C57BL/6

Origin:
Developed in 1921 by Little from brother - sister pair (female 57 x male 52) of Miss Abby Lathrop's stock. The same cross gave rise to strains C57L and C57BR. Female 58 mated with the same male gave rise to strain C58. Strains 6 and 10 separated prior to 1937. In 1946, to the Jackson Laboratory, Bar Harbor.

- **C57BL/6J Olahsd**
  In 1974, from the Jackson Laboratory to Laboratory Animals Centre, Carshalton. To OLAC (now Harlan UK) in 1983. In 1997 to Harlan Nederland.

- **C57BL/6JRccHsd**
  In 1973, from the Jackson Laboratory to the Biological Research Laboratories-RCC Ltd. Füllinsdorf, Switzerland. In 2005, Harlan obtained a breeding nucleus after acquisition of RCC Ltd.

- **C57BL/6NHsd**
  In 1974, from the Jackson Laboratory to the National Institutes of Health, Bethesda, Maryland. Harlan Sprague Dawley, In., derived the strain from this breeding nucleus.

Research Applications
Behaviour, learning, atherosclerosis, metabolism, alcohol preference anatomy, irradiation, carcinogenesis, immunology, infections.

Characteristics:
The C57BL is easily the most widely used of all inbred strain. Used as a genetic background for many mutants e.g. obese, diabetes and beige. This is a long-lived strain with few tumours, some spontaneous congenital abnormalities.

- **Anatomy**
cranial skeletal development every 2 hrs between days 11 and 13 of gestation has also been described (Miyake et al, 1996b)

- **Behaviour**

High alcohol (ethanol) preference (Fuller, 1964; Rodgers, 1966). The mean maximally preferred concentrations of ethanol were 17.9% for C57BL/6 and 6.8% for ICR mice. The consumption of ethanol represents a preferred source of calories for the C57BL/6 mouse (McMillen et al, 1998).

Achieve blood alcohol levels of 60 mg% when access to alcohol is restricted to 60 min per day (Le et al, 1994). Alcohol preference may be associated with strain differences in mesolimbic enkephalin gene expression (Ng et al, 1996). A quasi-congenic QTL introgression strain carrying a low alcohol consumption gene from BALB/c has lower voluntary alcohol consumption than C57BL/6, with 96% of loci in common (Vadasz et al, 1996).


- **Drugs**

Susceptible to skin ulceration by DMBA (Thomas et al, 1973). Susceptible to induction of subcutaneous tumours by 3-methylcholanthrene (Kouri et al, 1973; Whitmire et al, 1971). High incidence of lymphomas after methylcholanthrene administration by gavage (Akamatsu and Barton, 1974). Susceptible to toxic effects of DMBA (Schmid et al, 1966). Pre-treatment with beta-naphthoflavone 48 hr. before administration of N-nitrosothylurea (ENU), once weekly for 4 weeks caused a significant doubling in the number of lung tumour bearers (contrast 4 strains) (Anderson et al, 1990). Phenobarbitone in the diet to give an intake of 85 mg/kg per day resulted in 4% of animals developing basophilic nodules by 91 weeks of age (contrast 70% in C3H/He), but no increase in liver
carcinomas (Evans et al, 1992). However, there was a two-fold lower level of DNA synthesis in C57BL/6 mice relative to C3H mice after partial hepatectomy, though partial hepatectomy is a tumour promoter in C57BL/6 but not in C3H mice (Bennett et al, 1995). Sensitive to teratogenic effects of acetazolamide (Green et al, 1973). Resistant to teratogenic effect (cleft palate) by cortisone acetate (Kalter 1981). Hepatic epoxide hydrase activity induced by pentobarbital i.p. (Oesch et al, 1973).


