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A mouse genetic locus with death clock and life clock features

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Abstract

A senility syndrome, with weight loss and priapism, occurs in CBAT6/T6 mice, an exceptionally long-lived strain. Instead of dying at the expected time, these mice get senile weight loss and priapism and go on living. We have postulated that a mutant death clock kills the wrong neurons. Crosses with the NZW and C57BL/6 strains show causation by a single genetic locus (*Priap1*), with a pronounced gene dosage effect on timing. We report here that various cancers were the cause of death in 31 of 32 NZW mice, compared to only five of 22 CBAT6/T6 mice, a highly significant difference ($P < 0.001$). The longevity of (CBAT6/T6 × NZW)F1 hybrids, and the segregation of longevity with priapism and senile weight loss in (CBAT6/T6 × NZW) F2 hybrids, indicates that *Priap1*, or a linked gene, inhibits the cancers that usually shorten the lives of NZW mice. If a timer gene is involved, the cancer resistance action could be because the locus impedes the normal mid-life regression of *anti*-cancer defence. The priapism suggests loss of the medullary reticular formation neurons which normally inhibit male spinal sexual reflexes. In this region of the medulla there are also the respiratory and cardiac control centres, where apoptotic neuron destruction by the wild-type locus could govern maximal life-span. The CBAT6/T6 locus may be a mutant life-stage control clock. Its discovery could be the revelation of a new, major class of aetiology of disease.

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1. Introduction

The clock of life is wound but once
And no man has the power
To tell just where the hands will stop
At late or early hour.
Anon

Species of animals have life spans of different lengths. In man it is about 80 years, in mice, about 2 years. Some genetic mechanism must govern this diverse timing, the length of which has presumably evolved by Darwinian natural selection of reproductive advantage for each species. The nature of the governing mechanism is not yet known. Related to lifespan is evidence of error accumulation in the DNA of somatic cells. In mice, post-mortem examination of animals more than a year old provides a rich yield of tumors, in contrast to the pathologically-uninteresting, high prevalence of normality found in young animals. A similar situation pertains in man, but the high frequency of tumors is not seen until 50 years have elapsed rather than one. It is clear that some genetically-governed biological clock reduces the efficiency of DNA repair mechanisms much earlier in mice than in man.

In the course of studying somatic gene mutation, the cause of both cancer (Alberts et al., 1994) and autoimmune disease (Adams, 1996), we maintained mice for their whole lives, accidentally encountering evidence which suggested that a biological clock switches on genes that deliberately kill old animals. All CBAT6/T6 mice that live long enough develop a senility syndrome, with weight loss in both males and females, and priapism in the males (Adams et al., 1987, 1993). The extraordinary universality and uniformity of the syndrome suggest an origin in gene regulation, the switching on or off of genes, such as occurs at a lifestage event, like puberty. In crosses with the NZW and C57BL/6 strains, the syndrome is conserved (Adams et al., 1993), with occurrence of senile weight loss followed by priapism. In the F1 generations there is a pronounced timing effect of gene dosage, the mean onset time for priapism being delayed 35 weeks, from 116 weeks in the CBA mice to 151 weeks in the heterozygous mice (Adams et al., 1993). In the F2 generations, the frequencies of priapism, analysed in the light of those in the parental and F1 mice, indicate causation by a single gene or gene cluster (Table III in Adams et al., 1993). The syndrome does not shorten life and in F2 hybrids with the NZW strain it segregates with a 31-week delay in time of death, the significance of this longevity effect being $P < 0.001$ (Table IV in Adams et al., 1993).

The gene has been listed in the Mouse Genome Data Base (Blake et al., 1999) as Priapism1, symbol *Priap1*, and because of its potential relevance to human neu-

rodegenerative diseases, it is also listed in the Human Genome Data Base as PRIAPISM1.

In this paper we report a precise repetition of the senility syndrome in a further group of CBA mice and show its absence from NZW and C57BL/6 mice. We also report back-cross genetic studies which confirm the monogenicity of the senility syndrome and the gene dosage timing effect of its locus. Additionally, we report life-stage mortality rates in young, middle-aged and old mice of the CBA, C57 and NZW strains, and post-mortem studies which reveal a striking paucity of cancer in the CBA mice. The sum of the findings suggests that *Priap1* may be a mutant life-stage control locus.

2. Materials and methods

2.1. Mice

The mice used were males of the inbred strains CBAT6/T6, C57BL/6 and NZW, whose relevant features, diet, and housing are described in our previous paper (Adams et al., 1993).

