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Review article

Men and mice: Relating their ages

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ABSTRACT

Since the late 18th century, the murine model has been widely used in biomedical research (about 59% of total animals used) as it is compact, cost-effective, and easily available, conserving almost 99% of human genes and physiologically resembling humans. Despite the similarities, mice have a diminutive lifespan compared to humans. In this study, we found that one human year is equivalent to nine mice days, although this is not the case when comparing the lifespan of mice versus humans taking the entire life at the same time without considering each phase separately. Therefore, the precise correlation of age at every point in their lifespan must be determined. Determining the age relation between mice and humans is necessary for setting up experimental murine models more analogous in age to humans. Thus, more accuracy can be obtained in the research outcome for humans of a specific age group, although current outcomes are based on mice of an approximate age. To fill this gap between approximation and accuracy, this review article is the first to establish a precise relation between mice age and human age, following our previous article, which explained the relation in ages of laboratory rats with humans in detail.

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Contents

1. Introduction	0
2. Age determination of laboratory mice: common methods.	0
2.1. Weight of eye lens	0
2.2. Musculoskeletal examination: epiphyseal closure	0
2.3. Body weight assessment	0
2.4. TW pattern	0
3. Relation between mice age and human age	0
3.1. Relation between their lifespans	0
3.2. Weaning period of mice and human	0
3.3. Mice and human age to attain puberty	0
3.4. Age of adulthood onset in mice and its relation to human age of adulthood	0
3.5. Reproductive senescence in mice and humans	0
3.6. Post-senescence phase in mice and humans	0
4. Conclusions	0
Conflict of interest	0
Funding source	0
References	0

1. Introduction

Most studies in the field of life science (almost 59% of the experimental studies [1]) use experimental murine models (*Mus musculus*) for investigating the implications on human health and body (Fig. 1). In terms of their maximum lifespan, mice (4 years) and humans (120

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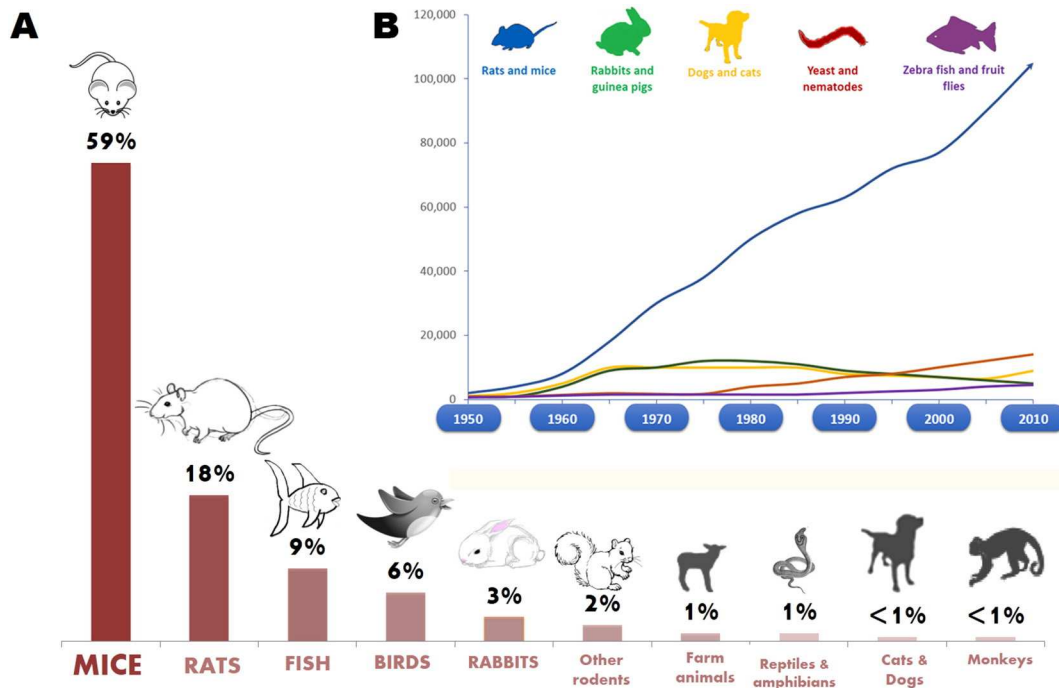