Low neural sensitivity to pentyleenetetrazol convulsions (Kosobud et al, 1992). Susceptible to biliary tract injury following oral dosing with 500 micrograms of the fungal toxin sporidesmin (Bhathal et al, 1990). Low histamine release from peritoneal mast cells induced by compound 48/80, a calcium dependent histamine releaser (Toda et al, 1989). Low histamine release from peritoneal mast cells induced by Ca2+ ionophore A23187, (contrast BALB/c, C3H/He, DBA/2 etc.) (Toda et al, 1989). Carries gene (Tpmt) for low levels of thiopurine methyltransferase activity, catalyzing the S-methylation of 6-mercaptopurine and other heterocyclic and aromaticthiol compounds (like AKR, unlike DBA/2) (Ottermess and Weinshilboum 1987a,b). More sensitive to acute toxic effects of aflatoxin B-1 than strains CBA/J or BALB/c (Almeida et al, 1996). Airways hyporeactive to acetylcholine (Zhang et al, 1995). High voluntary consumption of morphine in two-bottle choice situation (Belknap et al, 1993). Oestrogen induces an increase in VLDL and LDL-cholesterol (like C57L, contrast BALB/c and C3H) (Srivastava, 1995). Nine-fold higher ED50 for haloperidol-induced catalepsy than DBA/2, but this is not associated with numbers of cholinergic neurons (Dains et al, 1996). Accumulates three to five-fold lower levels of mercury in liver and blood than DBA/2 or A.SW after 4 weeks exposure to mercuric chloride, but higher levels in spleen following 8-12 weeks of exposure (Griem et al, 1997).
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- **Genetics**
  Coat colour genes – \( a, B, C, D \) : black.
  Histocompatibility – \( H-1^c, H-2^b, H-3^a \).
  Biochemical markers – \( \text{Apoa-1}^a, \text{Car-2}^a, \text{Es-1}^a, \text{Es-2}^b, \text{Es-3}^a, \text{Gpd-1}^a, \text{Gpi-1}^b, \text{Hba}^a, \text{Hbb}^a, \text{Idh-1}^a, \text{Ldr-1}^a, \text{Mod-1}^b, \text{Mup-1}^b, \text{Pep-3}^a, \text{Pgm-1}^a, \text{Pgm-2}^a, \text{Trf}^b \).

Four major substrains A, GrFa, 6 and 10 appear to be quite similar, and any differences are consistent with what might be expected from the accumulation of new mutations and a small amount of residual heterozygosity, though McClive et al (1994) have found that B6 and B10 differ at multiple loci on chromosome 4 including the microsatellite markers D4Mit69, D4Mit71 and D4Mit72. Additional microsatellites, which distinguish between B6 and B10 are given by Slingsby et al (1996). Substrains 6 and 10 differ at the \( H-9, \text{Igh-2} \) and \( \text{Lv} \) loci.

C57BL/6JOlaHsd mice lack \( \alpha \)-synuclein due to a small deletion of the locus (Specht and Schoepfer, 2001). \( \alpha \)-Synuclein belongs to a family of structurally related proteins expressed highly in the brain. However, \( \alpha \)-synuclein is not essential for spatial learning tasks (Chen et al, 2002). The deletion is not present in the C57BL/6JRecfHsd subline!

Description of the difference between FVB/N and C57BL/6J for 272 microsatellites (Neuhaus et al, 1997). A probe designated B6-38 to the pseudoautosomal region of the X and Y chromosome has a characteristic Pst I pattern of fragment sizes which is present only in the C57BL family of strains (Kalcheva et al, 1995). C57BL/6 mice carry the \textit{Mus musculus musculus} \( Y \)-chromosome, while others have the \textit{M. m. domesticus} type (Nishioka, 1987).

- **Growth Chart**

![Growth Chart](image)

C57BL/6JOlaHsd – Harlan Nederland

- **Immunology**
  High susceptibility to induction of amyloid by casein (Willerson et al, 1969).
  Poor immune response to type III pneumococcal polysaccharide (Braley and Freeman, 1971).
  Poor immune response to synthetic double-stranded RNA (Steinberg et al, 1971).
  Good immune response to cholera A and B antigens (Cerny et al, 1971).
  Resistant to induction of anaphylactic shock by ovalbumin
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- **Infection**