2.2. Pathology

The mice were weighed every week or two and observed for priapism and any other abnormality. Sick mice were observed daily and euthanased when moribund or suffering, most mice being found dead without prior warning. Post-mortem examination included weighing of organs and tumours and histological examination of paraffin tissue sections stained by haematoxylin and eosin.

2.3. Statistical methods

The principles are described by Snedecor (1962). Some of the execution was by the Stat View SE and Graphics programme of Abacus Concepts Inc. To determine the significance of differences, Student's t-test was used for measurement data and the χ^2-test for enumeration data.

3. Results

3.1. The universality and sequential timing of the CBAT6/T6 senility syndrome

Fig. 1 shows the relationship between age and cumulative percentage of senile weight loss, priapism and death, in a group of male CBAT6/T6 mice. For senile weight loss, the first mouse was affected at 71 weeks of age and by 118 weeks, all

the surviving mice were affected. The mean onset-age of senile weight loss was 96 ± 7 weeks. For priapism, the onset ages range from 99 to 144 weeks, with a mean of 120 ± 11. This is similar to the 116 ± 8 weeks observed in our previous study (Adams et al., 1993). All the surviving mice were priapic by 144 weeks of age, when 13 of the 25 mice that developed priapism were still alive. There were 39 CBA mice at weanling age, so the frequency of priapism from this age is 25/39, 64%, compared to 14/20, 70% in our previous study (Adams et al., 1993), the combined figure being 66%. The mean age at death of the 15 priapic mice not killed for brain histology is 144 ± 9 weeks, the longest survivor living 162 weeks.

3.2. Senile weight loss is absent from the NZW and C57BL/6 strains

Fig. 2 shows the occurrence of senile weight loss in CBA mice, but not in NZW or C57 mice. The last was unexpected, in view of the occurrence of senile weight loss in (CBA × C57)F1 hybrids (Table V in Adams et al., 1993). The cause of the senile weight loss is not yet known. Food intake is not reduced, blood sugar is not raised, thyroid glands are small and histologically inactive and catecholamine excretion is not raised. There may be hyper-reactivity to alarm, but we have not been able to measure this.

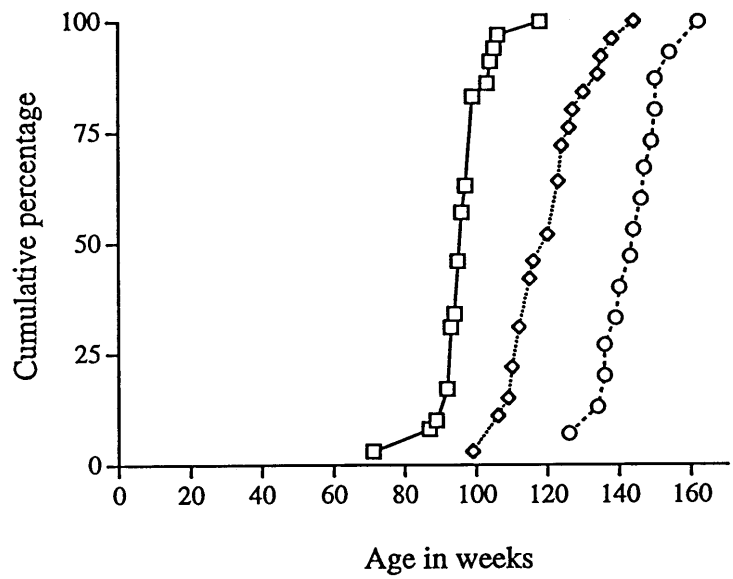

Fig. 1. The senility syndrome in a new group of CBAT6/T6 mice, showing the onset ages of the senile weight loss (squares, 34 mice) and priapism (diamonds, 25 mice) together with the ages at death (circles) of the 15 priapic mice that were not killed for brain histology. Onset of senile weight loss was the age when body weight decreased by 10% of the life-time maximum. The mice were maintained in boxes of 10, this number decreasing as they died. Individual animals were identified by ear punch numbering.

