Spontaneous Diseases in Commonly Used Mouse Strains / Stocks

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I. INTRODUCTION

The terms "gene", "genotype" and "phenotype" were introduced by the Danish botanist Wilhelm Johannsen in 1909. [2-4]

Gene is from Greek *genos* (race or offspring), and refers to a unit of heredity.

Genotype is from the Greek *genos* plus *tupos* (type), and refers to the genetic constitution of an individual organism.

Phenotype is from Greek *phainen* (to show) plus *tupos* and refers the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment. Thus phenotype reflects the nature and the nurture of the organism, with genetics or genetic constitution, including any spontaneous genetic alteration or intended manipulation, comprising the nature of mice, and with environmental and experiential factors, including microbial exposure, comprising their nurture.

Genome refers to the entire genetic constitution of an organism: all nuclear (chromosomal) DNA + mitochondrial DNA, including long regions that have no apparent product or function.

Phenome refers to the set of all phenotypes of an organism.

I.A. VARIABLES THAT AFFECT PHENOTYPE

I.A.1. NATURE: Genetics

- Mice of fully inbred strains should be genetically identical and homozygous at all loci (genes); (see below)
- Inbred strains continue to demonstrate important susceptibilities for which they were developed initially, such as lung tumors in A strains, lymphoma (leukemia) in AKR, C58 and SJL/J, mammary and liver tumors in C3H. [5]
- Due to genetic drift and or genetic contamination, contemporary strains and substrains differ genetically from mice evaluated 20 or 50 years ago.[6, 7]
- Historical data can provide insight for study design, but can be dangerous to use instead of adequate numbers of relevant concurrent control animals. [8-10]
- Inbred mice raised in a different environment and extremely similar lineage than those bred and raised at another study site or academic institution, can have substantial differences in phenotypes, or in incidence or expression of disease that may impact some studies. [11-13]
  - → This should lead to serious concerns regarding use of 'wild type' mice obtained from a commercial breeder or other source, as (+/+) 'controls' in studies of genetically engineered mice developed from laboratory colonies.
- Excluding strains derived from wild mice (*M. mus castaneus, M. mus molossinus, M. mus spretus*), prioritized strains of the mouse phenome database (MPD) 2007 rev. http://phenome.jax.org/db/q?rtn=docs/pristrains_tree (and Table 1) are emphasized here: 129, A/J, AKR/J, BALB/cByJ, BALB/cJ, C3H/HeJ, C57BL/6J, DBA/2J, FVB/NJ, NOD.
  - o Collaborative cross, B6;129, B6C3F1, outbred Swiss, DO, are discussed briefly.

I.A.2. NURTURE: Microbial Impacts on Pathology and Phenotype

Infectious or infesting agents are environmental factors that can cause pathology and impact phenotypes, whether the agents are introduced naturally or intentionally. Pathology or phenotypes of infectious diseases frequently are strain dependent and vary with specific genes, and with other factors including sex and age of the host, strain and dose of the agent, route of infection, copathogens or other endogenous microflora (the microbiome). Reviewed in [14] [15] Examples:

Mouse hepatitis virus [16-22]

Mycoplasma pulmonis [23-25] and Sendai virus [26-28] acting singly or in concert with other agents induce respiratory phenotypes that can interfere with studies of the respiratory or immune systems.

Helicobacter hepaticus liver and gut phenotypes, [29-31]

Microbiome and intestinal microbiota [32] [33] [34] [35]

Pinworms [36, 37].

Fur mites [38-42]

Mouse retroviruses are microbial agents of special interest because their genetic interactions blur the distinction between nature and nurture influences (reviewed in Morse 2005)

- >100 proviruses in the mouse genome, with strain dependent type, number and distribution, and estimated 40-60 proviruses per strain. [43-45]
- MMTV (notably in C3H mice) [46, 47]
- *Mtv* genes = loci = insertions of portions of mammary tumor viruses
- Lymphoma (notably in AKR, C58 and SJL/J mice) [48-52].
- *Emv* genes or loci represent insertions of portions of endogenous ecotropic murine leukemia viruses (MuLV)
- *Pmv* loci *from* polytropic murine leukemia viruses
- *Xmv* loci *from* xenotropic murine leukemia viruses
- *Xmmv* loci *from* xenotropic MCF leukemia viruses
- *Mtv* and *Emv* loci (proviruses) have been useful as genetic markers,
- Retroviral insertions that disrupt functional genes → mutant alleles, including:
  - ***rd1*** (retinal degeneration 1) in *Pde6b* gene [53, 54] also there is a point mutation, (formerly rodless retina (Keeler 1924))
  - ***d*** (dilute) in *Myo5a* gene [55, 56].
  - ***hr*** (hairless) in Hr hairless gene [51, 57]
  - ***prmd*** in dysferlin *Dysf* in A/J → muscular dystrophy
  - proviruses located near oncogenes may affect levels of expression and/or structure of oncogenes to contribute to tumor development.[58]
  - more about retrotransposons, intracisternal a particles (iap's) etc retroelements at [59]

Fostering and rederivation are widely used strategies to eliminate pathogens from mice.[60-63] Bittner agent) [47, 64, 65]

- may introduce other factors, and impact behavioral and other phenotypes. [66, 67]

I.A.3. NURTURE: Non Microbial Environmental Factors

Noninfectious environmental factors, including experiential or social factors, also impact phenotype. Examples include parity and age of dam, intrauterine position of fetuses, in utero stressors, population density during and after pregnancy, lighting, temperature, caging, bedding, exercise and diet. [1]

I.B. INTERNET RESOURCES

More and more information is becoming available via the internet. Major vendors provide useful information including hematology, serum chemistry, pathology and husbandry data for their major stocks and strains. The Jackson Laboratory provides data regarding many of the hundreds of strains that they distribute or have cryopreserved. Some useful websites include:

Academy of Genomic Pathology, Center for Genomic Pathology – distance learning initiative at UC DAVIS http://ctrgenpath.net/main/about

International Knockout Mouse Consortium IKMC https://www.mousephenotype.org/martsearch_ikmc_project/about

International Mouse Phenotyping Consortium IMPC www.mousephenotype.org

IMPRESS phenotype protocols https://www.mousephenotype.org/impress

THE ANATOMY OF THE LABORATORY MOUSE by MJ Cook 1965 http://www.informatics.jax.org/cookbook/

THE COAT COLOURS OF MICE by Wilys Silvers [68] http://www.informatics.jax.org/wksilvers/

Michael Festing's information on inbred strains [69] http://www.informatics.jax.org/external/festing/search_form.cgi

Mouse Genome Informatics **MGI** homepage http://www.informatics.jax.org/

MOUSE GENETICS by Lee Silver [70] http://www.informatics.jax.org/silver/

Mouse nomenclature homepage -- http://www.informatics.jax.org/mgihome/nomen/

Mouse Phenome Database **MPD** http://phenome.jax.org/

Mouse Resource Browser http://bioit.fleming.gr/mrb/Controller

Mouse Tumor Biology **MTB** Database http://tumor.informatics.jax.org/mtbwi/index.do

NCI Mouse Models of Human Cancers Consortium http://emice.nci.nih.gov/

NIAID Veterinary pathology home page http://www.niaid.nih.gov/dir/services/animalcare/VetPathology/VetPathology-index.html

NIEHS immunohistochemistry http://www.niehs.nih.gov/research/atniehs/labs/lep/path-support/immuno/protocols/

ORIGINS OF INBRED MICE by HC Morse III 1978 http://www.informatics.jax.org/morsebook/

Pathbase, the European mutant mouse pathology database, http://www.pathbase.net/

PHL Murine Immunohistochemistry Database http://ncifrederick.cancer.gov/rtp/lasp/phl/immuno/

RENI (Registry Nomenclature Information system) http://www.item.fraunhofer.de/reni/index.htm

I.C. NOMENCLATURE

Correct nomenclature of mice provides information on the origin and current source of the mice, breeding strategies, and on the mutation type, strategy and developer of the mutant. [6, 71]

- Mouse Genomic Nomenclature Committee (MGNC) website http://www.informatics.jax.org/mgihome/nomen/

Inbred strains should be genetically homogeneous, homozygous at all alleles, and can be traced to a single ancestral pair.

- brother x sister mated (sibling mated) > 20 consecutive generations.

Related inbred strains have a common origin, but were separated **before 20 generations** of inbreeding, when the strain of origin would be expected to be heterozygous at some-many loci (residual heterozygosity).

Substrains are derived from an inbred strain **after** it is fully inbred (i.e. after 20 generations of inbreeding).

F1 hybrid mice are the first generation progeny of two inbred strains. e.g. B6C3F1 are offspring of a C57BL6 mother and C3H father.

Recombinant inbred (RI) strains are created by crossing two inbred strains, followed by 20 or more consecutive generations of brother x sister mating.

- Used to study or map divergent traits in the strains.

Congenic strains are produced by repeated backcrosses to the inbred recipient strain, with selection for a particular marker from the donor strain. Fully congenic strains, are achieved by 10 generations of back crossing (N10) or the equivalent of marker assisted back-crossing [72].

Mixed or incipient inbred stocks, e.g. B6;129 including incipient congenic strains, derive from only 2 parental strains (one of which may be a gene-targeted ES cell line). Similar to congenic names, upper case abbreviations for the strains are used, but separated by a **semicolon (;)** instead of a **period (.)**.

Laboratory Codes indicate the source or origin. Some common Lab codes are listed in Table 2.

I.D. COAT COLORS

See Wilys Silvers' THE COAT COLOURS OF MICE. [68]

Tyrosinase *Tyr*: albino (c) –with multiple minor variations

- **Epistatic: *c/c* mice are albino regardless of other color genotypes**

Tyrosinase *Tyr*: chinchilla (*ch*)

Tyrosinase related protein 1 *Tyrp1*: brown (*b*)

Agouti (*A*)

Agouti: non agouti (*a*)

Agouti: white-bellied agouti (A^w)

Agouti: lethal yellow (A^y) and viable yellow (A^{vy})

Myosin Va *Myo5a* : Dilute (*d*)

Melanophilin *Mlph:* Leaden (*ln*)

Pink eye dilution (*p*)

Kit ligand *Kitl:* Steel (*Sl*)

Kit *Kit*: White spotting (*W, Wv*)

I.E. SEXUAL DIMORPHISMS IN MICE

1. **Body weight** Male mice are usually larger [73] [74]
2. **CNS -**Female mice are usually reported to have greater brain weight, spinal cord weight; brain:body weight ratios (with considerable strain variation) [75] [76] [74]
3. **Kidneys** -Male mice are usually reported to have larger kidneys by kidney weight, kidney weight:body weight, or % body weight (with considerable strain and age variation) [77] [78, 79] [74] or not [80]. Kidney weight also correlates strongly with body weight.
    a. Sexual dimorphsims are reported in GFR, corpuscle size, tubule epithelial vacuolation, granules, enzymes and other features
    b. Male glomeruli are more likely to have cuboidal cells in parietal epithelium - likely testosterone related
    c. Male tubules may be more likely to exhibit cytoplasmic vacuolation, usually presumed to be lipid, and likelier in bigger/fatter mice
4. **Adrenal glands** of male mice are smaller, attributed to less lipid; typically 1-3mg ea [80] [81] [82]
    a. **Adrenal X-zone in young mice surrounds** medulla. [82-84]
        i. Female X zone disappears at first pregnancy, but in virgin female mice, it may be visible for up to 30 weeks & undergoes prominent vacuolation. Male X zone appears at about 10 days postpartum and disappears rapidly at sexual maturity at approximately five weeks of age.
    b. **Adrenal subcapsular cell hyperplasia** and mast cell infiltration may occur at higher incidences in females than in males of some strains (e.g. A, C57BL/6, DBA/2), but can be found in both sexes. [85]
        i. type A cells = Elongate, spindled subcapsular cells
        ii. type B cells = Polygonal, lipid-laden, subcapsular cells that more closely resemble normal cortical cells
5. **Salivary glands – submandibular** (aka submaxillary) salivary gland is largest of 3 major salivary glands & is mixed (serous plus mucous)
    a. in intact adult male mice, submandibular gland is up to 2x female gland. [84, 86, 87]
    b. In intact adult male, granular convoluted tubules are larger with more prominent eosinophilic apical zymogen granules than in female. [88, 89]
        i. Granularity corresponds with higher amylase activity in male [90, 91]
    c. Female submandibular glands undergo "masculinization" during pregnancy / lactation, with ↑volume fraction, ↑area of granular ducts and ↑apical granulation of cells. [92]
6. **Parotid glands** have a more subtle sexual dimorphism
    a. male parotid gland is larger than female's, attributed to larger male acinar volume dt more / larger acinar cells, + larger intercalated duct volumes.[93]
    b. Branching patterns of ducts may be strain dependent. [94]

Female predispositions include

1. fibro-osseous lesion (myelofibrosis) [95-97],
2. pituitary tumors and mammary tumors [83, 84],
3. lymphoma and histiocytic sarcoma in C57BL/6

4. Susceptibility to *Helicobacter hepaticus* typhlocolitis [31].

Male predispositions include

1. Liver tumors esp in C3H and CBA [98, 99],
2. Chloroform nephrotoxicity (DBA/2 > C7BL/6) [79].
3. Respiratory mycoplasmosis [100],
4. *Mycobacterium marinum* and *M. intracellulare* [101, 102],
5. *H. hepaticus* hepatitis [31].

I.F. AGE RELATED PATHOLOGY (non neoplastic)

Multisystem

Acidophilic macrophage pneumonia (and hyalinosis) accumulation of acidophilic and often crystalline material in lungs (acidophilic macrophage pneumonia or acidophilic crystalline pneumonia), or in bone marrow or epithelial tissues (nasal mucosa, stomach, gall bladder) where it is has been called hyalinosis.

- Lung involvement presents with varying degrees of plump acidophilic macrophages + crystals in alveoli and bronchioles, and may be a significant or contributing cause of death in susceptible strains (especially 129, C57BL/6, some Swiss) [103] [104] [103, 105, 106],
- Also in some GEM
- May confound respiratory studies (asthma,expreimental infections
- Less common in BALB/c & CBA. [107]
- in non-pulmonary epithelial tissues, including nasal cavity, glandular stomach, trachea, gall bladder, bile duct, '**hyalinosis'**, present as cytoplasmic hyaline, intensely eosinophilic material, + needle-like, rectangular, square crystals [104]
- The enzymatically inactive mammalian **Chitinase-like proteins (CLPs)** especially Chi3L3/YM1, and Chi3L4/YM2 (formerly YM1, YM2) are overexpressed in susceptible strains in inflammatory, autoimmune or neoplastic conditions – e.g. parasitism, fungal infections, chronic infections, allergy, neoplasia, etc. [108] [109]
- – e.g. parasitism, fungal infections, chronic infections, allergy, neoplasia, etc.