Fig. 1. (A) Use of animals in research and other scientific purposes and (B) animals cited in biomedical research papers (1950–2010).

years) differ significantly, although murine models have been widely used to analyse human body functioning and its modulation (see Ref. [2]). In two pioneering studies, Sir L. Demeritus (published in 2005 and 2006) documented their similarities and differences in diverse metabolic processes, describing the molecular process of ageing in detail (see Refs. [2,3]), but not the precise correlation of their ages in different phases of their lifespan.

Despite the large differences in their lifespan, humans and mice show similar patterns in disease pathogenesis as well as organ and systemic physiology. Their cells contain similar molecular structures that regulate the functioning of cells, differentiation. Moreover, the molecular mechanism of ageing in mice is similar to that in humans (see Ref. [3]). For instance, mice acquire mutations in the spectrum of proto-oncogenes and tumour suppressor genes, similar to those affected in human cancers (see Ref. [4]). Almost 99% of mouse genes resemble the human genome, thus making the murine model an ideal candidate for studying the functions of human genes in health as well as in the regulation of multifactorial diseases such as cancer, cardiovascular diseases, diabetes and arthritis (Table 1). Acute promyelocytic leukaemia (APL), although previously untreatable, is currently treated in humans after successful experimentation in murine models. Although certain larger mammals can better simulate human genotypic and phenotypic features, they can be expensive and difficult to maintain or handle [5].

Mice provide analogous experimental conditions and comparable results to humans. Findings of general experiments with mice, pharmaceutical trials for newly designed drugs in murine models, or studies on different developmental phases of mice are intended to be applied on human health and life. In all such cases, using mice of an approximate age rather than precisely correlated age or phase with humans limits the accuracy of experiments and their implications for human physiology. It is imperative that researchers consider the phase and age of animals used in experiments in relation to human physiology, which was explained in detail in our previous review work on the relation between the age of rats and humans (see Ref. [6]). Thus, the aim of this comprehensive review is to precisely analyse the relation between mice age and human age in various life stages to bridge the gap between the approximation and accuracy of future research in the biomedical field.

2. Age determination of laboratory mice: common methods

Various methods have been used to correlate the ages of small mammals with human age, for example, by determining the weight of eye lens (see Refs. [7–11] and [12]), epiphyseal closure (see Refs. [13,14]), tooth wear (TW) pattern [15], and body weight correlation [15]. As these methods provide a relative age that does not exactly coincide with the exact age, more than one method is required for a closer

Table 1
Commonly used strains of laboratory mice and their research applications.

Mostly used strains	Strain abbreviation	Rotation length (weeks) ^a	Mean litter size	Wean to born ratio	Research applications
BALB/C	Cby	30	4.40	0.88	Mostly in immunological research
C3H/HEJ	C3	22	4.60	0.90	In a wide variety of research including cancer, infectious disease, sensorineural and cardiovascular research
C57BL/6J	B6	30	4.90	0.80	General purpose, cardiovascular research, background strain for mice carrying transgenes, spontaneous or targeted mutations
DBA/2J	D2	26	4.70	0.80	General purpose, atherosclerosis, glaucoma research.
SWR	SW	22	4.6	0.80	General purpose, highly susceptible to experimental allergic encephalomyelitis
129P3/J	129P	26	5.0	0.90	Spontaneous testicular teratomas, targeted mutagenesis
NZB/B1NJ	NZB	26	4.5	0.90	Autoimmunity

^a The average length of time a breeding unit reliably delivers progeny (also called the *optimum reproductive lifespan*).

approximation of the age of the experimental animal. To relate the life stages of humans and mice scientifically, we used methods of age determination in mice by reviewing previous articles.