Develops a slowly progressing parasitosis ("low responder") after infection with the Cornell strain of Toxoplasma gondii (Macario et al, 1980). Did not support sustained growth of six strains of Leishmania mexicana mexicana (contrast BALB/c) (Monroy-Ostria et al, 1994). Resistant to Leishmania major (contrast BALB/c) (Laskay et al, 1995; Scott et al, 1996). Susceptible to L. major mexicana, and vaccination against the parasite using liposomes with parasite membrane antigens was effective (cf CBA/Ca but contrast C57BL/10) (Lezama-Dávila, 1997). Susceptible to Salmonella typhimurium strain C5 (Robson and Vas, 1972). 100-fold more resistant to Listeria monocytogenes than A/J when measured by median lethal dose (Sadarangani et al, 1980). This seems to be associated with increased levels of gamma interferon and granulocyte-macrophage colony stimulating factor compared with susceptible A/J mice (Iizawa et al, 1993). Resistant to Mycoplasma fermentens (Gabridge et al, 1972). Resistant to Mycoplasma pulmonis infection (Cartner et al, 1996). Resistant to infection by Mycobacterium marinum (Yamamoto et al, 1991). Resistant to infection by liver fluke Opisthorchis felineus (Zelentsov, 1974). Resistant to infection with the helminth worm Angiostrongylus costaricensis (Ishii and Sano 1989). Relatively susceptible to infection with Helicobacter felis (contrast C57BL/6) (Mohammadi et al, 1996). Susceptible to infection by Helicobacter
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felis with moderate to severe chronic active gastritis in the body of the stomach, which increased over time (Sakagami et al, 1996). H. felis induces hypertropic gastropathy (Fox et al, 1996). Highly resistant to the mammary tumour virus which is thought not to be carried by the strain (Murray and Little, 1967). Resistant to Herpes simplex virus (Lopez, 1975). Resistant to herpes simplex virus-1 (contrast BALB/c) (Brenner et al, 1994). Susceptible to mouse hepatitis virus type 3 infection (Le Prevost et al, 1975).

Develops antibodies to mouse hepatitis virus which can be reliably detected by the complement fixation test, in contrast to five other strains (Kagiyma et al, 1991). Low mortality in a natural epizootic of ectromelia (Briody, 1966). High expression of RNA tumour virus group-specific antigen in some substrains but low in others (Whitmire and Salerno, 1972). Resistant to development of leukaemia on infection by Friend virus (Dietz and Rich, 1972). Resistant to diabetogenic effects of encephalomyocarditis virus, but treatment with carrageenan to compromise macrophage function makes the mice susceptible (Hirasawa et al, 1995). Susceptible to measles virus induced encephalitis, which correlates with a high cytotoxic T-lymphocyte response (like C3H, contrast BALB/c) (Niewiesk et al, 1993). Resistant to the development of tumours following inoculation with polyoma virus, in contrast with C3H/Bi (Freund et al, 1992). Resistant to the development of chronic Chagas' cardiomyopathy in postacute Trypanosoma cruzi infection (Rowland et al 1992). Resistant to infection with Trypanosoma congoense with an initial peak of parasitemia on day 6, followed by rapid apparent clearance in an average of 3 days (contrast BALB/c) (Ogunremi and Tabel, 1995). Infection with larval Echinococcus multilocularis by transportal injection of hydatid homogenate results in a multivesiculation form of hydatid development (Nakaya et al, 1997). Susceptible to mouse adenovirus type 1 which causes a fatal hemorrhagic encephalomyelitis (contrast BALB/c) (Guida et al, 1995). Less susceptible to Streptococcus suis type 2 including the type strain, two isolates from meningitis in pigs and two isolates from tonsils of clinically healthy pigs (Kataoka et al, 1991). Resistant to carditis on infection with Lyme borreliosis (Borrelia burgdorferi) (contrast C3H, SWR, BALB/c) (Barthold et al, 1990). Thymectomized C57BL/6 mice that were intravenously infused with monoclonal antibody to selectively deplete CD4+ T cells are susceptible to disseminated Mycobacterium avium infection. The increased susceptibility is comparable to that of C57BL/6-bg. The course of such infections can be markedly restrained and in some cases the infections can be sterilized by treatment over a 120-day period with the antimycobacterial agent rifabutin (Furney et al, 1990). Susceptible to infection with M. avium strains 101 and 2-151, and can be used to test anti-mycobacterial agents (Furney et al, 1995). Susceptible to infection with M. paratuberculosis (contrast C3H/HeJ) (Tanaka et al, 1994). Resistant to infection with Yersinia enterocolitica associate with a good interferon gamma response (contrast BALB/c) (Autenrieth et al, 1994). Susceptible, with high amylase response to the fungus Paracoccidioides brasiliensis (Xidieh et al, 1994). Mouse mammary tumor proviral loci have been identified by Lee and Eicher (1990). Resistant to infection with Ehrlichia risticii...
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(Williams and Timoney, 1994). Highly susceptible to *Plasmodium berghei* with all mice developing erythrocytic infection following intravenous injection of 50 sporozoites. The same level of infection could only be established in BALB/c with 10,000 sporozoites (Scheller et al, 1994). Infection with *P. berghei* results in low blood parasitaemia and death with neurological symptoms within 8-10 days, in contrast with the more resistant BALB/c (Moumaris et al, 1995). Resistant to chronic weakness and inflammation following infection with Tucon strain of coxsackie virus B1, in contrast with C57BL/10 and B10 congenic strains (Tam and Messner, 1996).