Amyloidosis -- incidence and severity can be related to age, genetics and environmental factors. Systemic amyloidosis in mice can include senile ApoAII amyloid (AApoAII) as well as secondary or reactive AA amyloid.

- extracellular and should stain with Congo Red, oil red O, Alcian Blue, thioflavine T [110, 111] Thicker sections may improve staining. Plastic cover slips may interfere with polarization.
- deposits are mainly in the stomach (glandular), heart, small intestines, kidney, liver, spleen, thyroid, parathyroid, adrenals, salivary glands and ovaries, but not in the brain, spinal cord, bone or bone marrow. [110-119]
- Nasal olfactory, submucosal, periglandular accumulations of eosinophilic material, historically referred to as'Nasal amyloidosis', tends to stain with PAS, +/- trichrome, and usually not Congo red, is composed primarily of collagen and complex polysaccharides. [120, 121]

- **Secondary or reactive amyloidosis,** AA amyloid protein is derived from serum amyloid A (SAA) protein precursor, which is elevated in the blood during inflammation. [118]
  - Spleen, liver, gut and kidney are predilection sites for AA-amyloid deposition and it is often associated with inflammatory lesions of the skin. [114, 122]

- CBA/J, C57BL/6 strains and some Swiss stocks are among the most susceptible, and A/J mice have been considered to be resistant to secondary or reactive amyloidosis [123, 124]

- **Senile amyloidosis,** identified initially in senescence accelerated SAMP mice
  - Earlier and more extensive deposition of AApoAII, especially in liver and spleen, is associated with c (highly amyloidogenic) allele of the apolipoprotein AII (ApoAII) gene, as in A/J, SJL/J and some SAMP lines. [112, 125]
  - Deposition is primarily in intestine, lungs, tongue, and stomach but not in the liver or spleen, in strains that possess the less amyloidogenic ApoAIIa allele, including several C57BL strains, [125, 126] .
  - SPF outbred Swiss stocks (e.g. CD-1) are susceptible to senile and reactive amyloidosis with gut, heart and lung being predilection sites for ApoAII deposition. [114]

Arteritis Aka polyarteritis, periarteritis, systemic arteritis
- Morphologic similarities to rat or human 'periarteritis nodosa'
- In multiple tissues including heart, pancreas/mesentery, head, spleen, urinary bladder
- Usually an incidental finding in older mice; Severe arteritis in heart or vital tissues may contribute to death
- Associated with hypertension in mice [127] and rats [128] [129]
- Associated with autoimmunty (vasculitis vs arteritis) [130]

Liver - hepatocyte karyomegaly and cytomegaly [84, 131, 132], or polyploidy [133], hepatocellular inclusions [84],

Bone fibroosseous changes (Myelofibrosis) [97, 134],
- osteoporosis in C57BL/6

Brain cerebral thalamic mineralization [135],
- cerebral neuronal lipofuscin [136-138],

Ovary deposits or accumulations of ceroid pigments

Adrenal glands deposits / accumulations of ceroid pigments [139-142],
- adrenal subcapsular cell proliferation [85]

Special Senses

Hearing – many strains carry mutations that contribute to hearing loss, especially *Cdh23*^{ahl} (*Ahl*, age related hearing loss 1) [143] [144]; environmental noise can contribute to hearing loss [145] [146], as can otitis [147] [148]

Vision/eye – age associated cataracts are not especially common in mice, but may result from exposure to anesthesia or other chemicals, or cold. They may be transient, may interfere with assessment of vision e.g. by EEG or VEP. [149] [150] [151] [152] Some drugs or anesthetics can alter refractive index. [153]

II. INBRED STRAINS

Check phenome database for more recent growth curves and other phenotype data

http://phenome.jax.org/pub-cgi/phenome/mpdcgi?rtn=docs/home

II.A. 129 – See also table 3a, table 3b, table 4, table 5

Initiated by Dunn in 1928. [154]

At least 16 recognized substrains that include contributions from C3H and other strains. Most of these have contributed to named parental ES cell lines. [155-158] Table 4

Most 129 substrains carry the Dominant White-bellied agouti allele *W* (A^W). Not all have typical agouti hair coloring, because they also may carry albino, chinchilla or pink-eyed dilution alleles.

129**S1**/SvImJ was created by crossing 129/Sv with C3HeB/FeJ, backcrossing to the parental 129/Sv, and selectively breeding offspring with the highest teratoma incidence. The C3HeB/FeJ contribution is on Chromosome 7 and includes the wild-type alleles of the *Tyr* and *p* loci. [156-158]

- 129**S1** is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home

LC **Stevens'** (laboratory code **Sv**) studies on embryonal carcinoma cells derived from **testicular germ cell tumors (TGCT)** → (ES) cell cultures derived from his 129/Sv mice → ES cell technologies [159] [160-164].

- 129 derived ES cell lines usually are considered to be more robust, with better targeting efficiency (TE) and germ line transmission (GLT) than C57BL/6 etc ES Cell lines but improved culture conditions have improved results from other strains [165] [166] [167]
- Table 5 lists parental ES cell lines and strains of origin (2009). IMSR now lists the strain origin of the ES cell line in which a gene was targeted http://www.findmice.org/index.jsp .

129 mice maintained in different sites were 'contaminated' by intentional or inadvertent breeding with mice of other strains + underwent genetic drift. [157, 158] leading to:

- ↓ efficiency of homologous recombination [157]
- ↑ histocompatibility problems between 129 substrains, and thus Tm's.[168]
- → different behavioral and other phenotypes among substrains. [169-173]

In the 1999 revision of 129 nomenclature, '129' is followed by one of the letters P, S, T or X, which is followed by additional strain information [155].

'P' indicates origin from the parental stock;

'S' indicates origin from a line that had carried *Sl* (Steel allele on the *Kitl* gene, which is lethal when homozygous);

'T' indicates that the line carries/d the *Ter* (teratoma) gene;

'X' indicates that the line was genetically contaminated. [155] [157]

- 129X1/SvJ, has contributions by C57BL/6J on Chromosomes 5, 7, 14, 18, and 19, and by BALB/cJ on Chromosomes 7, 8, 10, 18, 19, and X, suggesting an F1 hybrid between these strains as the most possible contaminant.[156]

Non-neoplastic conditions

Hermaphroditism in chimaeric mice -- About half of chimeras produced by aggregation techniques or by injection of (usually) XY ES cells into XX or XY blastocysts are sex chimeras composed of both XX and XY cells. [174, 175]

- Most XX/XY sex chimeras develop as males and are fertile. [176, 177] → fewer phenotypic females, and only a few (about 11%) may achieve germline transmission.

Brain 129/J mice have a relatively large brain/body weight ratio (3rd highest of 25 strains evaluated), [75], and relatively small forebrain volume and neocortex [178],

- **corpus callosum** is reduced/absent in up to 80% of some groups of 129 mice. [13, 179-183]

Hearing129 substrains vary in progression and severity of hearing impairment [172], with a major age-related hearing loss mutation *Cdh23*^{ahl} (*Ahl*, age related hearing loss 1) identified in 129P1ReJ mice [144, 172, 184]

- 129SvEv mice are very resistant to noise induced hearing loss [185]

Vision Report of *rd1/rd1* retinal degeneration in a German (GSF) subline/ substrain of 129Sv/J (= 129X1/SvJ?) [186]

Blepharoconjunctivitis can be common in young 129/J mice (12-15% incidence) → 50% incidence by 20 weeks of age.

- Corynebacteria, lactobacilli and *P pneumotropica* may be isolated, but role as pathogens / opportunists is unclear. [187, 188]

Cardiovascular 129S1/SvImJ mice have relatively **high systolic blood pressure and left cardiac ventricle:body weight** ratio compared to 10 (non 129) inbred strains. [80]

- **Hepatic portal-systemic** shunts in some 129 substrains confer resistance to experimental schistosomiasis. [189-191]

Causes of / Contributors to Death Of 98 aging 129S4/SvJae mice, more than 50% of male and female mice survived to 2 years old. [104, 106] non-neoplastic contributors to death included

- **Acidophilic macrophage pneumonia and megaesophagus** with impaction = most common non-neoplastic proximate causes of death.
  - **Acidophilic macrophage pneumonia**, also referred to as acidophilic (or eosinophilic) crystalline pneumonia, was an important CoD and 87% incidence, with females overrepresented in [192]
- in males; arteritis, abscesses and MUS (urinary obstruction)
- in females; uterine hematomas and thrombi,

Megaesophagus with impaction contributed to death in 15% of females and 7% of males, and noted in 33% of females and 27% of males.

- cause not determined, also noted in B6;129 mice in this study. [106, 121]

Arteritis = contributor to death in ~ 7% of males, [106]

- 30% -50% incidence in males >> females (~10%)
- in multiple tissues including spleen, heart, urinary bladder,
- may be less common in B6;129 mice than in parental 129S4/SvJae. [106, 121]

Other non-neoplastic conditions noted in this study but considered **not** to be major contributors to death include: [104, 106]

1. cardiomyopathy (with or without mineralization or arteritis),
2. chronic nephropathy (frequently with mineralization),
3. myelofibrosis (fibrotic change in the bone marrow) especially in female mice;
4. melanosis in the meninges;
5. ovarian atrophy (with or without hyaline material), pigment (ceroid-lipofuscin), tubular or stromal hyperplasia;
6. cystic endometrial hyperplasia;
7. testicular tubular degeneration or mineralization,
8. prostate atypical epithelial hyperplasia;
9. gastric glandular epithelial hyperplasia;
10. pancreatic islet cell hyperplasia;
11. dental dysplasia of incisor teeth;
12. pituitary hyperplasia of pars intermedia and pars distalis;
13. cataracts,
14. increased extramedullary hematopoiesis in spleen; and
15. lymphocytic infiltrates or other inflammatory changes in various tissues, including Harderian gland; salivary gland, kidney, liver; gall bladder, nasal, trachea, thyroid, periovarian fat, epididymis, urinary bladder.

Neoplasia - *see also MTB and tumor frequency grid at http://tumor.informatics.jax.org/mtbwi/index.do*

Testicular teratomas or testicular germ cell tumors (TGCT's) = congenital anomalies as well as spontaneous neoplasms that develop from totipotent primordial germ cells during early stages of gonadal differentiation, starting at about day 12 of development. [193] [194]

- 129/Sv mice have been known for their high incidence since the 1950's, with 1-10% incidence noted by 3 weeks of age. [195, 196]
- usually contain multiple epithelial types, + well differentiated cartilage, bone, skeletal or smooth muscle, + well differentiated nervous tissue resembling cerebral cortex. Benign tumors tend to appear more differentiated with easily recognizable mature tissues. [197]
- incidence of TGCT's is influenced by up to 15 susceptibility genes including *Ter, Sl, Sl-J, Ay* and *Trp53 (*P53), with *Ter* having strongest effect, and detectable tumors in most *Ter/Ter* homozygotes by 3 weeks of age. [164, 193, 194, 198, 199]
- Extragonadal teratomas in chimeras derived from 129 ES cells usually are perigenital, on the tail or midline in young chimeras, arise from 129 origin ES cells. [200, 201]

Historically 129 strains have been considered to have a relatively low lifetime tumor incidence (F 21%, M 7%), e.g. [202]

1. primarily lymphoma (F 7%, M 2%),
2. soft tissue sarcomas (F 1%, M 2%), and
3. 'benign tumors' (F 2%, M 2%):

- However [203], reported **lung tumors** in 4-46% in a survey of multiple studies of 129 mice
- And [106] report 30/40 male mice with a total of 78 tumors, and 39 of 48 female mice with a total of 84 tumors
  1. **lung tumors** = most common neoplasm (F 31%, M 63%),

- + most common neoplastic contributor to death (15% of males and 4% of females),
- male > female incidence; adenoma > carcinoma

2. **Harderian gland tumors** also were common
   - male > female incidence; adenoma > carcinoma
3. **Liver adenomas** were less common & male > female incidence;
4. **Ovarian tumors** occurred in almost 1/3 of females and included adenoma, granulosa cell tumor, luteoma, hemangiosarcoma, theca/Sertoli cell tumor.
5. **Hemangiosarcomas** were relatively common in males and females and occurred in epididymis (vas deferens); liver; ovary, skin; spleen; uterus.

- Hematopoietic tumors, lymphoma, histiocytic sarcoma, were less common in 129S4/SvJae than in B6 or B6;129 mice, while lung tumors and Harderian gland tumors were more common than in B6 or B6;129 mice. [106]
- Neoplasms also noted but with lower incidences included: adrenal cortical adenoma, pheochromocytoma, renal tubular adenoma, nasal cavity hemangioma, nasal cavity malignant Schwannoma, pancreatic islet cell adenoma parathyroid adenoma, skin papilloma, small intestine adenoma, adenocarcinoma, gastric squamous papilloma, gastric squamous cell carcinoma testicular teratoma, thyroid follicular cell adenoma, thyroid C cell carcinoma, uterine stromal polyp, stromal carcinoma.

II.B. A See also table 3a, table 3b

The A strain was developed in 1921 by L.C. Strong from a cross between Cold Spring Harbor and Bagg albino random-bred stocks, and thus are related to BALB/c. They have been popular for research on cancer, especially lung tumors, and for research on teratology.[204-208]

- A and A/He mice are albino with coat color genotype *a/a Tyrp1^{b}/Tyrp1^{b} Tyr^{c}/Tyr^{c}* .
- intermediate life-span & intermediate breeding performance,
- intermediate size with mean female weight of 21g and mean male weight of 26g at 8 weeks old. [209]
- A/J is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home

Non-Neoplastic conditions

Spontaneous congenital malformations including cleft palate, cleft lip, polydactyly and prenatal open eyelids.[210-212] [213]

- Mouse eyelids normally open between postnatal days 12 and 14 (P12-14).