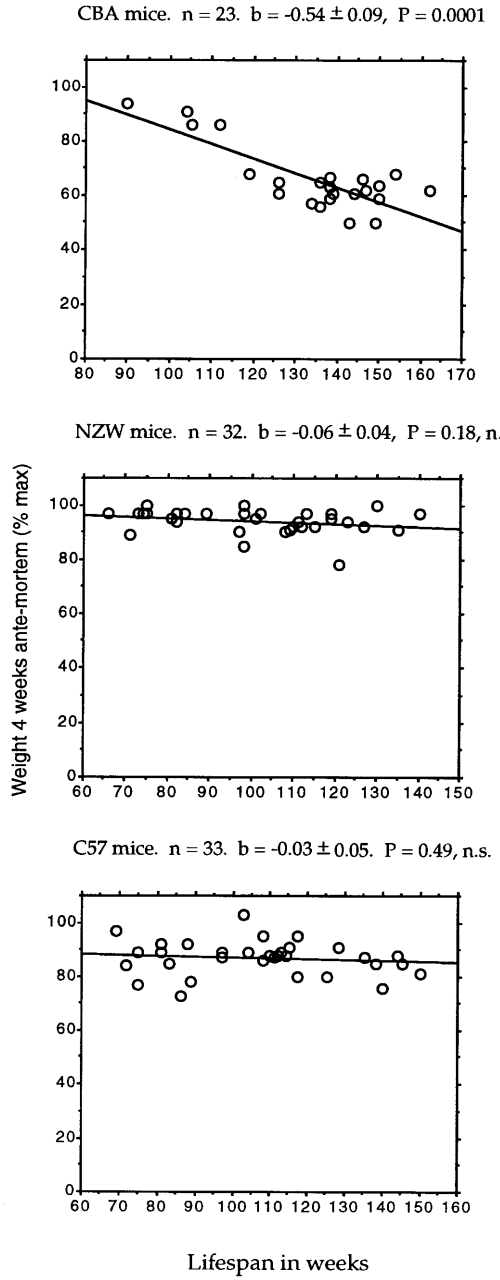

Fig. 2. Senile weight loss in CBAT6/T6 but not in NZW or C57 male mice. Each point represents a single mouse. The index of senile weight loss, which avoids agonal complication, is the change from lifetime maximal weight to the weight 4 weeks ante-mortem, expressed as a percentage of the maximum weight. For CBA mice the loss was 0.54% of maximum weight per week of senile life, compared to 0.06% in NZW mice and 0.03% in C57 mice.

Table 1
Absence of priapism in NZW and C57 mice

Mice	Number of weanlings	Number with priapism	Natural deaths[a]
CBAT6/T6	39	25	26
NZW	39	0	38
C57BL/6	36	0	34

[a] Animals not killed for histology.

3.3. Priapism is absent from the NZW and C57BL/6 strains

Table 1 shows that there was no occurrence of priapism in groups of NZW and C57 mice maintained for their whole lives, in contrast to a concurrently maintained group of CBAT6/T6 mice which showed senile priapism, as expected from previous studies and with the timing depicted in Fig. 1. In the priapic males there are no lesions in the genitalia and no lesions in the brain gross enough to be detectable by routine light microscopy.

3.4. Longevity is present in both the CBAT6/T6 and the C57BL/6 strains

Table 2 shows the lifespans of CBAT6/T6, NZW and C57BL/6 male mice and their (CBA × NZW)F1 and (CBA × C57)F1 hybrids in our laboratory, together with data from the massive study in which male mice of 24 strains had their lifespans recorded and reported to the Federation of American Societies for Experimental Biology by Altman and Katz. Important points are:

Table 2
Lifespans of male mice

Mouse strain	Number	Lifespan, weeks
Present findings		
CBAT6/T6	26	128 ± 5[a]
NZW	38	92 ± 4
C57BL/6	34	105 ± 5
(CBA × NZW)F1	20	137 ± 5
(CBA × C57)F1	20	128 ± 5
Previous findings		
Altman and Katz, 1979		
CBA/J	75 ± 2	
C57BL/6J	118 ± 5	
C57BL/10	118 ± 5	
22 other strains	81 ± 4	
Pugh et al., 1999		
C57BL/6	127 ± 3	

[a] Standard error of the mean.