2.1. Weight of eye lens

Several studies have used the weight of the eye lens across mammalian life stages as an indicator of the age correlation among different species [7–10]. The increase in the weight of the eye lens follows an asymptotic curve throughout the lifespan of most mammals [11]. In the late 1980s, this technique was considered a vital tool to correlate the ages of different mammalian species at various life stages. However, it serves as an important indicator only up to 3–4 months, beyond which the precision is not sufficient to determine the exact age of small mammals (see Refs. [12]).

2.2. Musculoskeletal examination: epiphyseal closure

As dental development is minimal in foetal animals, their age can be estimated based on bone formation such as long bone lengths, the development of the ilium, and the petrous portion of the temporal bone. Provided the measurements are accurate, formulae involving the correlation between bone length and age can be used to determine the corresponding age of the animal. The bones of the upper and lower limbs and hip joint are mostly used to analyse the age of the experimental animal. In young animals, metopic suture closure and the emergence of ossific centres are indicators of age. In addition, the growth of epiphyseal plates, and closure of the same in some species, is an indicator of the onset of sexual life in mammals, as observed in different mammalian species (see Ref. [13]). In humans, closure of the epiphysis in the bones of the upper body (namely, wrist, shoulder joint, humerus, ulna, radius, metacarpals and phalanges) is observed at the age of 14–18 years, whereas that of the lower body (femur and tibia) is detected at the age of 18–25 years. Bone remodelling and maintenance of bone indicate early adulthood, whereas late adulthood is marked by observations of bone wear and tear. Epiphyseal evaluation requires detailed examination of skeletal remains along with radiological assessment in fleshed material [14].

2.3. Body weight assessment

In studies using laboratory animals of varying unknown ages, it is important to differentiate the cohort groups according to their age. For this purpose, the frequency distribution of their body weights can be plotted to represent different cohorts. Then the statistical models in the body weight distribution are determined, from which the different age classes can be predicted [15]. The approximate age of mice pups can also be determined by their physical characteristics during the first 2 weeks of their life (Fig. 2).

2.4. TW pattern

As laboratory mice experience constant attrition of their molar teeth when grinding food, the degree of TW is proportional to the age of the

mice [15]. The skulls of mice have been observed under a dissecting microscope for dental eruption and wear patterns of the upper molar (M) (which are used in determining the age classes). Based on these observations, a standardized age chart is formulated:

TW age 1: M3 is partly erupted and unworn.

TW age 2: M3 is completely erupted and slightly worn, whereas M1 and M2 show negligible wear on their occlusal surface.

TW age 3: M3 is visibly roughly worn with a concave occlusal surface; M1 shows a protocone and paracone, and fused anterolingual and anterolabial conules; and M2 shows a protocone and paracone, as well as fused hypocone and metacone.

TW age 4: M3 becomes flat or concave; M1 shows a completely worn occlusal surface; and M2 shows greatly decreased anterolingual and anterolabial conules.

TW age 5: all cusps of M1 become more diminutive; the connections between the M2 protocone–paracone and hypocone–metacone are completed; and the anteroloph and anteroconule are considerably reduced.

TW age 6: M3 is concave; M1 shows connected protoconeparacone and hypocone–metacone; and all cusps of M2 are reduced further.

3. Relation between mice age and human age

Currently, biomedical studies achieve the highest accuracy and specificity due to the advances in technology. Therefore, in experiments with mice representing humans, the mice age must be precisely determined in relation to human age, in terms of both the lifespan and individual life stages. In the following section, we present human age in relation to different developmental stages of mice.

3.1. Relation between their lifespans

Mice have a shorter and accelerated early life, compared with humans. As the developmental stages of mice are not uniform compared with humans, the correlation between their entire lifespans cannot be used to determine human days in terms of mice days and vice versa, at every life stage.

Studies on the broad distributions of age at death within inbred strains and variances in the mean survival rate of mice under diverse conditions revealed the significant effect of environmental factors on longevity. Intercurrent infections, parasitism and fighting lead to unpredictable deaths. Three specific non-genetic factors (mammary tumour virus, breeding history and diet) affecting lifespan have been identified in controlled investigations. Individual alterations in these factors may result in differences in lifespan within a single colony of a particular strain. Other perceptible within-strain life-history variables, such as season of birth, age of parents at birth, or lifespan of parents, have no discernible effect on mouse lifespan. Differences between strains have also demonstrated the significance of genetic factors for lifespan.