Muscular Dystrophy A/J strain mice carry the mutant allele *prmd* in the dysferlin gene *Dysf* resulting in progressive muscular dystrophy relevant to dysferlin deficient human muscular dystrophies. [214]

- mutation and phenotype are not identical to *Dysf^{jm}* and muscular dystrophy MD of SJL/J mice
- MD is progressive, with increasing necrotic and regenerating fibers, phagocytosis and mononuclear cell infiltration, marked variation of fiber size, hypertrophic fibers, fiber splitting, fat replacement, perivascular inflammation, endomysial fibrosis and inflammation
- Proximal limb muscles quadriceps femoris and triceps brachii are earliest and most severely affected, with gastrocnemius, soleus, anterior tibial, biceps brachii, diaphragm, masseter and pectoral muscles having milder changes, even at late stages of the disease. [214]

Brain A/J have intermediate brain weight and brain: body weight ratio. [75]

- relatively small cerebral ventricles [215] and rare hydrocephalus (cf B6). [216]

HearingA/J mice have progressive hearing loss with onset between 3 and 5 months of age, and are homozygous for *Cdh23^{ahl}* (*Ahl*, age related hearing loss 1), [144, 172, 184]

Cardiovascular A/J mice have intermediate systolic blood pressure, low left ventricle:body weight ratio. [80]

Immunology

- **A/J, A/HeJ,** AKR/J, DBA/2J, NZB/B1NJ, SWR/J, B10.D2/oSnJ, NOD.ShiLtJ mice are genetically deficient in **complement C5**
  - *Hc^{0}* = deletion mutation in exon in gene Hc (hemolytic component) designated
  - Macrophages secrete truncated form not functional complement component c5.
  - [217-220]

Amyloidosis – variable incidence/susceptibilities reported – role of environment/infections?

- A/J carry the *c* (highly amyloidogenic) allele of *Apoa2*, and develop senile amyloidosis, esp in liver, spleen – tho may be later less severe than SJL/J [112, 125] (and SAMP mice) [221, 222]
- A/J mice have been considered to be relatively resistant to development of reactive SAA amyloidosis. [119, 123, 223]

- Under conventional conditions 55% of retired A/J breeders 3-28 mo had amyloid deposits, with similar amounts of senile AApoAII, reactive AA amyloid [118]

Bone A/J bones may be more brittle than C57BL6/J bones. [224], and compared to C57BL6/J, A/J mice have lower tibial and femoral bone mass, lower activity levels and smaller quadriceps muscles in both sexes, smaller testicles and lower testosterone levels in males, and larger ovaries and higher estradiol levels in females. [225]

Adrenal subcapsular spindle cell hyperplasia Aged female A/J mice have high incidence (almost 100% at 13-15 months of age) of adrenal subcapsular spindle cell hyperplasia >> male incidence ~ 20%. [85]

Neoplasia - *see also MTB and tumor frequency grid at* http://tumor.informatics.jax.org/mtbwi/index.do

Lung tumors A strain is known for high incidence of spontaneous lung tumors and susceptibility to induction of lung tumors, especially compared to more 'resistant' strains such as BALB/c, C3H/He, C57BL/6. [226]

- incidences in A & A/He substrains vary from < 10% to 90%. [203, 227]
- Variable sex predisposition wrt incidence and multiplicity
- Right lobes involved more than left ? [227, 228]
- Pulmonary adenoma susceptibility (*Pas*) genes[226] [228-231]
- Gross: yellow-white, discrete nodules 1-10 mm diam
- **Adenoma** of the lung = most common tumor type (aka bronchoalveolar or bronchioloalveolar adenoma etc) [232-237]
  - Adenomas usually < 4 mm diameter with acinar (solid) > papillary > mixed patterns.
- **Carcinomas** usually > 4 mm diameter with papillary >> mixed patterns.
  - Carcinomas are less common and may metastasize to liver.

Leukemia or lymphoma Reported incidences of leukemia or lymphoma in A strains vary from 0 to 43%. [203, 238]

Myoepitheliomas rare but occur in A/J and A/HeJ mice - arising from myoepithelial cells of various exocrine glands. [239]

Rhabdomyosarcoma –~70% of A/J > 20mo; relationship to dysferlin mutation? [240]

- Dystrophin / dysferlin double mutant mice have ~90% incidence at ~12mo [241]

Tumor frequency in breeding populations [242]

- most **frequent** neoplasms in 281 female A/J mice were **lung tumors, lymphoma, myoepithelioma, lipoma**, with frequencies of 0.5-1%.
- most **frequent** neoplasms in 236 male A/J mice were **myoepithelioma and rhabdomyosarcoma**, with frequencies of 0.5-1%

Susceptibility to selected experimental conditions and infectious agents

Notable responses of A strain mice under experimental conditions include

1. high susceptibility to induction of cleft palate by cortisone and other teratogens [243, 244],
2. high susceptibility to chemical induction of lung tumors. [245, 246]
3. High susceptibility to diet induced cholelithiasis, with various *Lith* genes implicated in susceptibility to gallstones [247] [248] [249]
4. Resistance to diet-induced atherosclerosis or fatty streaks [250-252],

5. low-intermediate serum cholesterol levels on chow diet (<100mg/dl), with greatest increase (to >500mg/dl) in response to high fat diet compared to other inbred strains. [253]
6. Susceptibility to diet induced obesity but resistance to diet-induced diabetes mellitus in contrast to C57BL/6J mice. [254-256]

Notable responses of A/J mice to infectious agents include

1. high susceptibility to lethal mousepox dt Ectromelia virus [257-259];
2. high susceptibility (especially of males) to hepatitis due to Helicobacter hepaticus (which increases their susceptibility to carcinogen induced liver tumors) [29, 30, 260-262];
3. high susceptibility (especially of females) to typhlocolitis due to Helicobacter hepaticus [31];
4. high susceptibility to death due to Listeria monocytogenes infection [263],
5. high susceptibility to death due to Mycobacterium tuberculosis infection [264], attributed to genetic deficiency of complement c5 [265]
6. high susceptibility to candidiasis, attributed to genetic deficiency of complement c5 [218, 219]

II.C. AKR See also table 3a, table 3b

The AKR strain was developed in the 1920's and 1930's for its high incidence of 'leukemia', by Jacob Furth, and then inbred by Clara Lynch at the Rockefeller Institute, now the Rockefeller University. [266, 267]

- AKR mice are albino, with color genotype *a/a* Tyr^{c}/Tyr^{c}
- Short life-span in conventional or SPF conditions with mean life spans < 1yr dt early onset thymic lymphoma ('leukemia'). [203, 268, 269].
- relatively large mice with mean female wt 31g and mean male wt of 34g at 8 weeks old. [209]
- tend to resist being held and vocalize (squeak) when held. [270]
- AKR/J is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home

Non Neoplastic conditions

CNS AKR/J mice have relatively high brain weight (3rd of 25 strains), but intermediate brain:body weight ratio (15th of 25 strains).[271]

Cardiovascular AKR/J have intermediate systolic blood pressure and left cardiac ventricle:body weight ratio compared to 10 inbred strains.[80]

- AKR/J mice have an anomalous (preduodenal) portal vein, ventral to duodenum in most (98%) AKR/J mice, and dorsal to duodenum in 52 other inbred mouse strains in one mouse colony.[272]

Immunology

- A/J, A/HeJ, **AKR/J**, DBA/2J, FVB/NJ, FVB/NMob, NZB/B1NJ, SWR/J, B10.D2/oSnJ, NOD.ShiLtJ mice are genetically deficient in **complement C5**
  - $Hc^{0=}$ deletion mutation in exon in gene Hc (hemolytic component)
  - [220, 273-275]

Thymus AKR/J and C57BL/6J mice have later onset involution & ~2x larger thymus than most other strains (A/J, DBA/2J, BALB/cJ, CBA/J, C3H/HeJ, 129/J, C57BL/ 10J).[276, 277]

Mouse urologic syndrome (MUS) aka urinary obstruction, obstructive uropathy) AKR mice may be more susceptible to MUS when in suspended wire caging [278]:

- Findings can include bladder distension, unilateral or bilateral hydronephrosis, with abdominal distention, hydroureter; peripreputial urine staining, dermatitis, balanoposthitis, paraphimosis;
- Urinary tract infections also can lead to obstruction and pyelonephritis

Reproduction – testicular oocytes are reported in young male AKR (also MRL) mice [279]

Neoplasia - *see also MTB and tumor frequency grid at http://tumor.informatics.jax.org/mtbwi/index.do*

Thymic T cell lymphomas (currently classified as precursor T cell lymphoblastic lymphomas) AKR have high incidence before 1 yr of age, and most die of the condition by 18 months. [50, 203, 269]

- result from interactions of multiple endogenous retroviruses (EMV's formerly AKV's [48, 280, 281]
- These lymphomas also occur early with high incidence in C58 mice [282, 283], NOD-scid/scid mice [284], scid mice [285, 286], and in HRS/J mice that are heterozygous or homozygous for the hairless mutation (hr) [52].
- Most common lymphoma type induced by viruses, chemical carcinogens or irradiation. [269, 280]

Susceptibility to selected experimental conditions and infectious agents

Notable responses of AKR mice under experimental conditions include

1. strong preference for high fat diet, and susceptibility to dietary obesity, [287, 288]
2. low-intermediate susceptibility to diet-induced atherosclerosis or fatty streaks [250, 289],
3. resistance to diet-induced cholelithiasis. [247]

Notable responses of AKR mice to infectious agents include

1. susceptibility to age-dependent poliomyelitis with paralysis following LDV infection, attributed to their endogenous murine leukemia viruses. [290-292]
2. intermediate susceptibility to mouse pox due to ectromelia virus [257-259],
3. intermediate susceptibility to M pulmonis. [293]

Important substrains or related strains

Senescence Accelerated Mice (SAM) originated from an inadvertent cross between AKR/J and an unknown strain, and multiple strains were developed at Kyoto University in the 1970's. [221, 294-296]

- SAM**P** are considered to be **p**rone & SAM**R** **r**esistant to accelerated senescence.
- SAMP → signs of early senescence including ruffled coat, lordokyphosis, skin lesions, reduced activity, shortened life span, systemic senile amyloidosis.
- Abscesses, chronic renal disease, arteritis ('angionecrosis', 'angiitis'), thymic lymphomas, non thymic lymphomas and histiocytic senile and secondary amyloidosis, osteoarthritis, osteoporosis, cataracts, brain atrophy (especially frontal cortex) are reported in the various lines
- Senile amyloid AApoAII (also known as senescence accelerated or ASsam amyloid) was identified initially in SAMP mice [297] but amyloidosis may not be seen under SPF conditions.[298]
- Some SAMP strains used to model age related cognitive decline and pathology [299] [300]

II.D. BALB/c, BALB/cBy See also table 3a, table 3b

BALB/c originated with Halsey Bagg in 1913. His **B**agg **ALB**ino mice were distributed among various laboratories, and brought to Jackson by George Snell in 1935 who added '/c' referring to their albino color allele. After the 1947 fire, Scott's inbred BALB/c colony was used to resurrect the line and became the progentiors of current BALB/cJ. In 1961 DW Bailey (By) acquired BALB/c mice from NIH. In1974 at F136 these were transferred to J production colonies and became BALB/cByJ (surrently prioritized in MPD). [BALB/cAn derive from Bagg Albino's transferred to Andervont (An) in 1935] [301] [302]

- albino with color genotype *A/A Tyrp1^{b}/Tyrp1^{b}* ***Tyr^{c}/Tyr^{c}.***
- tend to develop plasmacytomas after injection of mineral oil or pristane became useful for generating monoclonal antibodies [303-306]

BALB/cJ (formerly prioritized in MPD, removed in 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home)

- intermediate life-span & intermediate-poor breeding performance [307] [203, 209, 268, 308]
- intermediate size with mean female wt 22g / male wt 28g @ 8wo.
- high variability in vertebral formulae (12-14 thoracic and 5-7 lumbar vertebrae) compared to other strains [309]
- unkempt dirty or oily appearance.
- high intrastrain aggression (especially males)

BALB/cByJ is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home

- **bigger?; less aggressive, better? breeding performance than BALB/c**, with 58% of dams having at least 4 litters, about 7 pups/ litter, 91% weaned:born ratio.[209] [302]
- relatively placid and easier to handle. [270]

Non-Neoplastic conditions

CNS BALB/cJ have large brain, and brain to body weight ratio (2nd of 25 strains), and large spinal cord. [75]

- **Corpus callosum** may be absent in 30-40% of BALB/c mice, several genes seem to be involved. [13, 310, 311]
- Hydrocephalus is rare in BALB/cJ and BALB/cByJ mice, <0.01% [216]

Hearing BALB/cJ mice have age-related hearing loss [312], not attributed to *Cdh23^{ahl}*.

- BALB/cByJ is homozygous for *Cdh23^{ahl}*, with progressive hearing loss onset after 10 months of age.[144]

Vision/Eye

- **Spontaneous corneal opacities** may occur in BALB/c with incidence of about 10%, was reduced by more frequent cage changing. [313, 314]
  - aka corneal dystrophy or corneal mineralization.
  - Higher incidences occur in strains that develop soft tissue mineralization and cardiac calcinosis (C3H ~ 16% and DBA/2 ~ 29%)
- Distinguish from Cataracts related to anesthesia or other chemicals, or cold, which may be transient, [149] [150] [151] [152]
- **Ulcerative blepharitis and periorbital abscesses** in BALB/cJ and BALB/cByJ. [187, 315].

- P pneumotropica is a likely isolate.

Cardiovascular

- **Dystrophic cardiac calcinosis** in BALB/c mice manifests as epicardial mineralization that increases slightly with age. Similar condition occurs in related C3H & DBA. [203, 316] [317]
  - primarily /exclusively involves RVFW epicardium in BALB/c, with higher incidence in males (11%) than in females (4%). [316]
  - *Dyscalc* loci implicated.[318, 319] abcc6 [320]
- **Age-related cardiopathy or cardiomyopathy,** females > males, in some studies [321, 322]
  - myocardial degeneration or necrosis, fibrosis (scarring), inflammation or mononuclear infiltration, with or without mineralization or arteritis.
- **Left auricular thrombosis** = common in earlier longevity studies, with incidence up to 66% in older breeding females. [323]
- **Polyarteritis** in up to 4% when mice were examined after natural death rather than at timed sacrifice. [324, 325]

Malocclusion in BALB/cJ and BALB/cByJ has similar low incidences of 0.0018% and 0.0015% respectively, in populations from which affected mice are culled at weaning. [326-328]

Amyloidosis in BALB/c mice is relatively uncommon [329], although some studies report a relatively high incidence in group-housed males.[330]

Reproduction – BALB/c usually are reported to have intermediate to poor breeding performance. Associations with relatively frequent vaginal septa or imperforate vagina in some colonies have been suggested.