- **Life-span and Spontaneous Disease**

Primary lung tumours 1% in males, 3% in breeding females and zero in virgin females. Lymphatic leukaemia less than 2%, mammary adenocarcinomas less than 1% (Hoag, 1963). Leukaemia 7% (Myers et al, 1970). Rare "lipomatous" hamartomas or choristomas have been noted (Adkison et al, 1991). Susceptible to the development of atheromatous lesions on wall of aorta after 20 weeks on a high-fat diet (Thompson, 1968; Roberts and Thompson, 1976). Develop fatty streak-like lesions in the valve sinus region of the ascending aorta after 10-20 weeks on a diet enriched in saturated fat and cholesterol. After a further 15 weeks fibro-fatty lesions with many of the characteristics of human atheromatous plaques are found (Stewart-Phillips and Lough 1991).

Exhibit aortic cartilaginous metaplasia (contrast C3H) (Qiao et al, 1995). Susceptible to diet-induced aortic fatty streak lesions which correlates with a low level of paroxinase mRNA (contrast C3H) (Shih et al, 1996). Develops non-insulin-dependent diabetes mellitus and hypertension when fed a high fat-high simple carbohydrate diet, whereas A/J mice do not (Mills et al, 1993). Susceptible to the development of atherosclerosis on a semi-synthetic high fat diet (Nishina et al, 1993). Blood glucose levels and insulin insensitivity in crosses between diet-induced type II diabetes sensitive C57BL/6 and resistant A/J are genetically independent (Surwit et al, 1991). High simple carbohydrate diet for five months induced hyperglycaemia, hyperinsulinaemia and hypercholesterolaemia and non-insulin-dependent diabetes mellitus which appeared to be associated with the metabolic characteristics of visceral fat (Rebuffe-Scribe et al, 1993). Gain more weight on high fat diets without consuming more calories than A/J mice and develop adipocyte hyperplasia. However, animals fed a low fat, high sucrose diet were leaner than those fed a high-complex-carbohydrate diet. These results suggest that genetic differences in metabolic response to fat are more important in the development of obesity and diabetes than caloric intake (Surwit et al, 1995). Loci on chromosomes 1, 3, 5 and 11 are associated with variation in high density lipoprotein levels with coordinate expression of cholesterol-7-alpha hydroxylase in a cross involving atherosclerosis resistant C3H/HeJ mice (Machleder et al, 1997). Hepatic stearoyl CoA desaturase mRNA levels significantly elevated compared with atherosclerosis-resistant BALB/c mice, and was reduced in mice fed a high fat diet (Park et al, 1997). Congenital abnormalities 10%, including eye defects, polydactyly and otocephaly (Kalter, 1968). Microphthalmia and anophthalmia 8-20% and hydrocephalus 1-3% (Dagg, 1966). Ocular defects appear to be due to defects in development of
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the lens (Robinson et al., 1993). Develop spontaneous auditory degeneration with onset during young adulthood, with enhanced susceptibility to acoustic injury and delayed effects of toluene (contrast CBA/Ca) (Li, 1992, Willott et al., 1993; Li et al., 1993; Li and Borg, 1993). This is associated with early hair cell changes including bent and fused stereocilia, bulging of the cuticle plates, hair cell loss and swelling of affected dendrites (Hultcrantz and Li, 1993).