1. The mean lifespan for 22 strains, excluding CBA, C57 and NZW, is 81 ± 4 weeks.
2. The CBAT6/T6 mice are the longest-lived strain, at 128 ± 5 weeks. They have a lower fiducial limit for lifespan of 109 weeks at the $P = 0.001$ level, showing that they are significantly longer-lived than the 22 strains and are therefore likely to be longevity mutants.
3. The C57BL mice are also long-lived. The four groups shown in Table 2, which include a recent report by Pugh et al. have a mean lifespan of 117 weeks. Our current group of C57 mice are significantly longer-lived than the 22 strains, but have a shorter lifespan than the three other C57 groups shown in Table 2, possibly due to their losses from rectal prolapse and a Behcet-like illness with skin ulceration (see Section 3.8 and Table 5). No such illneses ocurred in the concurrently maintained CBAT6/T6 and NZW mice.
4. The longevity of the C57 mice accounts for the lack of segregation of priapism with longevity in the (CBAT6/T6 × C57BL/6) F2 generation, where longevity is not confined to the priapic animals, but is general (Table VII in Adams et al., 1993).
5. The CBA/J strain do not show longevity, having a lifespan of 75 ± 2 weeks. As the CBAT6/T6 substrain is derived from the CBA strain, the longevity mutation must have occurred after the strains diverged.
6. The NZW strain does not differ significantly in lifespan from the 22 strains and can therefore be considered to be wild-type for longevity, as well as being wild-type for priapism absence and senile weight loss absence.

3.5. The gene dosage effect on priapism onset age shows in the backcross generations

As mentioned, in the F1 generations of crosses of CBAT6/T6 mice with the NZW and C57 strains, the senility syndrome is delayed, the mean onset age for priapism being 35 weeks later (Adams et al., 1993). Hence, there are two versions of the senility syndrome, early-onset and late-onset, depending on whether the mice are homozygous or heterozygous for *Priap1*.

Table 3 shows that NZW and C57 F1 hybrids back-crossed to CBA mice, have a priapism onset age of 129 ± 18 weeks, significantly later than the 119 ± 10 weeks of the pooled CBA mice, in accord with the backcross mice containing the expected mixture of ca. 50% homozygotes, and ca. 50% heterozygotes with their later onset age.

3.6. The mutant C57 allele

In F1 crosses of CBAT6/T6 mice with the C57BL/6 strain, the *Priap1* allelle causes early senile weight loss, but this does not occur in F1 crosses with the NZW strain (Tables V and VI in Adams et al., 1993). This suggests that the C57 mice

Table 3
Priapism onset ages in back-cross hybrids accord with these being the expected mixture of homozygotes and heterozygotes for *Priap1*

Mice	Number	Priapism onset age, weeks
CBA	39	119 ± 10
BX hybrids[a]	122	129 ± 18
Difference		10
Student's $t = 3.3$, $P < 0.005$.		

[a] 54 CBA × (CBA × NZW)F1 and 68 CBA × (CBA × C57)F1 backcross hybrids.

have a mutant allele which causes early senile weight loss, but not priapism, when with the *Priap1* allele. We propose the name Priapism1[f], symbol *Priap1*^{f}, for this C57BL/6 mouse allele.

Fig. 3 shows that the effect of *Priap1*^{f} is demonstrable in the backcross mice, where early senile weight loss, before 130 weeks, occurs in the non-priapic (predominantly heterozygotes for *Priap1*) C57 hybrids, but not in the equivalent NZW backcross hybrids. Late senile weight loss, prior to priapism at an average age of 151 weeks, occurs in both types of F1 hybrid.

3.7. Life-stage mortality rates

The number of deaths at three life-stages of the three strains of mice are shown in Table 4. There are two spectacular differences. In accord with human life-stage mortality rates, there are only 7 deaths in the young mice, compared to 60 in the middle-aged, a highly significant difference ($P < 0.001$). The second difference is between the CBA and the other two strains of mice, with 18 CBA mice surviving to old age, compared to only 5 NZW and 8 C57 mice, again highly significant in both instances, the bulk of the NZW and C57 mice dying in middle-age.

Table 4
Deaths at three life-stages of NZW, C57 and CBA mice[a]

	NZW	C57	CBA
Youth, <60 weeks	6	1	0
Middle-age, 60–120 weeks	27	25	8
Old age, >120 weeks	5	8	18
	38	34	26

[a] Significance of fewer deaths in youth than in middle-age: $\chi^2 = 40.4$, $P < 0.001$; Significance of greater survival to old age: CBA v. NZW, $\chi^2 = 18.7$, $P < 0.001$; CBA v. C57, $\chi^2 = 10.7$, $P < 0.005$; C57 v. NZW, $\chi^2 = 2.2$, n.s.