- **Imperforate vagina with associated hydrometra and mucometra** - 12 of 35 diagnosed at TJL over 2 yr were in BALB/cJ. Affected mice are infertile, and develop progressive abdominal distention (from enlarging uterus), which may be mistaken for pregnancy. Perineal swelling is characteristic of mice with significant hydrometra, mucometra. [331]
- 7% incidence of **hydrometra** was reported in a study of virgin female BALB/c mice maintained up to 1001! days. [332]
- **Vaginal septa** (usually dorso-ventral longitudinal, some may be transverse) associated with reduced reproductive performance, were reported in up to 38% of recently weaned BALB/cJ female mice; < 8% frequency in 2 other BALB/c substrains + 8 different inbred strains [333, 334]; ~14% incidence in BALB/cByNarl substrain [335]; (up to 11% incidence in a C57BL/6J breeding colony [336]

Adrenal Gland

- **Adrenal subcapsular spindle cell hyperplasia** Both female and male BALB/cJ mice have almost 100% incidence at 13-15 months & may be associated with mast cell infiltration. [85]
- **Accessory adrenal cortical nodules,** may occur in > 50% of BALB/c or C57BL/6 mice, and are less common in A and C3H mice. [142, 337]

In SPF BALB/c mice from a study of virgin and breeder mice maintained up to 689! days, [317] the most common non neoplastic changes were:

1. hepatic fatty metamorphosis (especially in male mice),
2. uterine hemosiderosis and mineralization in multiparous females,
3. uterine polyps and ovarian cysts primarily in virgin mice,
4. testicular atrophy,

5. epicardial mineralization more common in males,
6. adrenal subcapsular spindle cell hyperplasia.

In a report of 2376 non-treated control female SPF BALB/c mice maintained to 33 months of age [332], the most common non neoplastic changes were:

1. uterine stromal polyps (32%),
    a. only lesion with incidence > 10% in mice < 24 months of age
2. foci of vaginal dysplasia (31%),
3. ovarian vascular lesions or thrombi (23%)
4. brain (thalamic) mineralization (28%),
5. corneal mineralization (25%),
6. adrenal subcapsular cell hyperplasia (24%).
7. cardiac mineralization noted in only 1.2% of mice.

Neoplasia - *see also MTB and tumor frequency grid at http://tumor.informatics.jax.org/mtbwi/index.do*

Most common neoplasms [338] [317, 332] [330] are usually:

1. **Hematopoietic tumors** ('reticulum cell sarcomas' now classified as lymphoma or histiocytic sarcoma, and lymphomas) (up to 75% incidence in the oldest age group),
    a. may be important cause of morbidity and mortality in chronic studies
    b. most common = type B reticulum cell sarcoma (~ follicular B cell lymphoma)
2. **Lung tumors** [226] (may be more common than lymphoma in some studies) [317]
3. **Harderian gland tumors**
4. **Adrenocortical adenomas**
5. liver tumors
6. mammary adenocarcinomas
7. myoepithelioma – very high incidence in female BALB/cJ in [339]
8. Rhabdomyosarcomas, angiosarcomas, ovarian tumors, uterine polyps

In a study of the **frequency** of neoplasms in primarily breeding populations of inbred strains over a 13 year period, [242]

1. **Myoepithelioma** in both sexes of BALB/cJ with 1-10% frequency
2. Of 899 female BALB/cJ, lymphoma, papilloma, rhabdomyosarcoma and mammary tumor occurred with frequencies of 0.5-1%.
3. Of 349 male BALB/cJ, lymphoma, papilloma, rhabdomyosarcoma and testicular interstitial cell tumor occurred with frequencies of 0.5-1%.
4. Of 516 female BALB/cByJ, myoepitheliomas, lymphoma, papilloma, hemangioma occurred with frequencies of 0.5-1%.
5. Of 256 male BALB/cByJ, myoepitheliomas, lymphoma, papilloma, rhabdomyosarcoma occurred with frequencies of 0.5-1%.

Myoepitheliomas from myoepithelial cells of various exocrine glands, especially salivary glands, are relatively rare in mice but occur more commonly in BALB/cJ and BALB/cByJ than in other strains. [84, 239, 242, 339-341]

- most common in submaxillary (submandibular) or parotid salivary glands and rare in sublingual gland.
- mammary myoepitheliomas can be induced with DMBA, but seem to be very rare spontaneous lesions. [342]
- biphasic: large pleomorphic cells including elongated or spindle-shaped mesenchymal type cells, mixed with areas of polyhedral epithelioid cells.
- Areas of degeneration and necrosis can result in pseudocysts filled with mucus and necrotic cell debris.
- neoplastic cells may palisade around blood vessels.
- Larger tumors may metastasize to lung.

Lung tumors can have incidence of 30-40% in males, lower in females [226] [317]

Mammary tumors in breeding populations usually are papillary adenocarcinomas that not infrequently metastasize to lung.

- multilobulated, papillary, cystic and locally invasive. [339]
- adenoacanthoma, sometimes called adenosquamous carcinomas, with adenosquamous being currently preferred descriptor for neoplasms with glandular plus squamous differentiation; occur in old retired breeders, more common in BALB/c than in other common strains. [343-345] see also FVB

Hemangiomas and hemangiosarcomas are relatively rare in mice but occur in [317, 346]

- skin, seminal vesicles, liver, muscle tissue, cerebellum, heart etc tissues.
- Cavernous & Capillary hemangiomas -- Mitotic figures are rare
- Hemangiosarcomas are non-circumscribed and locally invasive.
- neoplasms may be difficult to distinguish from non neoplastic distended vascular spaces referred to as peliosis or telangiectasis.

Muscle - Rhabdomyosarcomas are rare in mice but more common in BALB/c and BALB/cBy (also A/J) than in other strains. [240] [339] [347]

Adrenal cortical tumors are not common in mice but more common in BALB/c than in outbred Swiss mice or in B6C3F1 mice. [332, 348, 349]

- Female > male ; Adenomas > carcinomas
- pheochromocytomas (adrenal medulla tumors) are rarer
- Neonatal gonadectomy induces adrenal cortical tumors in various strains [348]

Ovarian tumors in BALB/c rare before 1 year of age [350]

- Luteoma > tubulostromal adenoma (tubular mesothelioma) > granulosa cell tumor > thecoma, cystadenoma

Leydig cell tumors (interstitial cell tumors) of the testicle are rare in mice, but more common in BALB/cJ and BALB/cByJ mice. [317] [84, 351, 352]

- ~2% in virgin and breeder males
- hyperplastic foci may be distinguished by size (<3 seminiferous tubules diameter) and non-compression,
- adenomas are larger (> 3 seminiferous tubules diameter), compress adjacent tissue and exhibit some cellular pleomorphism.
- Large, invasive or metastatic tumors are carcinomas.

Kidney tumors ? bilateral renal adenocarcinomas in BALB/CFCd Claude substrain [353] [354] [96]; rare renal tumors in control or treated BALB/c [355]

Susceptibility to selected experimental conditions and infectious agents

Notable responses of BALB/c mice under experimental conditions include

1. High susceptibility to some skin carcinogenesis protocols [356],
2. High susceptibility to MMTV and carcinogen induced mammary tumors [357, 358] (reviewed in [344];
3. High susceptibility to AAF induced urinary tract tumors. [355, 359]
4. Susceptibility to carcinogen induced osteosarcomas [360],
5. Susceptibility to carcinogen induced brain tumors [361],
6. Intermediate susceptibility to carcinogen induced lung tumor [229, 231, 245],
7. Resistant to diet induced atherosclerosis. [250, 362]

Notable responses of BALB/c mice to infectious agents include reported **susceptibilities. E.g:**

1. acute lethal mousepox (Ectromelia virus) [257-259];
2. some mouse hepatitis viruses [18-20];
3. EMCV diabetes and myocarditis [363-366];
4. MCMV myocarditis and congestive heart failure [367, 368];
5. Murine gammaherpesviruses arteritis and lymphoproliferative disease [369-371];
6. *Helicobacter hepaticus* hepatitis[30];
7. *Borrelia burgdorferi* myocarditis [372, 373];
8. *L. monocytogenes* gastritis [374];
9. cariogenic streptococci [375, 376];
10. mite associated ulcerative dermatitis [39, 40].

BALB/c mice have been reported to be relatively **resistant** to:

1. polyomavirus induced tumors [377];
2. experimental lethal MAV 1 hemorrhagic encephalomyelitis [378-382],
3. *Helicobacter felis* gastritis [383, 384];
4. *Borrelia burgdorferi* arthritis [372, 373].

Related Strains and Substrains

BALB/cWt has a relatively high incidence of true hermaphroditism (3%). [385-387]

II.E. C3H See also table 3a, table 3b

The C3H strain was developed in the 1920's from a cross of Bagg albino female with a DBA male then selected for a high incidence of mammary tumors. The related strain CBA was selected for low incidence of mammary tumors (see below). **C3H/HeJ** is the most common C3H substrain, is prioritized in the phenome database and is emphasized here. [388]

- He (as in C3H/He) is the laboratory code for Heston
- C3H mice are agouti with color genotype *A/A*.
- Most C3H and C3H/He strains currently available have been cesarean derived to eliminate MMTV. [389]
- intermediate life-span [203, 268].
- poor- intermediate breeding performance, [209]
- lowest systolic blood pressure of 11 (non wild) inbred strains. [80]
- high lung volume and alveolar size compared to other inbred strains, ~ 50% more lung volume than C57BL6. [390, 391]
- intrastrain and inter-substrain variability in vertebral formulae with either 5 or 6 lumbar vertebrae.[309]
- C3H/HeJ is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home

Non-Neoplastic conditions

Tlr4 Between 1960 and 1968 C3H/HeJ substrain developed a mutation in the *Tlr4* gene, then called '*Lps*' (for lipopolysaccharide),

- → resistant to endotoxin, but paradoxically susceptible to *S typhimurium* & some other agents.[69, 392, 393]

Vision -- *rd1* C3H, C3H/He and related strains are homozygous for $Pde6b^{rd1}$, the *rd1* mutation in the phosphodiesterase 6B gene, also called 'rodless retina' [394]

- described (beautifully) by Keeler in 1924[395],
- almost no photoreceptor nuclei by 20do [54, 213]
- mice that lack rod and cone photoreceptors still use their eyes to detect light to regulate their circadian rhythms, suppress pineal melatonin, modify locomotor activity and modulate pupil size. [396-398]

Spontaneous corneal opacities may occur in C3H mice with an incidence of about 16%. [313]

Hearing is normal and cochlear function is excellent in C3H/HeJ and C3H/HeSnJ up to 14 months of age

- LPS sensitive C3H/HeJ mice may have more otitis media than normally LPS-responsive C3H/HeSnJ. [147, 399]
- Otitis media affects hearing [147]

Dystrophic cardiac mineralization or dystrophic cardiac calcinosis

- more common and more severe in females than in males.
- Simiar to condition in Balb/c & DBA, from which C3H derive
- Usually subclinical but mortality with pleural effusion & severe mineralization reported in pregnant or lactating mice.

- Myodegeneration, necrosis, and mineralization can occur throughout myocardium, but typically not epicardium, of both ventricular walls and septum. [400-403]
- Dyscalc loci (Dyscalc 1-4) on different chromosomes. [318, 319, 404]
- Diet implicated in earlier onset and increased severity, + mineralization of renal arteries and tubules, pulmonary arteries and septa, rectus capitis and posterior femoral muscles. [405-407]

Hematopoietic C3H mice tend to have higher megakaryocyte ploidy than other strains [408, 409]

- more 32N and 64N megakaryocytes than other strains
- males have higher ploidy than females
- Larger spleens, lower platelet count, higher megakaryocyte ploidy than C57BL/6, attributed to ↓platelet lifespan and ↑platelet production in C3H [408, 409]

Hamartomas and choristomas are rare, non inherited tumor-like conditions that are more common in C3H/HeJ and C57BL/6J than in other inbred strains. [410]

- soft, raised masses on the dorsal midline, usually over sutures
- overlying epidermis is intact
- usually contain just adiposa, but may contain normal appearing thyroid, intestine, respiratory epithelium lined cysts, squamous epithelial cysts, bone and marrow, cartilage, glands, and angiomatous anomalies.
- may enter brain, or expand into the ventricles
- resemble "lipomatous" hamartomas, a congenital defect in humans

Integument - Alopecia areata develops spontaneously in female C3H/HeJ from 5 months of age [411] [412] [413] [414] [415]

- develops later in males
- Frequency may approach 20% in a colony by 18 mo of age.
- non scarring, inflammatory hair loss condition
- Several genetic loci have been linked to this condition in mice

Bone C3H/HeJ mice have high femoral bone density.[416] [417]

Adrenal subcapsular spindle cell hyperplasia Aged female and male C3H/HeJ mice have similar high incidence (almost 100% at 13-15 months of age) not associated with mast cell infiltration of the cortex in this strain. [85]

Neoplasia - *see also MTB and tumor frequency grid at* [*http://tumor.informatics.jax.org/mtbwi/index.do*](http://tumor.informatics.jax.org/mtbwi/index.do)

Mammary tumors Non fostered C3H and C3H/He mice that carried exogenous MMTV historically had very high incidences of early onset mammary adenocarcinomas: 95-100% in breeding females, slightly lower in virgin females, and < 1% in males. [418, 419]

- Fostered or rederived C3H virgin and breeding females still develop mammary tumors later in life. [203] with high incidence [420]
- Most spontaneous or MMTV-induced mammary tumors in mice have been classified as type A, B or C adenocarcinomas according to Thelma Dunn's original 1959 classification, and do not resemble most human breast cancers.

  A. Type A, (acinar) or microacinar adenocarcinomas -- also referred to as adenoma and tubular carcinoma.

B. Type B or ductal tumors are most common, have more variable histologic features, with well- and poorly-differentiated regions of neoplastic cells in cords or sheets or papilloma-like configurations.

C. Type C (cystic) tumors are less common than A or B tumors, and feature cystic epithelial structures in more abundant stroma.

- Spontaneous mammary adca most commonly metastasize to lung -- C3H mice can have 49% incidence of metastasis in retired breeders.
- recent classifications are more relevant to neoplasms induced genetically to recapitulate human breast cancers. [343-345, 421]
- **Hyperplastic alveolar nodules (HAN)** are common preneoplastic findings in MMTV-infected and MMTV-free mice, as well as in carcinogen-treated mice. [343-345]
  - 1-5 mm nodules, frequently outlined by yellow pigment.
  - foci of lobuloalveolar hyperplasia,
- **Plaques** are epithelial proliferations that occur in mouse mammary glands during pregnancy or after hormone induction, but regress after withdrawal of the stimulus. [344, 345]
  - formerly known as type P or pregnancy dependent tumors.
  - radiating ducts surrounded by dense connective tissue.

