VOLUME 58, NO. 4 THE QUARTERLY REVIEW OF BIOLOGY DECEMBER 1983

THE QUARTERLY REVIEW of BIOLOGY

ENERGY METABOLISM, BRAIN SIZE AND LONGEVITY IN MAMMALS

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ABSTRACT

The mathematical relations between basal energy metabolism, brain size, and life span in mammals have been investigated. The evolutionary level of brain development, or encephalization (c), is a function both of brain weight (E) *and of body weight* (P) *according to*

$$c = E/P^{0.732}.$$

Brain weight was found to be a linear function of the product of encephalization and basal metabolic rate.

The oxygen consumption of the brain (M_{brain}) *is proportional to both encephalization and body weight according to*

$$M_{brain} \propto cP^{0.59}.$$

The ratio of metabolic rate in the cerebral cortex to that in the brain as a whole depends solely upon the degree of encephalization and is independent of the size of the animal.

The maximum potential life span of a mammal was found to be proportional to the product of its degree of encephalization and the reciprocal of its metabolic rate per unit weight.

Life span may be regarded as the algebraic sum of two components: (1) a deduced somatic component (L_b) *inversely related to the basal metabolic rate per unit weight, and (2) an encephalization component* (L_e) *related directly to the evolutionary increase of relative brain size.*

INTRODUCTION

QUANTITATIVE relations in comparative biology between parameters of different nature (such as morphological or physiological) can generally be described by means of an allometric equation of the form:

$$y = ax^{\alpha} \quad (1)$$

where x and y are the variables, coefficient α is the slope (i.e., major axis) in the logarithmic transformation, and log a is the y-intercept (Huxley, 1932; Kermack and Haldane, 1950; Gould, 1971). This singular power function has been shown to be an important descriptive tool for examining the fundamental relations among organ weights, organ functions, and the size of the organism (e.g., Bertalanffy, 1957; Kleiber, 1961; Stahl, 1965; Jerison, 1973; Günther, 1975).

One of the functions that has been statistically well established in physiology is the basal metabolic rate of mammals, in which the oxygen consumption or heat production of an animal per unit time is proportional to the 3/4 power of body weight (Brody, 1945; Kleiber, 1961). The wide range of body sizes for which the relation holds true along with the high correlation between the parameters ($p > 0.98$) suggests that a basic biological principle underlies this relationship.

Metabolic rate, however, is only one example of a large number of parameters that have been examined in relation to body weight. Another variable is brain weight in mammals, which is generally assumed to scale to body weight according to the 2/3 power (Von Bonin, 1937; Jerison, 1970; Gould, 1975). Recently, however, higher values for this exponent were derived, based upon larger samples that were equally distributed among the mammalian orders and upon more adequate statistical techniques than were used in previous studies (Bauchot, 1978; Martin, 1981; Hofman, 1982a). It has been found that in mammals brain weight is correlated with body weight according to an exponential value of approximately 0.73. This revision of the exponent in the brain to body weight relationship, together with the high energy requirements of the brain, led to the present inquiry into the relationship of brain weight to metabolic rate in mammals.

Furthermore, since it has been found that the longevity of mammals has a strong positive correlation with brain weight (Friedenthal, 1910; Sacher, 1959; Mallouk, 1975; Cutler, 1976a; Economos, 1980a), but that life span is also (inversely) correlated with the rate of energy metabolism (Rubner, 1908; Sacher, 1959; Hansche, 1975; Boddington, 1978), a further inquiry will be made here into the contribution of these two variables to the maximum potential life span of an organism. The physical model that will be derived from this analysis could enable us to determine that particular part of the animal's life span which is correlated with its evolutionary level of brain development—i.e., to encephalization.

METABOLIC RATE IN MAMMALS

The standard or basal metabolic rate (M_{body}) of mammals can be determined by measuring the heat production or the oxygen consumption per unit of time under standard conditions.

Half a century ago Kleiber (1932) and Brody and Proctor (1932) independently examined the relationship between the metabolic rates of eutherians and their body sizes, and found the basal metabolic rate to be approximately proportional to the 3/4 power of body weight. Further investigations confirmed the metabolic rate to body weight relationship also for passerine and nonpasserine birds, marsupials, and poikilotherms (Brody, 1945; Kleiber, 1947, 1961; Hemmingsen, 1960; Schmidt-Nielsen, 1977; for a review, see Kayser and Heusner, 1964).

The relationship between the basal metabolic rate (M_{body}) and the body weight (P) in vertebrates is given by the allometric equation:

$$M_{body} = aP^{b} \qquad (2)$$

where b is the differential growth ratio defined by Huxley (1932), and which here is approximately equal to 3/4.

The physiological meaning of coefficient a is still to be explained, and depends upon the class of vertebrates being investigated. Attempts to explain the 3/4 exponent have been discussed elsewhere (Kleiber, 1961; McMahon, 1973; Günther, 1975; Economos, 1979b, 1982; Calder, 1981; for a critical examination of the exponents, see Heusner, 1982).

In the present study, Brody's equation will be used, in which M_{body} is expressed in ml $O_2 \cdot min^{-1}$ and body weight in grams.

For eutherians the relationship is given by the equation:

$$M_{body} = 0.064P^{0.734} \qquad (3)$$

Marsupials, however, exhibit a reduced metabolic rate ($M_{body} = 0.043\ P^{0.737}$) and a lower body temperature ($T_{body} = 35.5°C$) in comparison with eutherian mammals (Dawson and Hulbert, 1970; MacMillen and Nelson, 1969). Body temperature in mammals may be considered to be nearly constant and independent of size (Morrison and Ryser, 1952). The basal metabolic rate can also be expressed per gram of body weight, which leads to

$$M^*_{body} = 0.064 P^{-0.266} \quad (4)$$

where M^*_{body} is the basal metabolic rate in ml $O_2 \cdot g^{-1} \cdot min^{-1}$. Dimensional analysis of M^*_{body} reveals that this term scales according to the reciprocal of time ($MM^{-1}T^{-1}$), a relation which is in accordance with many observed frequency rates (Stahl, 1963, 1967; Günther, 1971; Lindstedt and Calder, 1981).