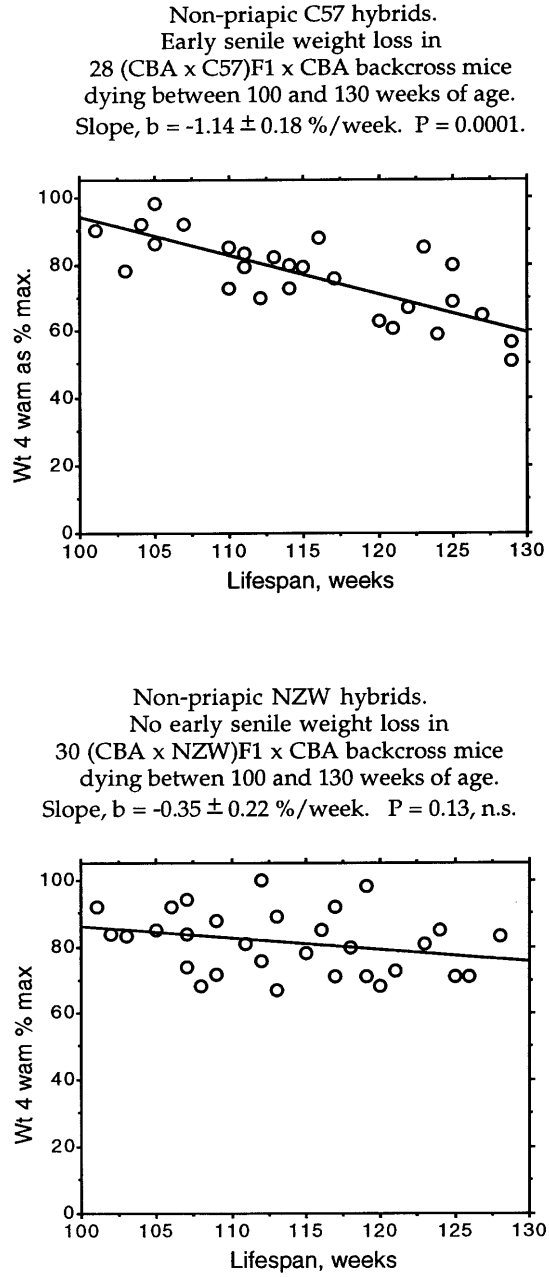

Fig. 3. The mutant C57 allele. Non-priapic C57 backcross hybrids, but not NZW ones, show early senile weight loss, prior to 130 weeks of age. This is a confirmation of the occurrence of early senile weight loss in (CBA × NZW)F1 hybrids.

3.8. Causes of death

Table 5 shows the pathology and ages at death of the NZW, C57 and CBA mice dying naturally. Of the 32 NZW mice dying naturally and examined post-mortem, 31 died of a variety of cancers, the commonest being in the lung, liver, and spleen. As well as the variety of sites, the tumors varied in their malignant characteristics, some being highly infiltrative, others causing death by massive size, with gross loss of functional lung or liver tissue or by obstructive pressure on lungs, ureters or gut. This variation is in accord with the random element in the somatic cell gene changes which cause malignant transformation.

Of the 33 C57 mice examined post-mortem, 17 died of a variety of cancers, most commonly in the liver. In the second year of their lives, 12 of the C57 mice died of a condition with extensive skin ulceration, unresponsive to *anti*-bacterial or *anti*-fungal topical therapy. Two of these mice had extensive intravenous clots at post mortem, one involving the inferior vena cava. This hints that the disorder was an autoimmune vasculitis, similar to Behcet's syndrome, an autoimmune vasculitis in man (Moutsopoulos, 1994; Sohn et al., 1998). Another disorder peculiar to the C57 mice, was rectal prolapse, which affected four animals around 2 years of age.

Of the 22 CBA mice examined post-mortem, 5 died of cancers, 4 in the liver and 1 a retinoblastoma. Hemiplegia preceded death at 104 weeks in one mouse. No cause of death was apparent in 16 of the oldest CBA mice, as discussed in Section 3.12.

The frequency of cancer in the NZW mice is significantly greater than in the other two strains. The greater cancer frequency in the C57 over the CBA mice does not quite reach significance.

3.9. Inhibition of cancer by Priap1 or a linked locus

The effect of CBA genes on the life-spans of NZW mice is shown in Table 2. In the F1 generation, the lifespan is increased from 92 to 137 weeks, showing that heterozygosity with a CBA allele inhibits the life-shortening cancers detailed in Table 5. In the F2 generation, the senility syndrome, with senile weight loss and priapism segregates with longevity (Table IV in Adams et al., 1993). This indicates that the locus where the CBA allele inhibits the NZW F1 cancers is either *Priap1* itself or tightly linked to *Priap1*.