Liver tumors high incidence in fostered and unfostered substrains (up to 90% in males at 14m) [203, 422-427]

- males have a higher incidence and multiplicity than females. [98, 424, 428, 429]
- C3H/HeJ mice carry multiple *Hcs* (hepatocarcinogen sensitivity) loci. [430, 431]
  - **Hepatocellular adenomas** in mice also have been referred to as hepatomas, and type A nodules or **type A tumors.**
    - Typically distinctly demarcated or circumscribed nodules, 1-10 mm diameter, that lack lobular organization, compress adjacent parenchyma and may bulge from the liver surface.
    - do not invade adjacent parenchyma or vessels and do not metastasize.
  - **Hepatocellular carcinomas** in mice also have been referred to as type B nodules or **type B tumors.**
    - usually have distinct trabecular or adenoid patterns, solid patterns are less common, & cells can be poorly to well-differentiated.
    - may arise within adenomas.
    - Metastases are typically to lung, & occur in up to 40% of male B6C3F1 or C3H mice with hepatocellular carcinoma that are allowed to live out their lifespan.
    - Metastases usually occur only when tumors are large (> 10 mm).
  - **Hepatoblastomas** are rare spontaneous or induced liver tumors that possibly arise from poorly differentiated areas of hepatocellular carcinomas, as they usually are found within or adjacent to carcinomas.
  - **Cholangiomas or cholangiocarcinomas,** of bile duct origin, also are rare spontaneous tumors but may be induced with carcinogens

Lung tumors, lymphoma and Harderian gland tumors also have been noted in C3H mice, but are less common than mammary and liver tumors. [203]

Pheochromocytomas, not common in mice, but may be more common in C3H than in other inbred strains, [349, 432]

- may be induced by polyomavirus in C3H mice

Ovarian tumors in C3H mice are rare before 1 year of age, then increase [350]

- tubular mesothelioma (adenoma) > thecoma > luteoma, granulosa cell tumor, cystadenoma.

Susceptibility to selected experimental conditions and infectious agents

Notable responses of C3H or C3H/He mice under experimental conditions include

1. high susceptibility to hepatocarcinogenesis [431, 433],
2. high sensitivity to estrogen & estrogen induced mammary tumorigenesis [434]
3. resistance to diet induced atherosclerosis [250].

Notable responses of C3H mice to infectious agents include **susceptibilities** to

1. acute lethal mousepox (Ectromelia virus) [257-259],
2. some mouse hepatitis viruses [20, 21, 435, 436];
    a. Increased disease & mortality from MHV1 infection in C3H/HeJ is attributed to their *Tlr4* mutation.[437]
3. polyomavirus induced tumors [377, 438] [439] and necrotizing arteritis in some substrains [439]
4. murine respiratory mycoplasmosis (M pulmonis) [293, 440, 441],
5. *Helicobacter hepaticus* hepatitis [30];
6. *Helicobacter felis* gastritis [383, 384];
7. Lyme borrelliosis arthritis and myocarditis [442];

C3H mice have been reported to be relatively **resistant** to

1. experimental lethal MAV1 hemorrhagic encephalomyelitis [378-382],
2. MCMV myocarditis [321, 443].

C3H strains vary in reported susceptibilities to mycobacterioses [101, 444-449], and to other infections.

High **susceptibility of C3H/HeJ** but not other C3H strains to some gram negative agents often is attributed to their ***Tlr4* mutation, $Tlr4^{Lps}$** . In some reports the strain or substrain of C3H is not clear, and *Tlr4* functionality may play a role. Toll-like receptor 4 (TLR4) is the cognate receptor for LPS. The dominant negative Lps mutation confers resistance to LPS, but paradoxical (?) susceptibility to various gram negative agents, perhaps by failure to recruit critical chemokines, cytokines.

- *Salmonella typhimurium* [450] [451] [452] [453]
- *Klebsiella oxytoca* [454] [455]
- *Bordetella pertussis* [456] [457]

Significant related strains or substrains

C3H/He-*Avy*

A^{vy} viable yellow mutation arose spontaneously in C3H/HeJ. C3H/He-A^{vy} vary from yellow to sooty in color. They are obese and highly susceptible to tumors, especially mammary and liver tumors. [458-462]

CBA

The CBA strain was selected for low mammary tumor incidence from the same Bagg albino female X DBA male cross that gave rise to C3H. CBA mice are known for longevity and low tumor incidence.

- CBA mice are agouti A/A, and homozygous for Pde6brd1.
- CBA mice have only modest sensorineural hearing loss late in life [463], and are used as 'normal hearing' controls in some surveys. [172]

[464] The most common non-neoplastic findings were

1. mild glomerulonephritis (F 66%, M 84%),
2. dystrophic calcinosis (F 78%, M 75%),
3. cystic endometrial hyperplasia (F 45%),
4. testicular atrophy (77%),
5. thyroid follicular cysts (F 51%, M 36%),
6. thymus cysts in males (16%).

- Amyloidosis, arteritis and acidophilic macrophage pneumonia were not common in contrast to C57BL/6 mice on the same study.

[464] The most common neoplasms were

1. **liver tumors (F 19%, M 34%),**
2. lung tumors (F 7%, M 11%),
3. ovarian tubular adenoma (71%);
4. ovarian granulosa theca cell tumor (12%),
5. testicular interstitial cell tumor (11%).

- Lymphoma and histiocytic sarcoma were unusual in contrast to C57BL/6 mice on the same study.
- Both C3H and CBA mice are known for susceptibility to spontaneous and induced liver tumors, with strong male predisposition. [428]

- female CBA/J mice were moderately susceptible to ENU induced lung tumors, [465]

II.F . C57BL/6 See also table 3a, table 3b

C57BL originated by CC Little in 1921: Female 57 X Male 52 from Miss Abbie Lathrop's stock. [69]

- Same dam → same X chromosome in C57L, C57BR strains
- most common C57BL strains are C57BL/6 and C57BL/10.

- C57BL/6 blastocysts are used commonly for injection of manipulated ES cells to give rise to targeted mutant or knockout mice.
- often used as host, recipient or background strain for generation of congenics carrying spontaneous or induced mutations.
- black (non-agouti) *a/a*.
- considered to be refractory to many tumors,
- relatively long life-span ~ 730-895 d[203, 268, 308, 466].
- usually good breeding performance. [209]
  - C57BL/10J mice have poorer breeding performance (than C57BL/6J),
- C57BL/6J intermediate size - female ~ 19g and male ~ 25 g @ 8 wo. [209]
  - C57BL/10J are similar size female ~21g, male ~ 27 g @ 8 wo.
- C57BL/6J have relatively low lung volume and alveolar size compared to other inbred strains. [390, 391]
- C57BL/6J DNA used in mouse genome project, [467, 468]
- **ALL C57BL/6 are not identical**: C57BL/6J *(Hall → Jax (J) 1948) vs*
  - C57BL/6N (AKA C57BL/6NCr [Cr = NCI lab code] *(Jax → NIH (N) 1951 @F32)* *http://web.ncifcrf.gov/research/animal_production_program/strain_information/01C55.asp) vs*
    - C57BL/6NCrl *(NIH → Crl 1974) vs*
    - C57BL/6NHsd *(N → Hsd 19??) vs*
    - C57BL/6NTac *(N → Tac 1991 @F151)*
    - C57BL/6ByJ was separated in 1950s from C57BL/6NCr [156]
  - *phenotypic and genomic analysis of C57BL/6J and C57BL/6N mouse strains[469]*
  - *C57BL/6J is glucose intolerant dt spon mutation in Nicotinamide Nucleotide Transhydrogenase Nnt [470, 471]*
  - *B6J climb their tails more than B6N - [472]*
  - *B6J vs B6N wrt Aryl Hydrocarbon Hydroxylase Induction [473]-*
  - *At least 5 SNP differences distinguish C57BL/6J from C57BL/6ByJ and C57BL/6NJ [474]*
  - *rd8 mutation of Crb1 gene in C57BL/6N mice [469]*
  - *B6J vs B6N wrt Th17 responses and segmented filamentous bacteria ? [34] [35]*
- C7BL/6J is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home
- '**Albino B6' strains** –some derive from spontaneous mutations including:

  C57BL/6-*Tyr*$^{c\text{-}Brd}$ arose spontaneously in C57BL/6 in Allan Bradley's lab
  - *Limited information at MGI, IMSR, EUroPhenome*

  B6(Cg)-*Tyr*$^{c\text{-}2J}$/J -*Tyr*$^{c\text{-}2J}$ arose c1970 at J on a C57BL/6J congenic strain at N20

- *Can be used to generate blastocysts for microinjection of C57BL/6J embryonic stem cells → easily identified chimeras on C57BL/6J genetic background.*
- *http://jaxmice.jax.org/strain/000058.html*

Non-neoplastic conditions

CNS C57BL6/J have intermediate brain size among inbred strains [75], but have larger cerebral ventricles [215, 475]

- Hydrocephalus is more common in C57BL strains than in other common inbred strains with 0.36% and 0.029% of C57BL/KsJ and C57BL/6J respectively culled at weaning for domed cranium indicative of hydrocephalus [216]
- C57BL/6J **cerebellum** (60mg) ~ 18% larger than DBA/2J (50mg). [476-478]
  - Cerebellar folial patterns vary among inbred strains
  - C57BL/6J have intraculminate fissure between vermian lobules IV and V. (cf absent in DBA/2J)
- C57BL/6J mice may develop neurodegenerative lesions of hippocampus suggestive of tauopathy. [479, 480]
  - granular deposits predominantly in hippocampus from 6m
  - granules not apparent with H&E, but stain with PAS or GMS
  - Similar changes reported in AKR-derived SAM strains but absent in DBA/2J and BALB/cJ.
- **Lipofuscin** also stains with PAS & can be found in neurons, neuroglia, and endothelial cells especially in the hippocampus of aging mice.[138]

Eye abnormalities esp Microphthalmia and anophthalmia noted early in the history of C57BL/6 & C57BL/10 mice.

- females > males, OD > OS [481, 482]
  - Affected mice often develop ocular infections,
- **Anophthalmia** is highly unusual
- **Corneal opacities** / corneal mineralization reported in about 5% of mice in some C57BL/6 colonies [313], but << BALB/c, C3H/He and DBA/2 mice.
- **Retinal degeneration** (far milder changes than *rd1/rd1*) due to *rd8* mutation of *Crb1* gene in C57BL/6N mice [469]

Hearing C57BL/6 mice are homozygous for $Cdh23^{ahl}$, have presbyacusis, with deafness linked to cochlear degeneration.

- later onset (after 2 months), slower progression than DBA & BALB/c,
- susceptible to noise-induced hearing loss. [144, 463, 483-485]
- Cochlear pathology includes disruption and loss of both outer and inner hair cells, culminating in degeneration and collapse of organ of Corti, [486-488]

Thymus C57BL/6J and AKR/J mice have later onset involution & larger thymus (approximately 2-fold) than most other strains (A/J, DBA/2J, BALB/cJ, CBA/J, C3H/HeJ, 129/J, C57BL/ 10J). [276, 277]

Malocclusion occurs sporadically in C57BL strains.[326]

Hamartomas and choristomas are rare but more common in C3H/HeJ and C57BL/6J than in other inbred strains. [410]

Overgrooming, or barbering is common in C57BL6/J and related strains.

- distinctive pattern common to several mice in cage. [489]
- usually nibbling not plucking
- Dominance behavior? (Dalila effect), whiskers are plucked? [490]
- female bias = model of human trichotillomania/OCD? [491]

Ulcerative dermatitis may occur in > 20% of animals in of some colonies.

- female > male incidence/severity
- associated with secondary conditions such as reactive lymphadenopathy, leukocytosis, and amyloidosis. [492]
- severe lesions complicate studies by requiring early termination for humane reasons.
- ad lib fed mice may have much higher incidence [493]

Melanosis of spleen etc tissues is common in black mice. Black areas may be visible grossly, especially in the cranial pole. [494-496]

- melanin also common on heart valves, dura, and interstitially in Harderian glands and parathyroid glands in pigmented strains. [121, 497]
- brain may have abundant melanin in melanocytes in meninges and along cerebral capillaries. [498]

Adrenal C57BL/6J have small adrenal glands compared to other inbred strains. [80]

- adrenal subcapsular spindle cell hyperplasia ~ 80% at 13-15 months in aged female C57BL/6J [85]
  - may be associated with mast cell infiltration
  - not expected in male C57BL/6J
- Accessory adrenal cortical nodules, may occur in >50% of C57BL/6 or BALB/c mice, and are less common in A and C3H mice. [142, 337]

Imperforate vaginas with associated hydrometra and mucometra - 6 of 35 cases were in C57BL/6J mice. [331]

- **Vaginal septa** up to 11% incidence in a C57BL/6J breeding colony [336]
  - incidences in C57BL lines - from 1% in C57BL/6By to ~ 26% in 2 lines congenic with C57BL/10ScSn; septum ~ 15 x more likely than imperforate vagina.[334]

Amyloidosis C57BL6 mice are considered to be relatively susceptible to secondary (SAA) amyloidosis as well as to senile (AApoAII) amyloidosis. [118, 499]

- Carry intermediate susceptibility ApoAIIa allele along with AKR/J, and DBA/2, [125, 500]
- Was common age-related non-neoplastic finding in some studies [464] > 80% of C57BL/6 males affected
- Stressors, such as group housing and infections, have been implicated. [116, 501]

Bone C57BL6/J mice develop age related **osteoporosis and osteoarthritis.** [502]

- lowest femoral cortical bone density of multiple inbred strains (AKR/J, BALB/cByJ, C3H/HeJ, C57BL/6J, C57L/J, DBA/2J, NZB/B1NJ, SM/J, SJL/BmJ, SWR/BmJ, 129/J) [416, 503-505]
- cf [225]compared to A/J, DBA/2J and BALB/cByJ mice, C57BL6/J have high tibial and femoral bone mass. [225]

Acidophilic macrophage pneumonia C57BL/6J are susceptible although usually at <10% incidence. [107, 464, 506]

- Infection with *C neoformans* → ↑incidence [507].
- ?? → susceptibility to certain agents, and complicate studies of respiratory phenotypes ?? [508]

In SPF virgin and breeder C57BL/6 mice [317] common non-neoplastic changes included:

1. hepatic fatty metamorphosis especially in males,
2. mild chronic inflammatory changes, lymphoid accumulations or mononuclear aggregates in liver, lung and lacrimal gland;
3. proteinaceous renal casts;
4. cystic endometrial hyperplasia,
5. ovarian atrophy, ovarian cysts and ceroid pigment esp in virgin;
6. pituitary cysts.