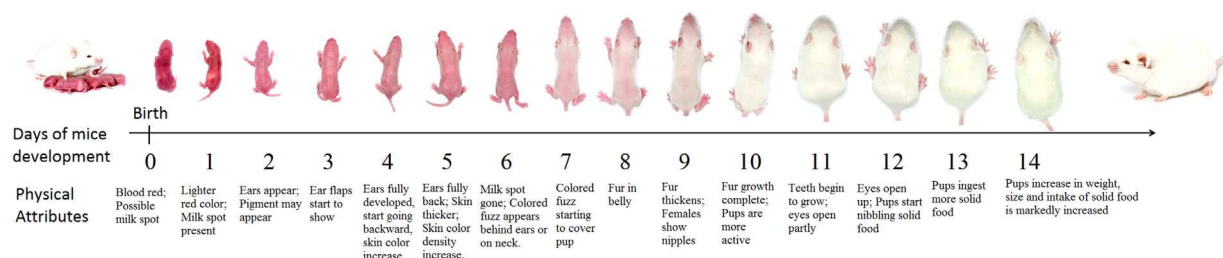


Fig. 2. The approximate age of mice can be determined by their physical attributes during the first 2 weeks of life.

Table 2
General physiology and reproductive data of laboratory mice.

Common physiological data		Reproduction data	
Body temperature	36.5–38 °C	Age at pairing (mating)	6–8 weeks (male)
Respiratory rate	80–230 breaths/min	Weight at pairing	20–30 g (male)
Heart rate	310–840 beats/min	Age at pairing (mating)	6–8 weeks (female)
Daily water consumption	5–8 ml/100 g body weight	Weight at pairing	18–35 g (female)
Daily food consumption	5–7 g/100 g body weight	Length of oestrous cycle	4–5 days
Litter size	2–10	Duration of oestrus	8–16 h
Birth weight	1–2 g	Time of ovulation	8.5 h after onset of oestrus
Breeding duration	10–15 months	Menopause	17–18 months
Male adult weight	20–30 g	Time of copulation	Midpoint of previous dark cycle
Female adult weight	18–35 g	Time sperm is detected in vagina	16–48 h
Lifespan	1–3 years	Time of implantation	Late day 3.5
Blood volume	1.5–2.5 ml	Length of gestation	18–21 days

The average lifespan of laboratory mice is about 24 months [16] (Table 2), whereas the life expectancy of humans globally is about 80 years, which varies among countries based on economic status [17].

Therefore, considering both lifespans, the correlation can be calculated as follows:

$$(80 \times 365) \div (2 \times 365) = 40 \text{ human days} = 1 \text{ mice day};$$

and

$$365 \div 40 = 9.125 \text{ mice days} = 1 \text{ human year.}$$

Thus, one human year is almost equivalent to 9 mice days when correlating their entire lifespan.

3.2. Weaning period of mice and human

Mammals are altruistic as they nurse and feed their young ones, which later withdraw from mother's milk and learn independent feeding habits and survival strategies in their environment. According to the medical dictionary, 'weaning is the transition of the human infant from breast-feeding or bottle nursing and commencement of nourishment with other food' (see Ref. [18]).

Mice are weaned at 3–4 weeks, approximately on 28th days (P28), after birth. While weaned, the pups become robust, active, their eyes open up, teeth and fur develop well and are able to jump, feed themselves and drink on their own [19]. On the other hand the average weaning age for humans is about 6 months (180 days) (see Ref. [6]).

Thus,

$$180 \div 28 = 6.43 \text{ human days} = 1 \text{ mice day and } 365 \div 6.43 = 56.77 \text{ mice days} = 1 \text{ human year.}$$

Therefore, in this developmental phase, one human year equals 56.77 mice days.