There must be some explanation why physiological processes in animals should vary in proportion to the fourth root of their body weight. According to the principle of geometric similarity, in which the size of an organism changes without a change of form, time periods are proportional to lengths, which in turn scale to the 1/3 power of body weight (Gould, 1971; Günther, 1975). The implication for M^*_{body} would be that $M^*_{body} \propto P^{-1/3}$, instead of $P^{-1/4}$ (Eq. 4). Günther and Martinoya (1968) tried to solve this problem by proposing a correction factor, or operational time exponent Γ, with a mean value of -0.065. By adding the correction factor Γ to the theoretical value for the exponents, one brings them into line with the experimental values. Economos (1979a) criticized Günther's approach as being only descriptive and not explanatory. McMahon (1973, 1975) proposed a different mathematical model, one in which animals are viewed as being geometrically dissimilar, and the further theoretical assumption is made that length is proportional to the 1/4 power of the body weight. Although McMahon's model provides a logically consistent explanation for the exponential value, his derivation of Kleiber's law ($M^*_{body} \sim P^{-1/4}$) might have been valid only because of an accidental agreement with his assumption concerning mammalian shape, as Economos (1979a) has pointed out.

Adolph (1949), Hill (1950), and Stahl (1962, 1965, 1967) tried to explain the phenomenon by introducing the concept of physiological time, where the durations of physiological, developmental, and ecological cycles are related to each other according to fixed multiples, independent of body size. As a consequence, however, a time-scale proportional to (body weight)$^{1/4}$ may be difficult to synchronize with environmental cycles, such as circadian and circennial rhythms. According to Lindstedt and Calder (1981), it is this asynchrony of physiological time and astronomical time that has in fact resulted in the need for biological clocks.

Whatever the biological explanation of this principle may be, the main point is that weight-specific metabolic rate $\propto P^{-0.266}$, a value which has been confirmed by MacMillen and Nelson (1969) for both placental mammals and dasyurid marsupials.

One major exception to the relationship between metabolism and body weight has been found for hibernating mammals during their hibernating season. Kayser and Heusner (1964) found that the metabolic rate in homeotherms during hibernation is correlated with body weight according to the relation $M_{body} \propto P^{1.02}$, which means that the weight-specific metabolic rate in these animals is independent of the size of the animal ($P^{1.02}/P^{1.00} = P^{0.02}$). In further analyses, in which metabolic rates appear, one has to take these particular cases into account.

METABOLIC RATE AND RELATIVE BRAIN SIZE

A difficult problem in analyzing the energy metabolism of an animal is the contribution of the metabolic rate of the brain to the total metabolism. Most of the resting metabolism of a mammal is derived from the metabolic activity of the principal internal organs, that is, to the brain, liver, lungs, heart, and kidneys (Holliday, Potter, Jarrah, and Bearg, 1967). The sizes of these organs—with the exception of the brain—are nearly linear functions of body weight, and the associated metabolic rates are also closely correlated with body size (Stahl, 1965, 1967; Holt, Rhode, and Kines, 1968; Günther, 1975). The size and metabolic rate of the mammalian brain, in contrast, displays a wide interspecific variation of relative brain size that leads to a much more complex relationship to overall energy consumption.

In species where brain weight accounts for a relatively high percentage of the body weight—for example, in man, monkeys, and some squirrels ($\sim 2\%$), the contribution of the brain metabolism, M_{brain}, to the whole will be larger than in species where the brain-to-body weight ratio is low (e.g., elephant, 0.18%; opossum, 0.20%). Another

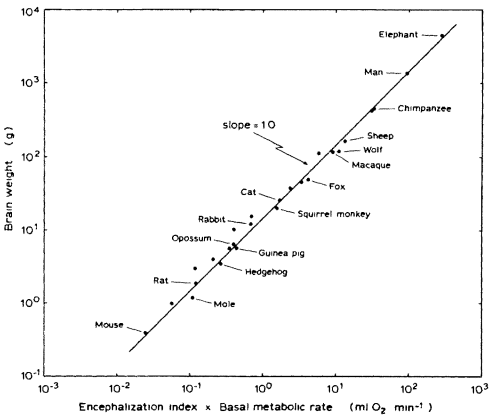

FIG. 1. BRAIN WEIGHT AS A FUNCTION OF THE DEGREE OF ENCEPHALIZATION (INDEX c) MULTIPLIED BY THE BASAL METABOLIC RATE
The line represents the theoretical line for a linear relationship between the parameters of Equation 7 (see text).

relevant aspect is the constantly high metabolic activity of the brain, regardless of the behavioral activity of the animal.

In order to determine the M_{brain}/M_{body} ratio, in general, we first have to determine the size of the brain of an animal, and then multiply it by its weight-specific metabolic rate. A way of determining the size of the brain is to estimate its weight from body weight. Many studies have been devoted to this subject (Von Bonin, 1937; Jerison, 1963, 1973; Stephan and Andy, 1964; Stephan, 1977; Bauchot, 1978; Hofman, 1982a). For the interspecific brain-to-body weight relationship in mammals the allometric equation

$$E = c\,P^{0.732} \qquad (5)$$

will be used in this study, where E is brain weight (g), P is body weight (g) and coefficient c indicates the species' relative brain size. For living mammals, $\bar{c} = 0.064$ (S.D. $\pm$ 0.004) (Hofman, 1982a).

Generally the "encephalization index" c can be mathematically formulated as

$$c = 0.015\,e^{0.11n} \qquad (6)$$

where $n \geqslant 0$ by definition, for mammals (Hofman, 1982a). Exponent n indicates the evolutionary level of relative brain size and can be used as a measure of encephalization of a species. The highest value of n is reached in *Homo sapiens* ($n \approx 30$). The equation further shows that encephalization in mammals is an exponential process. It should be noted that brain weight scales to body weight in almost the same way as does the basal metabolic rate (cf. Eqs. 3 & 5). Combining Equations 3 and 5 yields the following relation:

$$E = 15.6\,cM_{body} \qquad (7)$$

or

$$E = 0.234\,e^{0.11n}M_{body} \qquad (7a)$$

where E is brain weight (g), M_{body} is basal metabolic rate (ml $O_2 \cdot min^{-1}$), and c is the index of encephalization. Notice that for species in which $c = 0.064$ (i.e., the mean index value for mammals), $E = M_{body}$. Armstrong (1982) arrived at a similar relationship by multiplying M^*_{body} by the body weight. Regression of brain weight against this product yielded a slope which was not different from isometry, a relation suggesting that "enlargements of brain size keep pace with the availability of energy sources as determined by body weight and O_2 turnover" (p. 104). To test this hypothetical linear relationship between brain weight and energy metabolism in mammals, the basal oxygen consumption of 26 mammalian species was correlated with their respective brain weights, to yield the equation

$$E = 0.244\,e^{0.11n}M_{body} - 16.5$$

with more than 99.8 per cent of variance in common. The hypothetical relation (Eq. 7) thus appears to fit the experimental data extremely well, as illustrated in Fig. 1. A reduced major axis of 1.00 points to a directly proportional relationship between the variables concerned, i.e., that the variables are isometrically related.