- **amyloidosis** in these SPF mice was very low – similar to BALB/c on same study

In a long term survival study of ***ad lib*** **fed and diet restricted** C57BL/6 mice, **nephropathy, cardiac thrombi and inflammation** were common findings that could contribute to death. [493]

In an earlier survival (not scheduled sacrifice) study with up to 15 C57BL (C57BL/KaLwRij) mice per cage (initially), [464]the most common non-neoplastic findings were

1. mild-moderate **glomerulonephritis** (F 100%, M 100%),
2. **amyloidosis (F 73%, M 83%)**
3. acidophilic macrophage pneumonia (F 16%, M 30%),
4. arteritis (polyarteritis) (F 36%, M 16%),
5. cystic endometrial hyperplasia (F 52%),
6. hydronephrosis (F 9%, M 6%).

Neoplasia - *see also MTB and tumor frequency grid at http://tumor.informatics.jax.org/mtbwi/index.do*

In virgin and breeder SPF C57BL/6 mice [317] the most common neoplasms were

1. **lymphoma**,
2. hemangiosarcoma
3. **pituitary** adenoma.

- Histiocytic sarcoma was more common, and
- Harderian gland and lung tumors were less common than in BALB/c mice on the same study.

In other chronic studies, [106, 316, 317, 464]

1. **lymphoma** usually is the most common neoplasm in C57BL/6 mice, with incidences up to 31% in females and lower incidence in males.
2. Histiocytic sarcoma (female bias),
3. lung tumors (male bias),
4. liver tumors (male bias),
5. **pituitary** tumors (female bias), and
6. testicular interstitial cell tumors can have significant incidences.

- Harderian gland tumors, hemangiomas, thyroid follicular adenomas also are noted.

Diet restriction → increase lifespan, reduce tumor incidence and delay tumor onset in multiple studies. [493, 509, 510] In a long term survival study of ad lib fed and diet restricted C57BL/6 mice, 40% diet restriction

- 40% diet restriction increased mean life span 15% and 25% → > 27 mo + extended maximal lifespan by 18% in both sexes. [493]
- **Histiocytic sarcomas** = most common apparent cause of death and most common tumor in DR mice found dead or moribund at any age, and occurred in almost 1/3 of the mice (337/991).
- DR female mice had fewer pituitary neoplasms (37% vs. 1% in diet restricted mice); lymphoma, (29% vs. 9% in diet restricted mice), and thyroid neoplasms (8% vs. 0.4% in diet restricted mice), but incidence of histiocytic sarcoma increased.
- DR male mice had fewer liver tumors (10% vs. 1% in diet restricted mice). [493]

Lymphoma -- most common spontaneous lymphoma in C57BL/6 mice has been classified primarily as a type B reticulum cell tumor, follicular center cell lymphoma or mixed cell lymphoma, and probably is most compatible with follicular B cell lymphoma under current classification.

- unusual before 12 mo, and typically involves spleen, mesenteric lymph nodes, liver and may involve small intestine Peyer's patches or GALT
- primary cell type is relatively pleomorphic, small or large with more cytoplasm than mature lymphocytes, and is admixed with plasma cells and lymphocytes. [106]
- Definitive identification and typing of lymphomas requires IHC and/or molecular techniques. [280]

Histiocytic sarcoma rare before 12 months of age and slightly more common in females than in males. Previous classifications Dunn's (1954) reticulum cell neoplasm, type A or malignant lymphoma histiocytic type, and histiocytic lymphoma. [511, 512]

- liver = most commonly involved organ in male mice;
- uterus and vagina often involved in females = sites of origin??
- spleen, lymph node, bone marrow, lung, kidney, ovaries = less frequently involved.
- Pulmonary involvement in hi %

Pituitary tumors, predominantly of mammotrophs or prolactin secreting cells, arising from **pars distalis** reported in >80% of female C57BL/6J > 22 months old, and occur primarily in lateral zones. [513-515]

Ovarian Tubular mesothelioma (adenoma), = most common ovarian tumor in C57BL/6 mice as well as in B6C3F1 mice. [350]

Susceptibility to selected experimental conditions and infectious agents

Notable responses of C57BL/6 mice under experimental conditions include

1. High susceptibility to diet-induced atherosclerosis [362, 516],
2. High susceptibility to diet-induced gallstones [247] [249];
3. High susceptibility to diet-induced obesity, non-insulin-dependent diabetes and hypertension [254-256, 517, 518];
4. preference for high fat diets.[287]
5. Susceptibility to irradiation induced lymphoma [280, 519];
6. Susceptibility to experimental autoimmune encephalomyelitis (EAE) [520, 521],
7. Sensitivity to exogenous estrogens [522-525]

C57BL/6 mice are relatively resistant to

1. audiogenic seizures, electroshock-induced seizures, cocaine-induced seizures, and to Kainic acid-induced seizures and neuropathology compared to other inbred strains [526-529];

2. DEN induced liver tumors [431, 433],
3. some skin carcinogenesis protocols [356].

C57BL/6 mice are known for resistance to many infectious agents and diseases including

1. mousepox (Ectromelia virus) [257-259] [258];
2. Sendai viral pneumonia [530, 531];
3. polyomavirus induced tumors [377];
4. EMCV induced diabetes or myocarditis [363, 364, 532, 533];
5. murine respiratory mycoplasmosis (*M pulmonis*)[293, 534, 535];
6. *Helicobacter hepaticus* hepatitis [260, 261];
7. Lyme borrelliosis [373, 442, 536],
8. *Listeria monocytogenes* mortality [263] (but not gastritis [374]);
9. *Mycobacterium tuberculosis* [264, 537-539].

C57Bl/6 mice are relatively susceptible to

1. Experimental lethal MAV1 hemorrhagic encephalomyelitis [378-382];
2. *Helicobacter felis* gastritis [383, 384, 540, 541] [542];
3. Cryptococcus neoformans pneumonia [507, 508]; and
4. mite associated ulcerative dermatitis [38, 42, 543, 544].

Related Strains and substrains

C57BL/6ByJ was separated in the 1950s from C57BL/6NCr, a substrain maintained at the National Cancer Institute (NCI) since 1951. Multiple allelic differences from C57BL/6J are attributed to residual heterozygosity at the time the J and NCr substrains were separated.[156]

C57BL/10J separated from original C57BL strain in mid-1930s, after ~ 40 generations of inbreeding. [69, 156]

- 49 (3%) of 1638 SNPs tested were polymorphic between these 2 strains.
- Unexpectedly high number of segregating loci after 40 generations of inbreeding exceeds what would be expected by chance, and suggests **selection** for residual heterozygosity at some loci during inbreeding.
- Behavioral, breeding etc differences compared to B6
- Dermatitis, microphthalmia, hydrocephalus

C57BLKS (formerly C57BL/Ks)

- Origin: C57BL/6J to Biesele in 1947, then pen bred, to Kaliss (Ks) in 1948. Ks resumed inbreeding. To J 1948. [69]
- 84% of alleles = C57BL/6 and 16% = DBA/2J indicate genetic contamination early in strain's history (e.g. pen breeding). [156]
  - DBA/2J segments on every chromosome except Chromosomes 2, 13.
  - Chromosomes 4, 9, 11, 15 have segments that suggest other contamination
- Spontaneous **hydronephrosis** may occur in > 60% of male C57BL/KsJ mice by 15 weeks of age. [545, 546]

- Diabetes (*Lepr^{db}*) and obese (*Lep^{ob}*) mutations maintained on C57BLKS/J inbred background → more severe diabetes phenotype compared to C57BL/6J inbred background.
- C57BLKS/J mice → age related hearing loss by 3 months of age.

C57BR

- Brown mice developed from same mating (57X52) as C57BL in 1921. Black and brown substrains were separated in the first generation. [68, 69, 389]
- High Ethanol preference [547]High intrastrain aggression
- Pituitary tumors in females. [5]

C57L

- Gray mice that carry Leaden (ln) coat color gene (*a/a Tyrp1^{b}/Tyrp1^{b} Mlph^{ln}/Mlph^{ln}*)
- developed from a C57Br (*a/a Tyrp1^{b}/Tyrp1^{b}*) substrain in 1933 [68, 69, 389]
- ? - Extremely susceptible to diet-induced **gallstones** and carry susceptibility alleles at Lith1 etc sites associated with gallstone susceptibility. [247, 249]
    - Helicobacter spp. especially H hepaticus & H rodentium implicated in C57L cholelithogenesis. [548, 549]
- **lymphoma** high incidence ~ 25% incidence at 21 months of age, resembles B cell lymphoma of SJL/J mice. [280, 550]
- susceptible to EAE.[551]

C58

- black mice (a/a). developed in 1921 from same litter as C57BL: Female 58 mated with the same male (52) gave rise to strain C58.
- used largely because of their high incidence **thymic precursor T cell lymphoma (leukemia)** by one year of age.[52, 282, 389, 552]

B6;129 mice and B6C3F1 hybrid mice are discussed below, after inbred strains.

II.G. DBA See also table 3a, table 3b

Oldest of all inbred strains of mice – initiated by CC Little in 1909 during coat color experiments from stock segregating for = recessive coat color genes: ***d, b, a*: dilute, brown, non agouti, and was named for those genes, now** *Myo5a*^{d}, *Tyrp1*^{b}, *a*.

- uniformly non-agouti, washed out (dilute), brown coat [68]
- substrains DBA/1 and DBA/2 were developed in 1929
  - substantial differences (including MHC H2 haplotype) probably due to substantial residual heterozygosity. [69, 389]
- DBA/2J is prioritized in mouse phenome database.[553]

DBA/1

Neoplasia - *see also MTB and tumor frequency grid at http://tumor.informatics.jax.org/mtbwi/index.do*

Low gross tumor incidence [268]. especially in males with

- lung tumors in 3% of males, 1% of breeding females;
- 'lymphatic leukemia' in < 1% of males

VS hi incidence lymphoma and lung tumor in some studies

- **lymphoma** 90% in breeding & 61% in virgin females [238],
- **lung tumors** in males & females (2-27%) [203].

Susceptibility to type II collagen induced arthritis, → model human rheumatoid arthritis. [554-556]

DBA/2

- intermediate lifespan [203, 268, 277] DBA/2J have
- Good breeding performance [307] poorer than DBA/1J [209]
- intermediate size with mean female wt~ 22g and male ~ 29g @8wo. [209]
- lowest brain weight of 25 inbred strains, but intermediate brain: body weight ratio (11th of 25).[75] Hydrocephalus is rare.[557]
- DBA/2J is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home

Non-Neoplastic conditions

Vision / Eye

- **Glaucoma** progressive form of secondary angle-closure glaucoma that appears to be initiated by iris atrophy and synechiae. [558-560]
  - Interactive loci → pigment dispersion, iris transillumination, iris atrophy, anterior synechiae,
    - ipd (iris pigment dispersion) on chrom 6
    - isa (iris stromal atrophy) on chrom 4 (assoc with Tyrp1^{b} homozygosity & iris atrophy in various aged b/b mice of diff strains)
  - ↑ IOP in most mice by 9 months.
  - optic nerve atrophy with cupping in most mice by 22 months

- **Corneal mineralization** with ulcers/erosions, acute keratitis, stromal neovascularization and mineralization of basement membrane zone, occur at higher incidence in DBA/2 (29.1%), than in other susceptible strains C3H (16.2%), CF1 (16.2%) and BALB/c (10.0%). [313]

Hearing progressive hearing loss severe by 3 months. [172]

- carry 3 recessive hearing loss genes, including Cdh23ahl. [144, 561, 562]

Cardiac calcinosis up to 90% affected by 1 year [402, 563] Similar to condition in related BALB/c & C3H. [316]

- Early lesions may include subepicardial eosinophilic myocarditis of RVFW. [564]
- Dystrophic calcification or mineralization also can occur in aorta, testes, tongue, skeletal muscle, cornea, kidney, stomach, small intestine, ovary with incidence / severity increasing with age and without apparent sex differences (in non-gonadal tissues).[565-569]
- Dyscalc loci (Dyscalc 1-4) on different chromosomes implicated.[318, 319, 404]

Malocclusion rare - 0.0130% in 2002 @ TJL. [326]

Adrenal adrenal subcapsular spindle cell hyperplasia with associated mast cell infiltration in almost 100% of females at 13-15 m > male incidence ~ 70%. [85]

Imperforate vaginas with associated hydrometra and mucometra -- 3 of 35 in DBA/2J (5 / 35 in DBA1/J) over 2 year @TJL. [331]

Immunology

- A/J, A/HeJ, AKR/J, **DBA/2J**, NZB/B1NJ, SWR/J, B10.D2/oSnJ, NOD.ShiLtJ mice are genetically deficient in **complement C5**
  - $Hc^{0=}$ deletion mutation in exon in gene Hc (hemolytic component)
  - [217-220]

Amyloidosis DBA/2 mice are unlikely to develop senile (AApoAII or ASSAM) and reactive (SAA) amyloidosis, despite intermediate susceptibility allele (ApoAIIa) for senile amyloidosis. [118]

Neoplasia - *see also MTB and tumor frequency grid at* http://tumor.informatics.jax.org/mtbwi/index.do

Most **frequent** neoplasms in breeding DBA/2J [242] mice were

1. **lymphoma** in both sexes with frequency of 0.5-1%
2. **mammary tumors** with frequency of 0.5-1% in females

Studies prior to 1973 [202, 203, 238] showed notable incidence of:

1. **leukemia or lymphomas** 2-12% in females, 0-10% in males;
2. **mammary tumors** in unfostered substrains 31% -48% in virgin females, 72% in breeding females, 0-1% in males;
3. liver tumors 6-35%, and
4. lung tumors 1-23%.

Susceptibility to selected experimental conditions and infectious diseases

Notable responses of DBA/2 mice under experimental conditions include their high susceptibility to

1. audiogenic seizures between 14 and 42 days of age, [570-572];
2. chloroform-induced renal injury in males [79];
3. N,N-diethylnitrosamine (DEN) - induced hepatocarcinogenesis in males [433];

4. skin carcinogenesis protocols [356]

DBA/2 mice are relatively resistant to

1. diet-induced atherosclerosis or fatty streaks [250, 289],
2. diet-induced cholelithiasis [247].