3.10. The CBA senile state

This is the state of the mice after the onset of progressive senile weight loss, at an average of 96 ± 7 weeks of age. It lasts an average of 48 weeks, with priapism occurring midway between weight loss onset and death, as shown in Fig. 1. Right to the end, despite the progressive weight loss, the mice are hyperactive, often swinging on their cage bars in acrobatic fashion. In this way they are different from starving people, as in prisoner of war or Nazi concentration camps, who become inactive. The mice have resemblance to the subset of elderly people who become

Table 5
Causes and ages of death in the three strains of mice, showing reduced cancer frequency in the CBA and C57 strains[a]

Pathology	NZW		C57		CBA	
	Number of mice	Age in weeks	Number of mice	Age in weeks	Number of mice	Age in weeks
Unknown, no p.m.	6	34–75	1	110	4	64–126
None seen, p.m.	0		2	138, 140	16	134–154
Renal failure	1	82	0		0	
Neurological	0		4	69–112	1	104
Skin ulcers	0		12	49–105	0	
Thrombosis	0		2	75	0	
Anal prolapse	0		4	88–117	0	
Cancers						
Lung	9	51–135	1	144	0	
Liver	6	74–113	9	108–150	4	99–144
Spleen	4	51–115	2	75–108	0	
Stomach	1	119	0		0	
Abdominal	4	75–101	2	97, 128	0	
Lymphosarcoma	2	98, 140	1	113	0	
Pancreas	1	108	0		0	
Lachrymal gland	1	73	0		0	
Salivary gland	0		1	145	0	
Retinoblastoma	0		0		1	105
Pelvic	2	66, 111	5	75–150	0	
All mice with cancer	31	51–140	17	75–150	5	99–144
Total deaths	38		34		26	

[a] Significance of differences in cancer frequencies, excluding mice with no post-mortem: CBA < NZW, $\chi^2 = 29$, $P < 0.001$; CBA < C57, $\chi^2 = 3.4$, not significant; C57 < NZW, $\chi^2 = 15$, $P < 0.001$.

Table 6
Genotypes and phenotypes of the parental and filial mice

Mice	Genotype	Phenotypes observed			
		Swl[a]	Priapism[b]	Longevity	Cancer resistance
CBAT6/T6	*Priap1*/*Priap1*	+	+	+	+
C57BL/6	$Priap1^{f}/Priap1^{f}$	−	−	+	+
NZW	$+^{Priap1}/+^{Priap1}$	−	−	−	−
(CBA × C57)F1	$Priap1/Priap1^{f}$	+	−	+	+
(CBA × NZW)F1	$Priap1/+^{Priap1}$	−	−	+	+

[a] Senile weight loss.
[b] Here, early priapism, onset ca. 120 weeks is recorded. As described in the text, late priapism, onset ca. 150 weeks, preceded by senile weight loss, occurs in the F1 hybrids, showing a gene dosage effect on timing of *Priap1* expression.

thin in old age with no known cause, an apparent life-stage step, but the weight loss in the mice is greater.

The 15 priapic mice not killed for histology, spent an average of 24 weeks in the priapic state, with continuing gradual weight loss, before being found dead at 144 ± 9 weeks of age, after declining to an average of 18 ± 2 g, compared to 25 ± 2 g at the onset of priapism and a maximal body weight of 35 ± 2.5 g.

3.11. A wall of death

Fig. 4 shows the times of death of the individual mice of the three strains. The NZW and C57 mortalities rise in regular sigmoid curves until all of the mice are dead, but the CBA mice hit a veritable wall of death at the late age of 138 weeks, half of the original number dying in the following 20 weeks.

3.12. Unknown cause of death in the oldest CBA mice

Table 5 shows that, in mice examined post-mortem, the cause of death was unknown in none of 32 NZW mice and in only 2 of 33 C57 mice. In contrast, 16 of the 22 CBA mice dying naturally and examined post-mortem, showed no apparent cause of death. The increased frequency of unknown cause of death in the CBA mice is highly significant, $P < 0.001$, against both the other strains. What killed these priapic CBA mice? Their pathology shows nothing but loss of fat and shrunken livers. One possibility is that a tardy death clock finally caused lethally-sufficient apoptosis of neurons in the respiratory or cardiac centres.

3.13. Gene nomenclature

Table 6 shows that the observed phenotypes can be explained by a single locus, with the wild type present in the NZW strain and different defective mutants in the

CBAT6/T6 and C57BL/6 strains. The Mouse Genome Database Group have approved the following nomenclature:

Priapism1, with symbol *Priap1*, for the mutant locus causing priapism in the CBAT6/T6 mice.