From these results it may be inferred that the adult brain size of mammals is a function of two major components: the animal's rate of energy consumption and the evolutionary level of brain development. It goes without saying that the latter itself is determined by a conglomerate of factors that are still enigmatic, although the energy requirements connected with the size of the brain are limited by the energy supply connected with body metabolism. That is, the energy de-

TABLE 1
Metabolic rate per unit brain weight for several mammalian species

Species	Brain metabolic rate (ml $O_2 \cdot g^{-1} \cdot min^{-1}$)	Body weight (g)	Reference
Rattus rattus (rat)	0.076	262	Nilsson and Siesjö, 1976
Felis domestica (cat)	0.050	2600	Geiger and Magnes, 1939
Macaca mulatta (rhesus monkey)	0.048*	4300	Schmidt, Kety, and Pennes, 1945; Bering, 1961
Homo sapiens (Man)	0.034*	68700	Kety, 1957; Lassen, 1959; Sokoloff, 1972

* Mean value based on data derived from literature.

mands of the brain must be compatible with the oxygen production and transport by the body as a whole. It is therefore important to determine the ratio of brain metabolic rate to body metabolic rate.

Unfortunately, there are scarcely any direct measurements available for the rate of oxygen consumption of the whole brain in vivo. Reliable data have been obtained so far for only four mammalian species: rat, cat, rhesus monkey, and man (Table 1). It must therefore be emphasized that, unlike the mathematical relations with regard to body weight versus brain weight, and body weight versus metabolic rate, the formulae for cerebral oxygen consumption and the mathematical derivations of these formulae have to be considered as hypotheses that may serve as a basis for further research.

Brain metabolism appears to be mathematically related to body weight, according to the equation

$$M^*_{brain} = 0.162\ P^{-0.143} \qquad (8)$$

where M^*_{brain} is the weight-specific metabolic rate of the brain (ml $O_2 \cdot g^{-1} \cdot min^{-1}$) ($r = -0.991$). Notice the declining rates of metabolism in larger species, a phenomenon probably caused by a decrease in neuron density with increasing brain size (Tower, 1954; Hofman, 1982b). That interpretation is in agreement, furthermore, with findings that the total respiration of the brain consists mainly of neuronal respiration (Hess, 1961; Epstein and O'Connor, 1965; Hertz, 1966). To determine the oxygen consumption of the whole brain, one has to multiply the body weight term in Equation 8 by the brain weight. Thus,

$$M_{brain} = 0.162\ EP^{-0.143},$$

and, furthermore, if E is replaced by Equation (5), we obtain

$$M_{brain} = 0.162\ cP^{0.589} \qquad (9)$$

or

$$M_{brain} = 2.4 \times 10^{-3}\ e^{0.11nP^{0.589}} \qquad (9a)$$

where M_{brain} is brain metabolic rate (ml $O_2 \cdot min^{-1}$), P is body weight (g) and c the species' relative brain size, referring to its degree of encephalization.

With the aid of the previously derived equations we may now calculate the brain-to-body metabolic ratio, which is the quotient of Equations (9) and (3):

$$\frac{M_{brain}}{M_{body}} = 2.53\ cP^{-0.145} \qquad (10)$$

where M_{brain}, M_{body}, c and P represent the same parameters as in previous equations. The mean metabolic rate ratio for 249 mammals ($\bar{c} = 0.064$; $\bar{P} = 5490$ g; Hofman, 1982a) is 4.6 per cent, a value which is in agreement with observations made by Mink and his colleagues (Mink, Blumenschine, and Adams, 1981), who determined the metabolic ratio of the whole central nervous system (brain + spinal cord) to body metabolism for 34 homeotherm species of vertebrates, and who came to a value of 5.5 ± 0.7 per cent. They found that vertebrates, whether poikilotherms or homeotherms, use 2 to 8 per cent of their resting metabolism for the central nervous system (CNS). Separate equations for cold-blooded and warm-blooded vertebrates were not necessary. Several taxa of homeotherms, including primates, whales, and elephants, appear to be exceptions to the 2 to 8 per cent rule. Mink suggested that very large animals may have attained a size at which the basic relation-

TABLE 2
Estimated oxygen consumption of the brain and body in mammals

Mammal*	Index** $c = E/P^{0.732}$	Body weight (g)	M_{brain}† (ml $O_2 \cdot min^{-1}$)	M_{body}†† (ml $O_2 \cdot min^{-1}$)	M_{brain}/M_{body} × 100%
Didelphis marsupialis[1]	0.0151	2210	0.230	12.5	1.8
Tenrec ecaudatus[2]	0.0187	832	0.160	8.90	1.8
Rattus rattus[3]	0.0401	150	0.125	2.53	4.9
Felis lynx[3]	0.0915	7.7×10^3	2.91	45.6	6.4
Elephas indicus[3]	0.0976	3048×10^3	106	3677	2.9
Macaca mulatta[2]	0.1317	7.8×10^3	4.22	46	9.2
Pan troglodytes[4]	0.1622	46×10^3	14.8	169	8.8
Delphinapterus leucas[5]	0.1882	395×10^3	61.1	820	7.5
Homo sapiens[6]	0.4017	68.7×10^3	46.5	227	20.5

* Data on brain-body weights have been compiled from [1]Elias and Schwartz, 1969; [2]Stephan, Frahm, and Baron, 1981; [3]Mangold-Wirz, 1966; [4]Stephan, Bauchot, and Andy, 1970; [5]Crile and Quiring, 1940; [6]Passingham, 1979.

** Index of encephalization = brain weight/(body weight)$^{0.732}$.

† Oxygen consumption of the brain calculated from: $M_{brain} = 0.162\, c\, P^{0.59}$ (Eq. 9).

†† Basal oxygen consumption of the whole body calculated from: $M_{body} = 0.064\, P^{0.734}$ (Eq. 3). For *Didelphis* the body O_2 consumption was derived by using the equation for marsupials: $M_{body} = 0.043\, P^{0.737}$.

ship breaks down. In my opinion, however, no such violation of the general rule takes place. From Equation (10) it follows that for species with a high degree of encephalization, such as most simians and the toothed-whales, the M_{brain}/M_{body} ratio will be high, whereas for species with large body weights such as elephants, several ungulates, and baleen-whales, the M_{brain}/M_{body} ratio will be below the mammalian mean. Table 2 shows the excessively high proportion of the body metabolism ($\sim$ 20%) devoted to the brain in adult humans. Even higher values are measured in infants and children up to four years of age, in which the O_2 consumption of the brain can account for half the O_2 consumption of the resting body as a whole (McIlwain, 1971). This is a surprisingly large proportion for an organ that performs no obvious external mechanical, osmotic, or chemical work. The explanation for this phenomenon lies in the fact of the relative stability of the brain metabolic rate (McIlwain, 1971; Sokoloff, 1972, 1977). The oxygen consumption of the brain is largely independent of the state of cerebral activity in nonexperimental conditions. Also, during sleep there is no significant reduction in brain metabolic rate (Mangold et al., 1955; Sokoloff, 1972).