C57BL/6 mice carry a single recessive gene different from that found in BALB/cBy and WB/ReJ, causing age-related hearing loss (Willott et al., 1995). Hearing loss is caused by degeneration of the organ of Corti, originating in the basal, high frequency region and then proceeding apically over time. This results in a severe sensorineural hearing loss by 14 months of age (Walton et al., 1995). More susceptible to noise-induced hearing loss than CBA/J (Erway et al., 1996).

Median life-span 22.4 months in C57BL/6 males and 23.6 months in C57BL/6 females (Storer, 1966). Median life-span 24.7 and 29.6 months in C57BL/6 males and 23.6 and 29.8 months in C57BL/6 females (Les, 1969). Median life-span 27.6 months in C57BL/6 males and 27.3 months in C57BL/6 females (Goodrick, 1975). Median life-span 29.3 months in C57BL/6 males and 26.5 months in C57BL/6 females (Kunstyr and Leuenberger, 1975). Median life-span 20.0 months (Curtis, 1971). Gross tumour incidence 70%, maximum life-span about 40 months in SPF conditions (Mewissen, 1971).

Dermatitis with intense pruritis leading to self-mutilation and death, and sometimes associated with the mite Myobia musculi appears to be more severe in this strain than others (Csiza and McMartin, 1976). Impaired axonal regeneration involving multiple genetic loci (Lu et al., 1994)

- **Miscellaneous**

  High degree of genetic distinctiveness (Taylor, 1972). Recommended host for the following transplantable tumours: mammary adenocarcinoma BW 10232 melanoma B16, myeloid leukaemia C 1498 and preputial gland carcinoma ESR586 (Kaliss, 1972). Embryonic stem cell lines have been established (Kawase et al., 1994). High rate of spontaneous mutations at the agouti and W loci (Schlager and Dickie, 1967). Characteristics of the A strain have been described by Festing (1997) and Lyon et al., (1996).

- **Physiology and Biochemistry**

  Low plasma cholesterol at 12 and 24 weeks (Weibust, 1973). Low plasma triglyceride levels (in By and in J substrains) and low plasma cholesterol (in By and in J substrains) (Jiao et al., 1990). Low serum ceruloplasmin levels in males but intermediate in females (Meier and MacPike, 1968). High blood sugar (Nishimura, 1969). Low serum cholesterol in C57BL/6-d’a (Bruell et al., 1962). Arterial blood has a low pH (Bernstein, 1966). Low concentration of prostaglandin F in epididymis (Badr, 1975). High liver tyrosine aminotransferase in fasted mice but low in C57BL/6-ob (Blake, 1970). Low brain L-glutamic acid decarboxylase (GAD) and acetylcholinesterase activity but high catechol-O-methyltransferase activity (Tunnicliff et al., 1973). Low calcium uptake by the heart (Mokler and Iturrian, 1973). Low sensitivity to thyrotropin (Levy et al., 1965). High brain sulphatide (Sampugna et al., 1975). High hepatic benz (alpha) pyrene hydroxylase activity (Kodama and Bock, 1970). Low hepatic delta-

Low basal levels of kidney catalase, superoxide dismutase and renal glutathione reductase (Misra et al, 1991). Iron overload causes inhibition of hepatic uroporphyrinogen decarboxylase and uroporphyrin in C57BL/10ScSn but not DBA/2 mice. This was not correlated with the Ah locus in a study involving 12 mouse strains (Smith and Francis, 1993). Low levels of apoA-IV messenger RNA in liver compared with 129/J (Reue et al, 1993). Low susceptibility to audiogenic seizures (Deckard et al, 1976). Long tau DD, the endogenous (free-running) period of the circadian pacemaker measured in constant environmental darkness (Schwartz and Zimmerman 1990). Has defective secretory group II phospholipase A2 gene (cf strains 129/Sv and B10.RIII) (Kennedy et al, 1995). Susceptible to severe hypercapnia with hypoxia assessed by elevated minute ventilation rate (Tankersley et al, 1994). Has a rapid and shallow breathing pattern phenotype (contrast C3H) (Tankersley et al, 1997). Susceptible to cerebral ischemia following bilateral carotid occlusion with 90% of mice showing typical neurological signs such as torsion of the neck and rolling fits with selective neuronal death in the hippocampus and caudoputamen after 20 minutes of ischemia (Yang et al, 1997).

- **Reproduction**
  

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