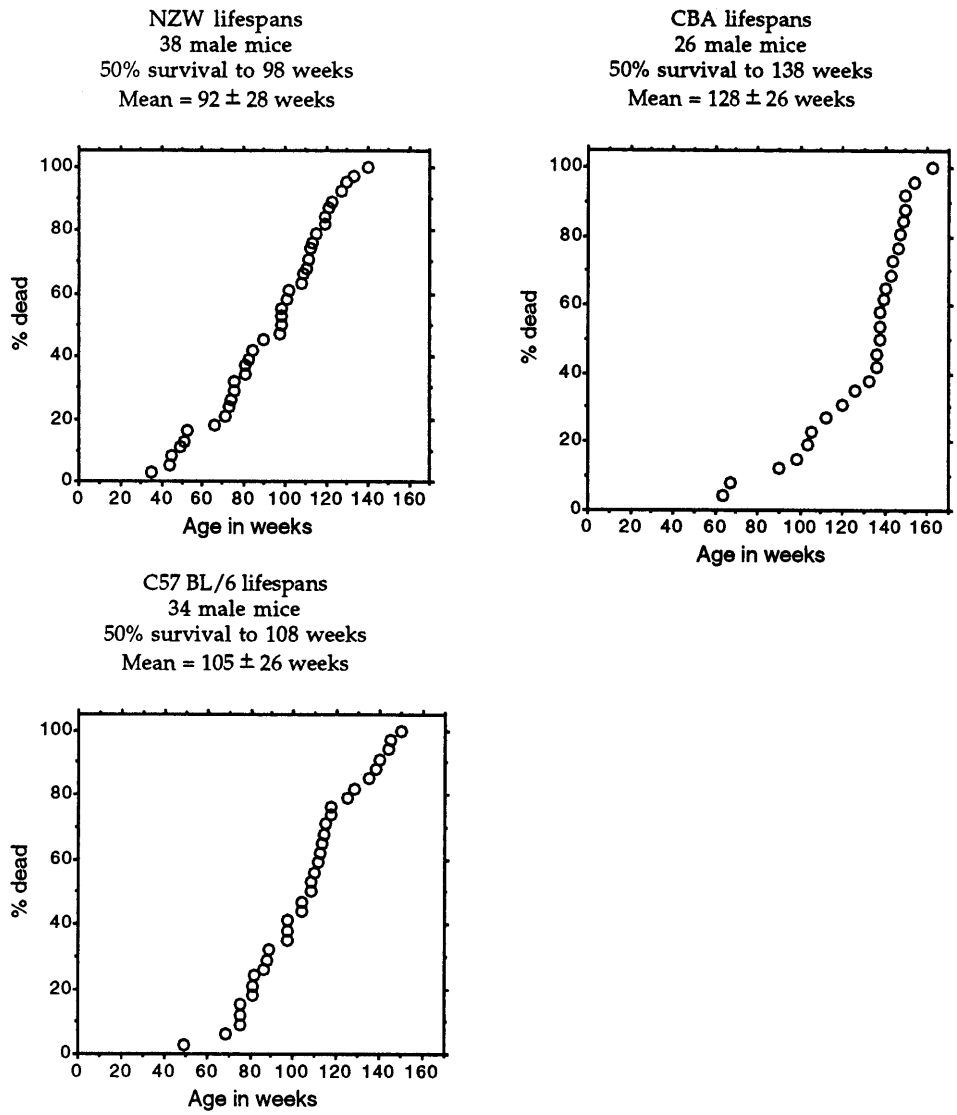

Fig. 4. Times of death of individual animals of the three strains of mice, showing the wall of death hit by the CBA strain at the advanced age of 140 weeks.

Priapism1^{f}, *Priap1*^{f} for the mutant C57BL/6 locus causing senile weight loss in the (CBAT6/T6 × C57BL/6)F1 mice, with *f* representing the first letter of fifty-seven, C being shared by the CBA mice.

Symbol $+^{Priap1}$ for the wild type locus in the NZW mice.

The name Priapism1 appropriately describes the abnormal reflex which provides an aetiological link with the central nervous system and is an invaluable gene marker for Mendelian studies, but a name better indicative of the timing actions and probable wild type function would have a clock connotation, such as Minute1.