3.3. Mice and human age to attain puberty

Puberty is the peak phase of maturation of the hypothalamo-pituitary-gonadal axis, which is characterized by alterations in gonadotropin levels in circulation and elevated levels of sex steroids. The most common markers of puberty onset in mice are vaginal cornification and onset of the oestrous cycle in females and balanopreputial separation (BPS) in males [20]. At birth, the pituitary glands of mice are physiologically undifferentiated from gonadotropins. Moreover, the ovaries are unresponsive to gonadotropin. Sex differentiation of the pituitary usually occurs by day 6 (P6) in males and before day 12 (~P12) in females. Typically, sexual maturity coincides with rising titres of circulating gonadotropin after 4 weeks of age. The first observable signs of puberty in females are oestrogen dependent: vaginal introitus and a cornified vaginal smear. The vagina may open as early as day 24 (P24), and it is

often reported open by 4 weeks (~P28) of age. In addition, oestrus, that is, the willingness to mate, does not always occur on schedule.

The average age at which mice attain puberty is about 42 days (P42) [21,22], and the average age in humans is about 11.5 years ($11.5 \times 365 = 4198$ days) [23].

Thus, in the prepubertal phase,

$$4198 \div 42 = 99.95 \text{ human days} = 1 \text{ mice day,}$$

and

$$365 \div 99.95 = 3.65 \text{ mice days} = 1 \text{ human year.}$$

Thus, in this phase, one human year is equivalent to 3.65 mice days.

3.4. Age of adulthood onset in mice and its relation to human age of adulthood

Adulthood is biologically defined as the age at which sexual maturity is attained in the case of mice or other animals, but it is associated with several psychological and social concepts in humans. Mice attain sexual maturity at 8–12 weeks of age, with an average of 10 weeks (P70) [23]. Mice weigh about 1–2 g at birth, with adult male mice reaching 20–30 g and adult female mice 18–35 g [23]. In humans, growth plate closure is used to differentiate between adolescence and adulthood, as growth plates in the scapula fuse last, at about 20 years of age on average ($365 \times 20 = 7300$ days) [13,24].

Therefore, from these data, it can be calculated that

$$7300 \div 70 = 104.3 \text{ human days} = 1 \text{ mice day,}$$

which indicates that

$$365 \div 104.3 = 2.60 \text{ mice days} = 1 \text{ human year.}$$

Thus, during the adult phase, 2.60 mice days are equivalent to one human year.

3.5. Reproductive senescence in mice and humans

Although senescent changes in mice begin in middle age (10–15 months), the biomarkers of ageing are not detected then. However, reproductive functions cease at the end of middle age, and the upper limit for the middle-aged group is considered to be 15 months (P450) of age in mice [25]. In humans, menopause in women is a marker of reproductive senescence, which is associated with the termination of the fertility cycle [26,27]. The average age of menopause in women, according to the American Medical Association, is 51 years ($51 \times 365 = 18,615$ days) (see Ref. [6]).

Thus,

$$18,615 \div 450 = 41.37 \text{ human days} = 1 \text{ mice day,}$$

and

$$365 \div 41.37 = 8.82 \text{ mice days} = 1 \text{ human year.}$$

Thus, during reproductive senescence, 8.82 mice days are equivalent to one human year.

3.6. Post-senescence phase in mice and humans

In mice, senescence is defined by a minimum age of at least 18 months [25], when the biomarkers of old age are prominently detected, with a lifespan of around 24 months, as stated in the previous sections. Thus, the post-senescence period in mice is about 2 months (60 days), and female humans may survive approximately for 10,585 days after senescence.

Thus,

$$10,585 \div 60 = 176.4 \text{ human days} = 1 \text{ mice day,}$$

$$365 \div 176.4 = 2.069 \text{ mice days} = 1 \text{ human year.}$$

Thus, in the senescence phase, 2.069 mice days are equivalent to one human year.

4. Conclusions

This article reveals the wide variations in the developmental durations and phases of mice versus humans, although murine models are essential in biomedical science to study human physiology and its modulations. The relative ages of mice differ depending on the life stage. Therefore, it is imperative that researchers know the precise correlation between mice age and human age at a specific life stage of the mice under their studies.

Conflict of interest

The authors declare that there are no conflicts of interest.

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