It should be noted that the metabolic ratio is in general less than 10 per cent, with minima for species with an exceedingly low brain-to-body weight ratio, such as the baleen-whales. Because of the continuing high energy demands of the brain, the basal metabolic rate of the body may not drop below a critical value without causing irreversible damage to the nervous system. Even in such extreme cases as the diving mammals (e.g., otters, seals, whales, and porpoises), the oxygen supply to the brain is assured during diving by an intense vasoconstriction of all arterial beds throughout the body with the exception of those of the brain and heart. With loss of perfusion to most tissues, O_2 consumption by these tissues ceases and body oxygen stores are available for maintaining the energy demands of the brain and thus maintaining its functional activity (Scholander, 1963; Packer et al., 1969). The larger the brain in a given species, the higher will be its oxygen requirements, and the shorter will be the maximal diving time. Assuming that longer diving times confer important biological advantages, such as for food gathering and a greater ability to escape from predators, Robin (1973) was moved to state that ". . . . relative stupidity may be more important for species survival under some conditions than relative intelligence" (p. 374).

Another way of coping with the energy demands of the brain under severe condi-

tions of O_2-depletion is the capability of the nervous system in some vertebrates to meet its energy requirements entirely from anaerobic glycolysis. An example is the brain of the pond turtle (*Pseudemis scripta elegans*), which continues to function even in the face of zero O_2 tension (Robin, 1973). The same may be true for hibernating mammals, in which the basal metabolic rate decays by a factor of 10 to 100 during the winter period, most prominently in small animals.

Once we have secured a suitable measure for estimating the brain's metabolic rate in mammals it would be useful to know the contribution of some of the major brain parts to the metabolism of the whole brain. The cerebral cortex is the part of the brain that ought to be considered first, because of the extensive comparative anatomical and physiological data available and because of its key role in the evolution of the brain (Diamond and Hall, 1969; Hofman, 1982a). The oxygen consumption of the cerebral cortex, M_{cortex}, in vivo can be estimated as follows:

$$M^*_{cortex} = 0.232P^{-0.151} \quad (11)$$

where M^*_{cortex} is the weight-specific energy metabolism of the cerebral cortex (ml $O_2 \cdot g^{-1} \cdot min^{-1}$) ($r = -0.992$). The equation is based on data supplied from the rat (Swaab and Boer, 1972; Eklöff et al., 1973; Hägerdal, Harp, Nilsson, and Siesjö, 1975; Norberg and Siesjö, 1976), the dog (Gregoire, Gjedde, Plum, and Duffy, 1978; Artru and Michenfelder, 1980), and man (Frackowiak, Jones, Lenzi, and Heather, 1980), and is calculated analogously to the allometric method for brain metabolic rate.

Multiplying both sides of Equation (11) by the cortical volume, V, we obtain the equation for the metabolic rate of the whole cortex:

$$M_{cortex} = 0.232\ VP^{-0.151} \quad (12)$$

where M_{cortex} is the metabolic rate of the whole cerebral cortex (ml $O_2 \cdot min^{-1}$) and V is the volume of the cerebral cortex (cm^3). Recently Hofman (1982a) demonstrated that the cortical volume in mammals is a function of brain size, according to the equation $V = 0.2e^{0.03n}E$. Substitution of the value for the cortical volume in Equation (12) yields

$$M_{cortex} = 0.0464e^{0.03n}EP^{-0.151}.$$

By replacing brain weight by $E = cP^{0.732}$ (Eqs. 5 & 6) we arrive at the following equation:

$$M_{cortex} = 0.7 \times 10^{-3}e^{0.14n}P^{0.581} \quad (13)$$

for the total metabolic rate of the cerebral cortex (ml $O_2 \cdot min^{-1}$). A comparison with brain metabolism reveals that

$$\frac{M_{cortex}}{M_{brain}} = 0.29e^{0.03n}P^{-0.008} \quad (14)$$

Since the value of the body weight exponent is very low, this term will hardly influence the outcome of the ratio. Further investigations with larger samples might reduce the exponent to zero. The ratio of cortex-to-brain metabolic rates thus depends only upon the degree of encephalization of the animal. For mammals, the value of n varies between $n = 0$ for the opossum (*Didelphis marsupialis*) and $n \simeq 30$ for man (*Homo sapiens*), so that ratio values will fall between 0.25 and 0.65. Table 3 shows the differences between M_{cortex} and M_{brain} for several mammalian species. Furthermore, weight-specific comparisons between the O_2 consumption of the whole brain (Eq. 8) and of the cerebral cortex (Eq. 11) demonstrate that cortex metabolism per unit weight is about 43 per cent higher than the weight-specific metabolic rate of the whole brain. Experimental measurements in vitro are in accordance with this finding (Elliott and Henderson, 1948; McIlwain, 1971). These local differences are due mainly to differences in tissue structure: gray matter possesses a much higher metabolic rate than does white matter (cf. Hess, 1961; Epstein and O'Connor, 1965; Mazziotta, Phelps, Miller, and Kuhl, 1981). The brain as a whole, being composed of both gray and white matter, will therefore have a lower mean metabolic activity than its cortical regions, where the considerable "subcortical" white matter is, by definition, excluded from consideration.