4. Discussion

4.1. A neurological basis for the priapism

Clinicians have shown that priapism results from interruption of spinal tracts (French, 1945; Bors and Comarr, 1960) and physiologists have demonstrated that there is a tonic descending inhibition of male spinal sexual reflexes, via the spinal cord's reticulo–spinal tract (Sachs and Meisel, 1988). Recently, Marson and McKenna (1990) have identified the exact site of the brainstem neurons mediating inhibition of the spinal sexual reflexes in male rats. It is the nucleus paragigantocellularis (PGiC) in the reticular formation of the ventral medulla (Andrezik et al., 1981). The PGiC is also the site of the cardiac and respiratory control centres (Azami et al., 1981; Brown and Guyenet, 1985; Van Bockstaele and Aston-Jones, 1995) and a pacemaker (Sachs and Garinello, 1980), making it a suitable site for the action of a putative death clock.

4.2. Gene dosage effect on timing

A similar gene dosage effect on timing to that described here, occurs in Down syndrome, where an extra copy of chromosome 21 causes premature ageing (Smith, 1985). In both instances the extra copy of the gene causes the effect to occur earlier.

4.3. The anti-cancer effect

The segregation of priapism and senile weight loss with longevity in the (CBA × NZW) F2 hybrids shows that *Priap1* or a tightly linked gene inhibits the cancers that shorten the lives of NZW mice. How? The CBA mice appear to provide the NZW hybrids with a tumor suppressor gene (Alberts et al., 1994), active in the heterozygous state. One possibility, favoured by the wide diversity of the cancers inhibited, is that this is a defective life-stage control gene, which differs from the wild-type in failing to cause the normal mid-life regression of *anti*-cancer defences. This normally-occuring regression is illustrated by the young, middle-aged and old age mortality rates shown in Table 4 and by the ages of cancer deaths shown in Table 5.

4.4. Similarities to Alzheimer's disease

In the CBA mice an average of 24 weeks of progressive weight loss, is followed by priapism, which changes from intermittent to continuous and is followed, after a similar interval, by death. There is chronological analogy with Alzheimer's disease, which Damasio (1992) describes as a 'progressive, selective degeneration of neuron populations'. The aetiology of Alzheimer's disease is not yet known, but the CBAT6/T6 mouse phenomenon raises the possibility that death clock genes cause senile dementia and that mutants with premature timing cause Alzheimer's disease.

4.5. Biological clocks

The sinus node of the heart oscillates with a period of about 1 s, without pause, in contrast to the cell division cycle clock which is frequently stopped (Alberts et al., 1994). The Drosophila Per gene, which controls the frequency of wing beat, has sequence homology with mammalian circadian clocks. These are particularly well characterised, with mouse (mPer) and human (hPer) homologues and the master circadian oscillator known to be in the suprachiasmatic nucleus of the hypothalamus (Zheng et al., 1999). Circannual clocks, involved in animal breeding and governed by day length, are not yet well characterised. In *Caenorhabditis elegans*, mutant genes which increase lifespan have been been discovered (Murakami and Johnson, 1996), but no mammalian equivalents yet.

4.6. List of features which suggest life clock actions of the Priap1 locus

1. The delay until end of life for onset of the senility syndrome.
2. Universality of action; all animals affected (see Fig. 1); cf. puberty.
3. Uniformity of action; all animals affected at similar age and to a similar degree (see Fig. 2, Adams et al., 1993); cf. puberty.
4. Gene dosage effect on timing, expression in heterozygotes being 35 weeks later than in homozygotes; cf. Down syndrome with accelerated ageing from trisomy 21.
5. Protection against cancer; possibly due to prolongation of efficient youthful DNA repair, protecting against the mutations which cause cancer.
6. Unknown cause of death in oldest mice; possibly death clock action through apoptosis of vital cardiac or respiratory control neurons in the medullary reticular formation, where cellular mistargeting would account for destruction of adjacent neurons which normally inhibit priapism.

4.7. Conclusion

A fundamental characteristic of all forms of life is a strictly limited lifespan. A strange mutation in CBAT6/T6 mice may be revealing mammalian life clock genes, which control developmental steps such as puberty, the midlife decline of DNA

repair mechanisms and, finally, by a death clock action, deliberately kill old animals that have survived trauma, poison, starvation, infection, autoimmune disease and cancer, to keep maximum lifespan within a set limit. Mutations in life clock genes could be responsible for neurodegenerative disorders, such as Alzheimer's disease and motor neurone disease, by mistimed and cellularly mistargeted apoptosis.

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