Notable responses of DBA/2 mice to infectious agents include

1. high susceptibility to lethal mouse pox (Ectromelia virus infection) [257-259] [258],
2. high susceptibility to Sendai virus pneumonia and death [26, 530].
3. susceptibility to some MHV's [573];
4. susceptibility to EMCV myocarditis, diabetes and demyelination [533, 574] [575, 576];
5. susceptibility to experimental lethal MAV1 hemorrhagic encephalomyelitis [378-382],
6. susceptibility to murine respiratory mycoplasmosis (M pulmonis) [534, 535],
7. susceptibility to Helicobacter felis gastritis[261, 383, 384] , and
8. susceptibility to cariogenic streptococci [375, 376].
9. Susceptibility to candidiasis attributed to complement c5 deficiency. [219]
10. resistance to polyomavirus induced tumors. [377]

II.H. FVB/N See also table 3a, table 3b [577]

- NIH Swiss origin selected for Friend leukemia Virus B strain susceptibility.
- fertilized eggs contain prominent pronuclei that facilitate microinjection
- albino with color genotype *A/A Tyr^{c}/Tyr^{c}*.
- relatively long lived with 60% survival to 24 m in both sexes [578]
- vigorous reproductive performance and consistently large litters.[307] [577]
- FVB/NJ is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home

Non neoplastic conditions

Vision rd1 - homozygous for the retinal degeneration allele *Pde6b^{rd1}*, which results in early onset retinal degeneration. [577]

- spatial learning deficit may be independent of their visual deficits [579]
- thigmotactic, hyperactive and higher levels of anxiety and aggression compared to C57BL/6J mice.[579]

Immunology

- A/J, A/HeJ, **AKR/J**, DBA/2J, FVB/NJ, FVB/NMob, NZB/B1NJ, SWR/J, B10.D2/oSnJ, NOD.ShiLtJ mice are genetically deficient in **complement c5**
  - *Hc^{0}* = deletion mutation in exon in gene Hc (hemolytic component)
  - [220, 273-275]

CNS / Seizures sometimes lethal epileptic syndrome, with apparently spontaneous seizures, or with seizure induction by tail tattooing, fur clipping, and fire alarms. [580]

- **Females** are affected almost 8 times more commonly than males.
- facial grimace, chewing, ptyalism with and clonic convulsions progressing to tonic convulsions and death
- histopathology may include neuronal necrosis and astrocytosis in the cerebral cortex, hippocampus, and thalamus.
- +/- centrilobular hepatic necrosis attributed to terminal hypoxia

Mammary hyperplasia Multiparous and virgin female FVB/N mice develop persistent mammary hyperplasia that may be associated with hyperplasia or adenoma of prolactin secreting chromophobe cells of pituitary pars distalis.

- glands have lobuloalveolar hyperplasia with distended secretory alveoli + ducts that resemble glands during pregnancy or delayed involution.
- frequently have small nodules of squamous epithelium
- Multiparous animals have higher incidence than virgin females

Neoplasia *- see also MTB and tumor frequency grid at http://tumor.informatics.jax.org/mtbwi/index.do*

In a study of survival to 24 mo, the incidence of mice with tumors at 24m was 55% in males and 66% in females [578]

- In females, most common tumors were
  1. **lung** tumors,
  2. pituitary gland adenomas,

3. ovarian tumors (combined types),
4. lymphomas, histiocytic sarcomas,
5. Harderian gland adenomas, and
6. pheochromocytomas,

- In males, most common tumors were
  1. **lung** tumors,
  2. liver tumors,
  3. skin tumors, and
  4. Harderian gland adenomas

- FVB/N may have relatively high incidence of lung tumors and low incidence of liver tumors and lymphomas compared to other strains.
- An unusual skin tumor on the pinna or tail of 5 mice in the study (3% of females and 10% of males), was a spindle cell neoplasm and was diagnosed as a neural crest tumor.

Mammary tumors Of only 6 carcinomas diagnosed in mammary glands from almost 500 wild type control FVB/N mice, 2 were adenosquamous, 3 were squamous cell carcinoma and 1 was adenocarcinoma. [581]

- By 13 mo > 40% of virgin females may have mammary hyperplasia and ↑prolactin levels.
- By 18-23 mo, 52% of virgin females had pituitary pars distalis hyperplasia and 19% had adenomas.
- Multiparous mice 18-23 months of age had 83% incidence of pituitary adenomas. [582]

Susceptibility to selected experimental conditions and infectious diseases

Notable responses of FVB/N mice under experimental conditions include

1. high seizure susceptibility [583-585]; and
2. susceptibility to some skin carcinogenicity protocols [586]
3. relative resistance to collagen-induced arthritis. [556]
4. highest serum cholesterol levels on chow diet (~100mg/dl), and only modest increases (< 2 fold) in response to high fat diet compared to other inbred strains. [253].

FVB/N mice also are susceptible to TMEV induced chronic inflammation and primary demyelination. [587]

II.I. NOD See also table 3a, table 3b

- **NOD (non obese diabetic)** mice derive from Japanese ICR outbred stock selected for high fasting blood glucose (diabetes) without cataracts.[588]
- Environmental factors strongly influence diabetogenesis [589]
- Females are more susceptible to diabetes
  - insulitis, ↓insulin in females c12 weeks of age, later in males (40-60% by 30-40 wo)
- Onset marked by moderate glycosuria + non-fasting plasma glucose >250 mg/dl.
- Hypoinsulinemia + hyperglucagonemia indicate selective destruction of beta cells.
- Susceptibility dt unique MHC haplotype (H2g7 = Kd, Aad, Abg7, Enull, Db).
- Immunoweird: H2g7 MHC haplotype; defective antigen presenting cell immunoregulatory functions, defects in T lymphocyte regulation, defective NK cell function, defective cytokine production from macrophages (Fan et al., 2004), Hc^0 (lack hemolytic complement c5).
- Thymic lymphomasa are common (and likely causes of death) in various NOD derived strains e.g. NODscid
- $Cdh23^{ahl1}$ → severely hearing-impaired
- **NOD/ShiLtJ** is the Prioritized Tier 1 strain in Mouse Phenome Database initiative, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home
  - Good breeding performance [307]
  - More Osteosarcomas than other inbred strains [590]

II.J. SJL/J See also table 3a, table 3b

- derive from 3 sources of Swiss Webster outbred stock brought to TJL between 1938 and 1943. [69, 389]
- popular for high incidence of lymphomas (formerly called reticulum cell sarcoma type B) that resemble Hodgkin's disease.[591]
- albino with color genotype *p/p* Tyr^c/Tyr^c.
- easy to handle (dt blindness?) [182], but
- known for intraspecies aggression. Most males killed by 4-5 months unless caged separately.[591-593]
- Demoted, deprioritized to MPD tier 2, 2007 rev. http://phenome.jax.org/db/q?rtn=strains/home
  - Good breeding performance [307]
- Unusual immune responses include
  - Exceptional radioresistance [594],
  - Relatively Low natural killer cell activity [595] possibly related to polymorphisms in Klra (Ly49) and Nkrp1 in the natural killer cell complex)[596],
  - Polyclonal B lymphocyte proliferation precedes lymphoma (more below)

Non- Neoplastic conditions

Vision rd1 Like some other Swiss strains and stocks & C3H mice, SJL/J is homozygous for $Pde6b^{rd1}$ → early onset retinal degeneration. [69, 389, 597]

Cataracts Early onset cataracts in some SJL/J attributed to beta crystalline mutation on chromosome 5 (N Hawes, Jax personal communication), and to Rct & Mrct loci on chromosomes 4 and 5 [598]

Muscular dystrophy A spontaneous recessive mutation (*im*) in the Dysferlin gene *Dysf*^{im}) arose in SJL/J mice and is maintained on that strain. [599-601]

- → ↂ levels of functional dysferlin protein → inflammatory myopathy (im) model for limb girdle muscular dystrophy 2B.
- Loss of muscle mass and strength → hind limb clasping and inability to spread hind limbs and digits when suspended by tails by about 8 mo.
- → muscle fibers with central nuclei, variation in fiber size, fiber splitting, inflammatory infiltrate, necrosis, and eventual replacement of muscle fiber with fat.
- weakness detected as early as 3 weeks of age but greatest pathology occurs after 6 months of age.
- A/J mice dysferlinopathy is a different allele (mutation) *Dysf*^{prmd}. [214]

Imperforate vagina with associated hydrometra and mucometra 4 of 35 were diagnosed in SJL/J [331]

Neoplasia - *see also MTB and tumor frequency grid at http://tumor.informatics.jax.org/mtbwi/index.do*

In a study of **frequency** of neoplasms in primarily breeding populations of inbred strains over a 13 year period, the most common neoplasms in SJL/J mice of both sexes were **lymphoma, plasmacytoma, histiocytic sarcoma**, with frequencies of 0.5-1%. [242] [602]

Lymphoma By 1 year of age SJL/J mice have high incidence (up to 90% by 18 m) of B cell lymphomas that have been classified as germinal center B cell lymphoma, pre-B cell lymphomas and, reticulum cell sarcoma, and have been associated with low natural killer cell activity in this strain as well as with high expression of several endogenous retroviruses. [550, 595, 603]

- Preceded by lymphoid hyperplasia in spleen, Peyer's patches/GALT, mesenteric nodes.
- After 6 mo, tumors 1st appear in GALT and mesenteric nodes and later in spleen, liver, thymus etc lymph nodes.
- Advanced cases have massively enlarged mesenteric lymph nodes and spleen, and very prominent GALT.
- Cells are pleomorphic or of apparently mixed-cell types, early tumors may be more plasmacytoid. [52, 280, 604-607]
- →model human Hodgkin's disease, and low grade B-cell non-Hodgkin's lymphoma. [608-610]

Susceptibility to selected experimental conditions and infectious diseases

Notable responses of SJL/J mice under experimental conditions include

1. High Susceptibility to autoimmune conditions such as EAE [611-615] and to experimental allergic myositis (which may be complicated by their muscular dystrophy phenotype) [616].
2. Exceptional radioresistance (and immunoweird) [594]
3. Resistance to diet-induced atherosclerosis or fatty streaks,[617] and diet-induced cholelithiasis. [247]

Notable responses of SJL/J mice to infectious agents include

1. High susceptibility to experimental lethal MAV1 hemorrhagic encephalomyelitis[379],

2. Susceptibility to TMEV inflammation and demyelination [618, 619],
3. intermediate susceptibility to mousepox [257-259]
4. Susceptibility to Lyme Borrelliosis arthritis but not myocarditis.[373]
5. Resistance to pneumonia virus of mice (PVM)[620]
6. Resistance to MHV induced demyelination and mortality attributed to lack of the virus receptor (Ceacam1) on target tissues. [17, 18, 621, 622]

II.K. Collaborative Cross [623] [624] [625]

Panel of multiparental **recombinant inbred (RI)** mouse lines, derived from 8 diverse strains, developed at 3 breeding sites in US, Israel, and Australia. Bred using a combinatorial funnel design to yield a large number of genetically independent RI lines, aiming for

- inbred strains with novel and random allele combinations, that model complexity of the human genome
- Support analyses of common human diseases with complex etiologies originating through interactions between allele combinations and the environment.

8 parental strains were

1. A/J,
2. C57BL/6J,
3. 129S1/SvlmJ,
4. NOD/ShiLtJ,
5. NZO/HlLtJ,
6. CAST/EiJ,
7. PWK/Ph,
8. WSB/EiJ

III. Non Inbred mice

III.A. B6;129

(the recipient (host) strain name precedes the donor strain in congenic (backcrossing) nomenclature)

B6;129 mice are generated from back crosses of 129 (donor) mice to C57BL/6 host or recipient strains. The semicolon (;) indicates that B6;129 is a mixed or incipient inbred strain. With continued backcrossing to C57BL/6, it would become congenic and be designated B6.129. [626]

- important dt tm mice generated from injection of 129 ES cells into B6 blastocysts.
- Chimera X B6 → N1 offspring, subsequent backcrosses to B6 are N2, N3 etc.
- Sibling mating of homozygous mutant mice before congenicity is achieved, (→ generate homozygous mutant mice for study) should be designated F1, F2, F3 etc.
- Depending on extent of backcrossing (and thus residual heterozygosity), B6;129 have very variable contributions from B6 and 129 genotypes,
- Backcrossing + sib mating should be indicated by following the (incipient) strain designation with the number of back cross generations and the number of brother x sister generations, e.g. (N3F6).

Non-neoplastic conditions

In a recent study of 99 B6;129 mice, [121] the most common non-neoplastic findings included

1. Eosinophilic amyloid-like material in nasal septum submucosa,
   - may not stain with Congo red, but does stain with PAS and trichrome stains [120] [126, 627],
2. otitis media, (cause / agents usually not discerned)
3. epididymal epithelial karyomegaly,
4. melanosis (esp brain, parathyroid, and spleen),
5. membranoproliferative glomerulonephritis,
6. hyalinosis with extracellular crystals in several tissues, especially nose respiratory and olfactory epithelium,
7. islet cell hyperplasia
8. esophageal dilation (megaesophagus)

- **Non-neoplastic contributors to death**[121]
  - 3 male mice were sacrificed before end of study dt ulcerative dermatitis.
  - < 5% - infection/septicemia secondary to skin ulceration
  - < 5% -inhalation pneumonia/choke
  - < 5% - arteritis.
- Compared to parental 129S4SvJae, hyalinosis in derivative B6;129 was much more likely in nose + gall bladder, and less likely in stomach, bile duct, trachea. [104]
- Compared to parental 129S4SvJae, acidophilic macrophage pneumonia was less common in B6;129 [104]

Neoplasia

In same study, [121] by 104-105 weeks, 30/49 (61%) of the females and only 14/50 (28%) of the males were still alive.

1. **Lymphoma** = most common neoplasm (67% F, 42% M) with most common sites being mesenteric nodes (where it most often appeared to originate), GALT and spleen.
   - also = most common contributing cause of morbidity or mortality identified (8/19 females & 9/36 males that died or were sacrificed.
   - characterized as a B cell lymphoma, with similarities to T-cell rich, B-cell lymphomas in humans.
2. **liver** tumors,
3. **lung** tumors,
4. thyroid follicular tumors,
5. ovarian tumors, and
6. uterine tumors

- Other than lymphoma, neoplastic contributors to death, each affecting < 5% of the animals on study were histiocytic sarcoma, duodenal adenoma and hemangiosarcoma. [121]
- Compared to their parental strains, these B6;129 mice had (high) lymphoma incidences ~ C57BL/6J, and >> in 129S4/SvJae, with a female bias in all 3 types of mice. [106]
- C57BL/6J had more histiocytic sarcomas than these B6;129 or 129S4/SvJae.
- 129S4/SvJae mice had more lung tumors and Harderian gland tumors than C57BL/6J or these B6;129, with a male bias
- All 3 types of mice have similar incidence of liver tumors with a male bias.

III.B. B6C3F1

B6C3F1 = F1 hybrid resulting from mating C57BL/6 female with C3H or C3H/He male

(female precedes male in hybrid nomenclature).