In order to determine the average O_2 uptake per neuron in the cerebral cortex, we have simply to divide the O_2 consumption of

TABLE 3
Estimated oxygen consumption of the cerebral cortex and whole brain in mammals

Mammals	Coeff.† n	M_{cortex}* (ml $O_2 \cdot min^{-1}$)	M_{brain}** (ml $O_2 \cdot min^{-1}$)	M_{cortex}/M_{brain} × 100%
Tenrec ecaudatus	2.00	0.046	0.160	28.7
Rattus rattus	8.94	0.045	0.125	36.0
Felis lynx	16.44	1.26	2.91	43.3
Elephas indicus	17.03	43.8	106	41.3
Macaca mulatta	19.75	2.01	4.22	47.6
Pan troglodytes	21.64	7.33	14.8	49.5
Homo sapiens	29.89	29.4	46.5	63.2

† Values for coefficient n are from Hofman (1982b), using Equations 5 and 6.
* Oxygen consumption of the cerebral cortex calculated from Equation 13: $M_{cortex} = 0.7 \times 10^{-3}\, e^{0.14nP^{0.58}}$.
** Oxygen consumption of the brain calculated from Equation 9a: $M_{brain} = 2.43 \times 10^{-3}\, e^{0.11nP^{0.59}}$.

the whole cortex by the total number of neurons. This procedure gives an acceptable approximation, since almost 95 per cent of the entire cortical respiration is neuronal (Elliott and Heller, 1957; Hess, 1961)—in spite of the fact that the neurons are vastly outnumbered by neuroglial cells, especially in large cortexes. The number of neurons in the mammalian cortex has been shown to be a linear function of the cortical surface (Hofman, 1982b), according to the equation:

$$N = 10^7 S \qquad (15)$$

where N is the number of neurons, and S is the total cortical surface (cm^2). In addition, the cortical surface is related to body weight according to the equation:

$$S = 4.35\, cP^{2/3} \qquad (16)$$

in which the parameters are the same as in previous equations (Hofman, 1982a). Combining Equations 13, 15, and 16 gives

$$\frac{M_{cortex}}{N} = 1.07 \times 10^{-9} e^{0.03nP^{-0.086}} \qquad (17)$$

where M_{cortex}/N is the average oxygen uptake per neuron (ml $O_2 \cdot min^{-1} \cdot cell^{-1}$). Using the values of body weight and of the coefficient n from Tables 2 and 3, we arrive at 10×10^{-10} ml O_2 per minute per neuron for man, and 9.1×10^{-10} ml O_2 per minute per neuron for the rat. These estimates are in agreement with findings by Epstein and O'Connor (1965) and by Ruščák, Ruščákova, and Hager (1968), respectively. The estimate for humans is slightly lower than the measured values, probably as a result of the high estimate of the number of neurons (30×10^9) for the human cortex that is used in the present study.

In conclusion, we may say that brain weight and body weight can be used as the principal parameters for estimating the metabolic rate of the whole body under standard conditions, as well as of the oxygen consumption of the brain, the cerebral cortex, and the average cortical neuron in normal adult mammalian species. Furthermore, it has been shown that the ratio of cortex-to-brain metabolic rates is independent of body size, and increases with the evolutionary level of brain development.

BRAIN SIZE AND METABOLIC RATE AS DETERMINANTS OF LONGEVITY

The concept of physiological time in relation to the weight-specific energy metabolism of an animal was already mentioned (pp. 496–497). Hence, if life span is considered to be the longest period of the organism's physiology, it should, like many other physiological periods or times (cf. Stahl, 1967; Lindstedt and Calder, 1981), be approximately proportional to the 1/4 power of body weight. Experimental evidence in fact supports this assumption, for mammals (see Sacher, 1959, and Economos, 1980b). The correlation between life span and body weight for mammals is rather low (r = 0.792), however, a value implying that the two variables have only 63 per cent of variance in common.

An attempt to correlate life span and brain weight has met with similar difficulties, in that brain weight was able to account for only 79 per cent of the life span variance

(Economos, 1980a). It appears that the assumption of a strict correlation between brain size and mammalian life span, based on the view of the brain as the main controller of physiological and hormonal processes, and thus of aging and longevity (Friedenthal, 1910; Sacher, 1959; Fischer, 1968; Cutler, 1976b), is not tenable.

Among other variables that have been conjectured to be strongly correlated with the life span are the rate of energy metabolism (Rubner, 1908; Sacher, 1959), liver weight (Economos, 1980a), and adrenal weight (Calder, 1976; Economos, 1980a). All those variables, however, have the same relatively low correlation with life span (r = 0.80) as was found for body weight and brain weight. An attendant problem is that these anatomical and physiological variables are themselves highly correlated among themselves. This complexity brought Sacher (1976, 1978) to carry out a multivariate analysis of the dependence of the life span on four variables simultaneously: brain weight, body weight, resting metabolic rate, and body temperature. He used a sample of 85 mammalian species. This method of analysis enables us to estimate the dependence of longevity on each single variable while holding the others constant. The relation was found to be:

$$L = 0.66E^{0.6}P^{-0.4}M^{*-0.5}_{body} \times 10^{0.025T_b} \quad (18)$$

where L is maximum life span in years, E is brain weight in grams, P is body weight in grams, M^*_{body} is weight-specific metabolic rate in ml O_2 per gram minute, and T_b is body temperature in degrees Celsius (r = 0.92). Since the error in estimates of life span is on the order of 10 per cent, the 85 per cent variance that was thus accounted for is as high as is possible, according to Sacher, until more accurate data become available.

Equation (18) gives the impression that there are four independent factors influencing the life span. The number of independent coefficients can, however, be reduced from four to two. For example, we can substitute the weight-specific metabolic rate for the body weight (Eq. 4) and determine the temperature in mammals. If we consider body temperature in mammals to be independent of size, if measured above thermal

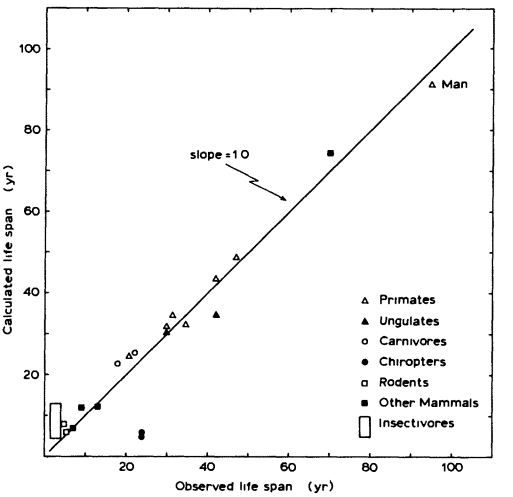

FIG. 2. COMPARISON BETWEEN THE ESTIMATED MAXIMUM LIFE SPAN AND THE ACTUAL RECORDED MAXIMUM LIFE SPAN IN MAMMALS

Note the two Chiroptera, having a much longer life span than would be expected on the basis of Eq. (19). Data for the Insectivora are given in Table 4.

neutrality, and T_b = 37.8°C (Morrison and Ryser, 1952; Calder, 1981), we obtain:

$$L = 23E^{0.6}P^{-0.267} \quad (19)$$

Apparently, life span is determined by two inversely related components: brain weight and body weight.

In order to test the predictive value of the above relation, an analysis was carried out on 34 species, derived from all major mammalian orders (Fig. 2). Data for the maximum life spans were compiled from Spector (1956), Altman and Dittmer (1972), Walker (1975), and Ordy (1975).

