIS	255.	1.0	203.000	14300.00	435.00	200000.0	0.4667	0.0715	8 36
CERVUS ELAPHUS	235.	1.0	103.000	4440.00	365.00	117000.0	0.2822	0.0379	19
CERVUS UNICOLOR	246.	1.1	96.000	4440.00	383.00	116000.0	0.2507	0.0383	11
ELAPHURUS DAVIDIANUS *	284.	1.0	177.000	11500.00					25
RANGIFER TARANDUS	225.	1.0	105.000	3760.00	288.00	105000.0	0.3646	0.0358	2
TAUROTRAGUS ORYX	255.	1.0	252.000	31500.00	480.00	560000.0	0.5250	0.0562	37
BOS GRUNNIENS	255.	1.0	187.000	18000.00	334.00	250000.0	0.5599	0.0720	25 4
BOS TAURUS	280.	1.0	199.000	25000.00	456.00	520000.0	0.4364	0.0481	8
CEPHALOPHUS DORSALIS	120.	1.0	39.100	790.00	93.00	13000.0	0.4204	0.0608	13
ANTILOPE CERVICAPRA	180.	1.0	62.000	2740.00	200.00	38500.0	0.3100	0.0712	25
AMMOTRAGUS LERVIA	158.	1.2	92.000	3730.00	210.00	66000.0	0.4381	0.0565	19
OVIS ARIES	150.	2.4	52.000	3000.00	125.00	48800.0	0.4160	0.0615	8 19
OVIS DALLI *		1.0	92.500	3220.00					13
CAPRA HIRCUS	151.	2.0	61.200	2180.00	106.00	30000.0	0.5774	0.0727	6

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