With the exception of the insectivores and chiropters, the correlation between the observed life span (L_{obs}) and the calculated life span (L_{calc}) is very high (r = 0.982). The two indicated species of chiropters, however, live about four times longer than would be expected from Equation (19), whereas the four species of insectivores live two to four times shorter than would be expected. To further document the differences between L_{calc} and L_{obs} in insectivores, a more extended list is given in Table 4. Whether the observed deviations are the result of a reduced metabolic rate in the bats during

TABLE 4
Longevity in Insectivora

Insectivora* (species)	Body weight (g)	Brain weight (g)	L_{calc}** (yr)	L_{obs} (yr)	Ref.†
Tenrec ecaudatus	832	2.57	6.7	2+	A
Erinaceus europaeus	860	3.35	7.8	4.2	A
Talpa europaea	76.0	1.02	7.3	3.5	Z
Neomys fodiens	15.2	0.32	5.6	1.6	W
Sorex araneus	10.3	0.20	4.7	1.5	W
Elephantulus fuscipes	57.0	1.33	9.3	3.3	W
Rhynchocyon stuhlmanni	490	6.10	13	3.3+	A

* Data on brain and body weights have been compiled from Stephan, Frahm, and Baron (1981).
** Estimated life spans were calculated from Equation (19): $L_{calc} = 23E^{0.6}P^{-0.267}$
† Data on recorded maximum life spans from: A, Altman and Dittmer, 1962, 1972; Z, Zepelin and Rechtschaffen, 1974; W, Walker, 1975.

hibernation (Walker, 1975), or to a disproportionally high metabolic activity in small animals, such as most insectivores (Walker, 1975), are questions still to be answered. The maximum life span in man calculated from Equation (19) is approximately 90 to 100 years, a figure in good agreement with published observations (Hansche, 1975; Walker, 1975).

Finally, we may say that the mathematical relationship between brain weight, body weight, and longevity generally holds true for mammals. Of course, this does not necessarily mean that there is a causal relationship among these variables. In order to identify the fundamental factors that determine maximum life span, Equation (19) has to be analyzed in more detail.

Instead of using brain weight, we would like to deal with an evolutionarily more appropriate brain parameter. The most significant and appropriate neural structure in this context appears to be the cerebral cortex, because of its exceptionally high correlation with the evolution of the brain (Diamond and Hall, 1969; Bauchot and Stephan, 1969). In particular, the surface of the cerebral cortex has been found to be correlated with brain weight (e.g., Elias and Schwartz, 1969; Jerison, 1979; Hofman, 1982a). Another reason for using the cerebral cortex instead of the whole brain is its supposed regulating function in rates of aging and mortality (see Hansche, 1975).

It has been found that brain weight (E) and cerebro-cortical surface (S) are strongly correlated, according to the equation $S = 3e^{0.01\eta}E^{0.914}$ ($r = 0.995$—Hofman, 1982a). The substitution in Equation (19) of cortical surface for brain weight yields:

$$L = 11.18\ (e^{-0.01\eta}S)^{2/3}P^{-0.267} \qquad (20)$$

where L is life span (yrs) and S is surface of the cerebral cortex (cm²). If both sides are raised to the 3/2 power we obtain:

$$L^{3/2} = 37.4\ e^{-0.01\eta}SP^{-0.40}. \qquad (21)$$

Furthermore, a relationship was found to exist between body weight and the cross-sectional area ($\emptyset$) of the medulla oblongata, according to the equation $\emptyset = 8 \times 10^{-3}P^{0.40}$ ($r = 0.996$, Hofman, 1982a). The substitution of the body-weight term in Equation (21) by $P^{-0.40} = 0.008\emptyset^{-1}$ leads to the following relationship between total cerebro-cortical surface (cm²), the cross-sectional area of the medulla oblongata (cm²), and longevity:

$$L^{3/2} = 0.3e^{-0.01\eta}S\emptyset^{-1}. \qquad (22)$$

The cross-sectional area of the caudal part of the medulla oblongata is not only a proper estimator of body size, but may also be used as a measure of input and output channels of the brain (e.g., see Jerison, 1973; Gould, 1975; Passingham, 1975).

Since, to a large extent, the nerve fibers passing through the caudal part of the medulla are connected with the surface area of the body, a close correlation between body surface and the hindbrain cross-sectional area was to be expected. The relation can be mathematically formulated as S_{body}

$= 3.3 \times 10^4 \emptyset^{5/3}$ (Hofman, 1982b) which, if substituted for $\emptyset$, enables us to determine the relationship between life span and body surface. This is important because the body-surface area of an animal enables it to interact with its environment, not only by a flow of sensori-motor information, but also metabolically, by means of heat exchange (Kleiber, 1972). Since heat flow and information flow are coefficients that can be reduced to the same physical entity—namely, energy—S_{body} is a demonstrably appropriate parameter for indicating the net energy transfer between the organism and its environment.

In discussing the role of the cortical surface in setting limits to mammalian longevity, it should be realized that this surface is assumed to be composed of two hypothetical components: (1) a component related to body size and associated with primary sensorimotor functions; and (2) a component correlated with evolutionary factors and presumably associated with higher-order brain functions (Jerison, 1977; Hofman, 1982a). In order to investigate which part of the life span of a species is directly related to mechanisms associated with body size and which part of it is determined by the evolutionary progression of relative brain size, the surface of the cerebral cortex was subdivided into a component related to body size (S_b) and a nonsomatic evolutionary component (S_e). The algebraic sum of the components has been conjectured to be equal to the surface of the whole cortex, so that $S = S_b + S_e$ (Hofman, 1982a). It was found, furthermore, that $S_b = 0.065\ P^{2/3}$ and $S = e^{0.11n} S_b$ (Hofman, 1982a). If Equation (21) is rewritten in accordance with these expressions, we obtain:

$$L^{3/2} = 37.4 e^{0.1n} S_b P^{-0.40} \qquad (23)$$

and the substitution of S_b for $0.065 P^{2/3}$ yields:

$$L^{3/2} = 2.4 e^{0.1n} P^{0.267}, \qquad (24)$$

where L is life span (yrs), n is the encephalization coefficient ($n \geqslant 0$, by definition, for mammals) and P is body weight. In this equation the somatic component has been distinguished from the encephalization component, in order to determine the contribution of each to longevity.

The equation enables us to compute, on the one hand, the part of the potential life span correlated with body size (L_b) and, more particularly, with body temperature and metabolic rate of the animal; and on the other hand, the part of the potential life span (L_e) that is linked to an evolutionary increase in the regulatory and information-processing capacity of the brain. It will be evident that total life span is the algebraic sum of its two fractions:

$$L = L_b + L_e,$$

or

$$L_e = [(e^{0.1n})^{2/3} - 1] L_b.$$

Table 5 shows these two fractions for a number of mammalian species. It shows that the long potential life span in humans is for the most part owing to the high human level of encephalization. It is to be noted that, if relative brain size—or encephalization—is taken into account, body size is positively related to life span (Fig. 3). As a consequence, if two species have the same degree of encephalization, the larger one will have the longer potential life span. On the other hand, large mammals, such as simians, carnivores, ungulates, and toothed-whales, generally exhibit a high degree of encephalization (Stephan, 1967; Jerison, 1973; Hofman, 1982a). Since both factors—i.e., body size and encephalization—reinforce one another as determinants of longevity, large mammals will tend to have a longer life span than small ones, as confirmed by zoological observations. Not all small mammals, however, show a low degree of encephalization or vice versa. Exceptions to this general rule are found among small species with a high degree of encephalization, such as prosimians, and among large mammals with a low degree of encephalization, such as several ungulates and baleen-whales. For these groups of animals the life-span factors are working in opposite directions, and the life span will depend on which factor predominates. If we consider the encephalization factor, the relation predicts a longer life span for a more highly evolved species than for a species with a low degree of encephalization, given equal body weights (see Fig. 3). Notice, for example, the dif-

TABLE 5
Estimated maximum life span in mammals

Mammals*	Coeff.* n	Body weight (g)	Basal life span (yr)**	Extra life span (yr)†	Total max. life span (yr)††
Didelphis marsupialis	0	2210	7.1	—	7.1
Tenrec ecaudatus	2.00	832	5.9	0.8	6.7
Rattus rattus	8.94	150	4.4	3.6	8.0
Felis lynx	16.44	7.7×10^3	8.8	17.6	26.4
Elephas indicus	17.03	3048×10^3	25.5	53.9	79.4
Macaca mulatta	19.75	7.8×10^3	8.8	24	32.8
Pan troglodytes	21.64	46×10^3	12.1	39	51.1
Delphinapterus leucas	23.00	395×10^3	17.7	64.4	82.1
Homo sapiens	29.89	68.7×10^3	13.0	82.5	95.5

* For references and calculation methods see Tables 2 and 3.
** Basal life span (L_b) was calculated from the equation, $L_b = 1.79\,P^{0.178}$ (cf. Eq. 24).
† Extra life span (L_e) was calculated using the equation, $L_e = L - L_b = [(e^{0.1n})^{2/3} - 1]L_b$ (cf. Eq. 24).
†† Maximum potential life span was obtained from $L = L_e + L_b$ or $L = (e^{0.1n})^{2/3}\,L_b$ (Eq. 24).

ference in predicted potential life span between the lynx and the macaque (see Table 5).

Before discussing the role of body size and encephalization as determinants of life span in somewhat more detail, let us replace the body-weight term in Equation (24) by a metabolic term, according to the formula $P^{-0.266} = 0.064M^{*-1}_{body}$ (Eq. 4). Thus we obtain

$$L^{3/2} = 0.154e^{0.1n}M^{*-1}_{body} \qquad (25)$$

where L is the maximum life span (yrs), n is the encephalization coefficient and M_{body} is the weight-specific metabolic rate (ml $O_2 \cdot g^{-1} \cdot min^{-1}$). It turns out that life span is a function of the species' degree of encephalization and varies inversely as the weight-specific metabolic rate. The encephalization coefficient can be shown, by dimensional analysis in terms of information theory, to be a measure of the neural information density, which can also be called the neural negentropy of the organism (Bergström, 1969; Sacher, 1976). The reciprocal of the metabolic rate likewise has the physical dimensions of negative entropy (Stahl, 1962; Günther, 1975). Therefore, the maximum potential life span of a species increases as its entropy associated with both of the processes under discussion decreases, according to the sum of the logarithms of the coefficients. In other words, the lower the degree of entropy in the organism, and the longer this high information content can be preserved, the longer its potential life span will be.

This hypothesis is in agreement with the model of dysdifferentiation (Cutler, 1982), which says that the aging rate of an organism is directly related to the innate ability of the cells of that organism to maintain their proper state of differentiation as a function of time. Since differentiated cells are inherently unstable as a consequence of the natural instability of DNA and the long-term interaction of the genetic apparatus with epigenetic/mutation-like processes, the aging of an individual is considered to be largely a result of a time-dependent, disorderly, dysdifferentiative process. A reduction of these "continuously-acting biosenescent processes" (Cutler, 1982), such as the oxidative metabolic reactions producing free radicals, could increase the life span (Demopoulos, 1973; Del Maestro, 1980; Harman, 1980). Minimizing these deleterious reactions by counteracting "longevity determinant processes," such as the production of protective enzymes, would reduce the degenerative rate of these processes and accordingly increase the life span of the organism.

There are several arguments for viewing Equation (25) as embodying a general principle underlying longevity in vertebrates. In respect to the metabolic factor, an increase of body temperature T_b caused by a decrease in thermal conductance C ($\Delta T \sim M_{body}/C$; Herreid and Kessel, 1967; McNab,

1970, 1980; Kleiber, 1972; Aschoff, 1981) ought to increase the life span accordingly. This can in fact be seen in birds, which have significantly higher body temperatures than mammals, and also have longer life spans for a given body weight (Sacher, 1978; Lindstedt and Calder, 1981). Another argument is that the life span increases with body weight even when there is a very low degree of encephalization, as can be seen in poikilothermic vertebrates. In this group, the reciprocal of the weight-specific metabolic rate is generally high, especially for such large animals as alligators, crocodiles, and sharks ($P/M_{body} \sim M^{*-1}_{body}$) and so leads to a predictably high life span.

The increase of metabolic rate in mammals and birds during their evolution does not seem to have been as clearcut an advantage as is generally assumed. The "price" that a homeothermic vertebrate must pay for a relatively large, energetically constant and active brain is high, particularly among some higher mammals.

The deviations that were found between expected and observed life spans in small mammals are also explained by Equation (25) (see Table 2). Kleiber (1972) has demonstrated that the difference between body temperature and the critical temperature—i.e., the ambient temperature below which extra heat production is necessary for temperature regulation—increases with increasing body size. He calculated a critical temperature of 31.2°C for a 10-gram animal, and T_c = 26.4°C for an animal weighing 100 gram. Since most small mammals live in an environment with an ambient temperature below thermal neutrality, their mean minimal rate of metabolism will invariably be higher than the expected basal metabolic rate (Dawson, 1955; McNab, 1970). This is because of an increase in the rate of heat production needed to maintain continuous homeothermy. The increased basal metabolic rate in such mammals leads to an increase of M^*_{body} and, with that, to a lower life expectancy. If the mean minimal rate of metabolism declines, as in hibernating mammals, the life span will be correspondingly longer than would be expected from Equation (25).

The relationships which have been found in this study between the maximum life span and several morphological and physiological parameters are significant, not only as predictive formulae, but also to gain insight into some of the general principles affecting mammalian longevity. The ultimate task for the gerontologist will be to search for the molecular-genetic mechanisms governing longevity, and to discover the nature of the life-limiting factors.

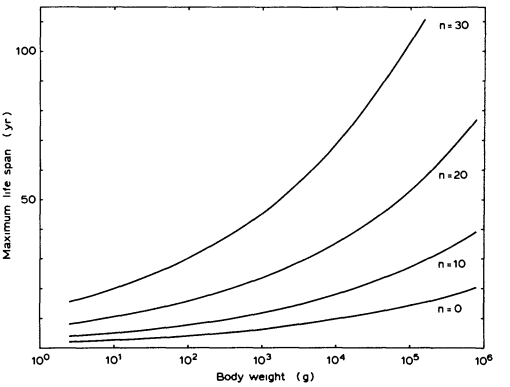

FIG. 3. MAXIMUM LIFE SPAN AS A FUNCTION OF BODY WEIGHT IN MAMMALS

Semi-logarithmic scale. The theoretical curves are given for several degrees of encephalization (n = 0, 10, 20, and 30) and calculated from Eq. (24) in text. The progressive significance of the evolutionary increase of relative brain size (= encephalization) for mammalian longevity is shown.

CONCLUDING REMARKS

In the present study it has been demonstrated that brain weight and energy metabolism in mammals are highly correlated. Such a connection was already assumed by Snell as early as 1891. Snell's theory, however, was based on the premises that the energy metabolism of the animal is a function of its heat exchange, and thus of the body surface, according to Rubner's "surface law" (Rubner, 1883), whereas the major input to the brain has its origin in sensory organs situated in the periphery of the body. Metabolism and brain weight were therefore thought to be functions of body surface, and to scale according to an exponent of 2/3.

Recent findings, however, do not support the body-surface hypothesis and arrive at somewhat higher values for the exponent. The revised exponential values appear to be

raised to an equal extent; that is, both brain weight and basal metabolic rate are related to body weight according to a similar exponential value (0.73, instead of 0.67). Furthermore, the ratio of brain weight to metabolic rate in mammals was found to be directly proportional to the degree of encephalization.

A consequence of the coupling of encephalization and basal metabolic rate is that longevity appears to be a compound function of both variables. Since basal metabolic rate represents the minimum energy transformation required to maintain the cellular and molecular integrity of the system, it is a predictor for the theoretically maximum life span. Most organisms, however, function throughout their life time at an energy level somewhere between this basal metabolic rate and the maximum energy that could be supplied through the molecular transformations of the system. Boddington (1978) has stated: "Since most organisms function during their life at a 'routine' metabolic level within their 'scope for activity' it means that they are exhausting their 'absolute metabolic scope' at a somewhat faster rate than if they functioned at the basal rate resulting in somewhat shorter life span" (p. 446).

The maximum rate of oxygen consumption in mammals is found to be nearly ten times the resting metabolism, and to scale more or less proportionally to $P^{3/4}$ (McMahon, 1975; Lechner, 1978; Prothero, 1979; Taylor et al., 1980). Therefore, a change in the routine metabolic level of an animal will influence its life span independently of its size and will vary with a factor less than 4.6 ($L_{max}/L_{min} = 10^{2/3}$). As a consequence, small mammals such as insectivores and many rodents, which exhibit higher routine metabolic rates than do larger mammals, because their food-gathering activities are necessarily greater if they are to maintain homeothermy, will have shorter life expectancies than those predicted from the life-span equation (Eq. 25).

On the other hand, mammals with a lower routine metabolic level during their life, such as hibernating bats, will live longer than would otherwise have been expected. As shown in the literature, the recorded life spans for these groups of animals do in fact agree with these predictions.

With respect to aging and longevity, the metabolic rate of the body and the number of neurons in the brain are conjectured to be of major importance in biosenescent processes, such as oxidative metabolism, hormone production associated with sexual maturation, and disturbances of intercellular relations (Cutler, 1982; Giacobini, 1982). The role of nerve cells in organismic aging is of particular importance by reason of the regulatory function the nervous system plays in the maintenance of physiological and hormonal processes. Cutler (1982) has postulated in his hypothesis on mammalian longevity that biochemical changes, specifically those related to aging, slowly destabilize the proper differentiated state of cells and that these dysdifferentiative processes can be counteracted by longevity-determinant processes, such as DNA repair processes, free radical scavengers, detoxification processes, and decreased rates of development and differentiation. According to this model, repair and protective mechanisms have evolved in mammals, rather than senescent or aging processes.

The molecular-genetic mechanisms that govern encephalization and energy metabolism, and thus probably longevity as well, are considered to be similar for all mammalian species, and to be correlated with the amount and rate of DNA repair and with a decrease in mutation rate during evolution (Hart and Setlow, 1974; Cutler, 1975, 1976a,b; Sacher, 1975, 1978). It seems likely that high rates of increase in encephalization and longevity are the result of changes occurring in only a few structural or regulatory genes. Models have been proposed in which a relatively small number of mutations in these genes or chromosomal rearrangements would be necessary to account for many different physiological functions, including longevity (e.g., King and Wilson, 1975). Such seemingly minor genetic changes would allow rapid evolutionary development, as in primates and, particularly, in hominids (Hofman, 1983, unpub.)

From the considerations presented in this paper the conclusion may be drawn that life

span, the degree of encephalization, and energy metabolism are closely interrelated in mammals. They are related in such a way that a low rate of metabolism per unit body weight and a progressive evolutionary increase in the number of neurons, which finds expression in an expansion of the brain relative to the size of the animal, are important conditions for the self-organizing ability of the organism and, with that, for greater longevity.

ACKNOWLEDGMENTS

I wish to thank H. B. M. Uylings, D. F. Swaab and M. A. Corner for useful discussions and for reviewing previous drafts of the manuscript. I am also grateful to H. Stoffels, the illustrator, to C. Sijpkens and A. T. Potjer, the photographers, and to W. Chen-Pelt for secretarial help.

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