- genetically identical, black agouti mice, heterozygous at all genetic loci where parental strains differ, with all males carrying a C57BL/ X chromosome and a C3H or C3H/He Y chromosome.
- Used widely in toxicology
- robust with long life span and less susceptibility to spontaneous pathologies than either parental strain. [628]
- Substantial variability in the incidence of lesions between and within laboratories has been attributed to variations in sources, environments and evaluators. [8, 10, 12, 629, 630]

Non-neoplastic conditions

The most common non-neoplastic findings [631] were

1. foci of cellular alteration in the liver,
2. pancreatic islet cell hyperplasia,
3. liver necrosis,
4. pituitary hyperplasia of the pars distalis (in females only),
5. thyroid follicular cell hyperplasia,
6. chronic nephropathy (especially in males),
7. splenic extramedullary hematopoiesis,
8. thymic lymphoid depletion,
9. thymic lymphoid hyperplasia,
10. ovarian atrophy,
11. ovarian cysts,
12. uterine cystic endometrial hyperplasia,
13. hydrometra,
14. cystic preputial gland ducts.

- Less common findings included hepatocellular vacuolization, hepatocellular necrosis, hepatic centrilobular hypertrophy, hepatic extramedullary hematopoiesis, pancreatic exocrine atrophy, pancreatitis, gastric squamous epithelial hyperplasia, chronic mesenteric inflammation, arteritis, adrenal subcapsular cell hyperplasia, lymphoid hyperplasia in lymph nodes and spleen, macrophage or plasma cell infiltration of lymph nodes, pigment in the lymph nodes, myeloid hyperplasia in marrow, lymphoid, reticular, erythropoietic and / or granulopoietic hyperplasia in spleen, ulcerative dermatitis, pulmonary alveolar hyperplasia, retinal degeneration; chronic renal inflammation, hydronephrosis; renal pigment (hemosiderin), ovarian hemorrhage, angiectasis, or hematocyst, epididymis sperm granuloma, testicular atrophy, preputial gland inflammation. [631]

Hepatocellular vacuolization dt fatty change can be common in control mice in some studies & reported under various terms including steatosis, lipidosis, fatty metamorphosis. [84, 422, 632]

- especially common in old obese control mice,
- more common in male than in female mice
- also may be a toxicant response.

Altered hepatic foci or foci of hepatocellular alteration increase with age in mice. [422, 425, 632]

- Eosinophilic and clear cell foci > basophilic foci in B6C3F1 mice,
- all types of foci are more common in male than in female mice.
- no obvious disruption of liver architecture, nor compression
- associated with carcinogens and development of hepatocellular neoplasms,
- biological and toxicological significance remains unclear.

Amyloidosis is notably absent here [631] as it is in other studies on this hybrid, especially in contrast to CD-1® mice, which also have been popular in chronic toxicology studies. [11, 110, 630, 633]

Obstructive urinary tract disease (mouse urological syndrome (MUS) has been recognized as an important cause of death of control and treated B6C3F1 male mice on some studies. [634, 635]

Fibroosseous changes (myelofibrosis, metaphyseal osteosclerosis) can occur with an incidence >33% in 2 year old female B6C3F1 mice, compared to <1% in 2 year old male B6C3F1 mice. [97, 134]

- Estrogenic compounds also may induce endosteal bone proliferation in mice. [636]

Neoplasia

Consistent with earlier studies,[12, 630] the most common neoplasms in this study [631] were

1. **liver tumors,** with male predilection for carcinomas
    a. incidence and male predisposition for liver tumors is similar to C3H or C3H/He strains, and contrasts with C7BL/6. [422, 631]
2. **lung tumors**
3. **lymphoma**

The most recent summary of NTP historical control data, involving 1158 female mice and 1159 male mice, treated with various control vehicles via various routes, in 20 chronic (2-year) NTP studies initiated between 1992 and 1998, corroborates these data. Mice in this report received NTP 2000 diet ad lib, female mice were housed 5/cage, and male mice were housed individually. [637]

- In female mice, the most common neoplasms were
    1. **liver** tumors with mean incidence of 22%, adenoma > carcinoma;
    2. **lymphoma** with mean incidence of 16%;
    3. **pituitary** gland adenomas with mean incidence of 11%;
    4. **lung** tumors with mean incidence of 8%, adenoma > carcinoma;
    5. **Harderian gland** tumors with mean incidence of 8%, adenomas >> carcinomas;
    6. hemangioma/hemangiosarcoma with mean incidence of 4%.
- In male mice, the most common neoplasms were
    1. **liver** tumors with mean incidence of 47%, adenoma > carcinoma
    2. **lung** tumors with mean incidence of 26%, adenoma > carcinoma
    3. **Harderian gland** tumors with mean incidence of 11%, adenoma >> carcinoma
    4. hemangioma/hemangiosarcoma with mean incidence of 6%;
    5. lymphoma with mean incidence of 5%.

Individual housing of males to reduce loss of due to fighting and sequelae has resulted in longer male survival, but also associated with increased body weight and increased liver tumors compared to earlier studies of group-housed male mice.[629, 638]

Hemangiosarcomas were more common than hemangiomas and occurred in skin, spleen, ovary, bone marrow, lymph nodes, uterus, testes, preputial gland, epididymis, urinary bladder, heart, intestine, kidney, liver, lung, muscle.[637]

Mammary tumors and histiocytic sarcomas are not common in these mice compared to some other strains. [628, 631, 637]

Ovarian tumors can be common on aging studies, with most ovarian tumors rare before 1 year of age, and increasing with age after 1 year. The most common ovarian neoplasms in B6C3F1 mice were cystadenomas (24%), tubulostromal adenomas (24%), benign granulosa cell tumors (21%), and benign teratomas (8%). [628, 639, 640]

Less common neoplasms include skin neurofibrosarcoma or Schwannoma, papilloma, squamous cell carcinoma, fibrous histiocytoma, melanoma, sebaceous adenoma, basal cell tumor; oral papilloma, squamous cell carcinoma; forestomach papilloma, squamous cell carcinoma; intestine adenoma/carcinoma, leiomyoma/leiomyosarcoma, fibrous histiocytoma; liver hepatoblastoma, cholangioma, cholangiocarcinoma; kidney tubule adenoma/carcinoma; adrenal cortex adenoma/carcinoma; adrenal phaeochromocytoma; pancreas islet adenoma; thyroid follicular adenoma/carcinoma, C-cell adenoma/carcinoma; mast cell tumor; brain meningioma, oligodendroglioma, glioma, or astrocytoma; pituitary pars intermedia tumors; ovary cystadenoma, luteoma, thecoma, teratoma, granulosa cell tumor; uterus adenoma/carcinoma, uterus stromal polyp/sarcoma, leiomyoma/leiomyosarcoma; testicular Sertoli cell tumor; prostate adenoma/carcinoma, seminal vesicle adenoma/carcinoma, coagulating gland adenoma; mammary fibroma, fibroadenoma; clitoral/preputial gland adenoma/ carcinoma; salivary adenoma/carcinoma; Zymbal gland adenoma/carcinoma; neural crest tumor; mesothelioma; osteosarcoma/osteoma; chondrosarcoma/chondroma; rhabdomyosarcoma; fibrosarcoma.[631, 637]

Susceptibility to selected experimental conditions and infectious agents

B6C3F1 mice may be

1. more susceptible to urethane induced tumors and mortality compared to B6CF1 (C57BL/6J X BALB/c) F1 mice.[641],
2. more susceptible to ENU-induced renal tumors than outbred Swiss mice [642, 643]
3. less sensitive to some skin tumor protocols than Swiss and SENCAR mice, [644]

III.C. Swiss Mice – derivative inbred strains and outbred stocks See also table 6

So-called 'Swiss' mice derive from two males and seven females obtained by Clara Lynch from Switzerland in 1926 [645, 646]

- Although today's commonly available non-inbred Swiss stocks descend from Lynch's original mice, and probably through Webster's colonies, their names typically indicate descent through ICR (ICR mice), though NIH (NIH Swiss mice), or more or less directly from Webster's colonies (Swiss Webster mice).
- heterogeneity of the Swiss stocks is limited by the small genetic base of the founders, early selective breeding and inbreeding programs [647], and subsequent rederivation efforts that 'reconstituted' an 'outbred' stock from a few mice, or from only one breeding pair,[648], and further complicated by closed colonies (with identical names) maintained at different sites.
- GWAS etc studies have assessed the heterogeneity (or lack thereof), and other genetic features of 'outbred' Swiss and other non inbred mice. [649] [650] [651]

Dr. Webster's inbred and random bred Swiss mice were transferred to commercial dealers and other laboratories in 1936-1937, and their descendants usually bear reference to his name, e.g. Swiss Webster (or SW). [646, 652]

Ha and ICR designations refer to Theodore **Ha**uschka at the Institute of Cancer Research (**ICR**) at Fox Chase Cancer Center, Philadelphia, PA. His breeding stock came from 6 sources of 'Swiss Webster' mice (from Webster's lines of Swiss mice) in the 1940's.

- Hauschka selected for high production and high growth rate characteristics and achieved exceptional production parameters with average 15 pups/litter, > 99% pups weaned, <23 day interval between litters. [652]

Nomenclature of outbred stocks differs from inbred stocks in that the facility designation (Laboratory code) **PREcedes** the stock identification and they are separated by a colon [653] [654], e.g. CRL:CD-1®(ICR)BR; Hsd:ICR(CD-1®); IcrTac:ICR.

- all outbred albino mice are NOT necessarily Swiss or Swiss origin. Despite the similarity in their names to Swiss CRL:CD-1® and CRL:CFW® mice, CRL:CF-1® mice derive from non-Swiss mice that were believed to be unrelated wild mice.

Non- Neoplastic conditions

Vision rd1 Retinal degeneration was noted in an inbred SW line and in about 13% of a random bred Swiss stock by the mid 1960's. [646] Several inbred Swiss derived strains (FVB/N, SJL/J, SW), [69] are homozygous for *Pde6b*^{rd1}.

- not discerned in 2 studies of CRL's CD-1® mice [655] [597]
- [597] detected:
  - No retinal degeneration in CRL's CD-1®,
  - retinal degeneration in about half of HSD:ICR mice that derive from CD-1®,
  - retinal degeneration in almost all of CRL:CFW stock examined.
  - retinal degeneration was found in only 1 of 120 mice in 2 stocks of non-Swiss albino mice (CRL:CF-1® and Hsd:NSA™ mice derived from them)

Corneal dystrophy or mineralization reported in ~ 4% of aged CD-1® mice. [313]

Cataracts reportedin up to 25% of CD-1® mice by 18 months of age. [656] In a study of ocular lesions in about 3,000 4- to 5-week-old, CD-1® mice, using indirect ophthalmoscopy (IO) and slit lamp,[655] findings included:

- lenticular opacities or other changes in 19% of mice,

  (also consider cataracts realted to exposure to anesthesia or other chemicals, or cold. [149] [150] [151] [152]
- Hyaloid artery remnants or floating bodies or hemorrhage in vitreous in up to 17%
- Abnormalities with incidence < 4% included mineralized and non-mineralized corneal opacities (visible with IO with or without additional lens), iridal changes (ectopic pupil dt coloboma, persistent papillary membrane, synechiae, miosis), colobomatous fundus, retinal fold, or retinal atrophy, few cases of chorioretinal atrophy, hemorrhage, or abnormal patterns of retinal vasculature, incomplete palpebral fissure, microphthalmia, exophthalmia, ophthalmic hemorrhage, scleral mass.

'progressive necrosing dermatitis of the pinna' sometimes associated with ulcerative dermatitis extending over neck and shoulders, with predilection for **male mice**, noted in CD-1® mice from various colonies, prevalence of 2-42%. [657]

Amyloidosis = important cause of morbidity and or mortality in some chronic studies.

- CD-1® mice are susceptible to senile (ApoA2) as well as to reactive (AA) amyloidosis. Immunohistochemical identification of the amyloid types reveal senile ApoAII amyloid primarily in gut, heart and lung, and reactive AA amyloid deposits primarily in spleen, liver, kidney and gut in mice with chronic dermatitis. [114]
- Disease status, intrastrain aggression, self trauma and skin lesions have been implicated in amyloidosis in Swiss mice [11, 633, 658]
- Incidence in mice less than 1 year old may be quite low, < 3%. [110, 117]
  - By about 2 years of age, the most commonly affected tissues are kidney, liver, duodenum, jejunum, ileum, ovaries, thyroid, adrenal.
  - less commonly affected tissues are: spleen, heart, salivary glands, glandular stomach, mesenteric lymph nodes, cecum, colon, testes.
  - Occasionally or rarely affected tissues include: rectum, larynx, skeletal muscle, vagina, tongue, skin, eye, lacrimal gland, pituitary, preputial gland, mammary gland, prostate, seminal vesicle, sciatic nerve, cervical lymph node, pancreas, thymus, gall bladder, urinary bladder, uterus, renal lymph node, lumbar lymph node, adipose tissue.

Non neoplastic conditions that have been considered to cause or contribute significantly to death on chronic studies include:

1. **Amyloidosis** with incidences varying from less than 1% to 54% in females, and from 2% to 56% in males. [11, 110, 117, 658, 659]
2. urinary tract obstruction with distended bladders and urethral plugs, sometimes called dysuria (cf **MUS**), in male mice [633, 660];
3. renal disease including nephropathy, glomerulonephritis, glomerulosclerosis or hydronephrosis, especially in female mice; [633] [660]
4. skin lesions including ulcers, abscesses, chronic dermatitis especially in male mice [633] [660], and sometimes attributed to fighting and self-trauma [11];
5. polyarteritis most commonly in thymus, ovary, uterus, kidney and heart [658] [633] [660];
6. cardiomyopathy [658] [660], and left auricular thrombi especially in males [633].

7. cystic endometrial hyperplasia can be a common finding. [11, 633, 660]
8. Subcapsular spindle cell hyperplasia in adrenal glands may be found in more than 80% of aged females and in fewer males.[83]
9. Spinal cord and sciatic nerve degeneration [11],
10. ovarian cysts [660]

Spontaneous Neoplasms

In early Swiss mice [646] living 6 months or more,

1. 44% had **lung tumors**,
2. 19% had **mammary tumors**, and
3. about 1% had leukemia (**lymphoma**).

- Of those living > 18 months,lung tumor incidence was 70-80%.

In the Ha(ICR) colony at ICR (before 1962) there was relatively high tumor incidence -- tho not examined systematically for other tumors or pathology.[652]

1. **mammary tumors** ~ 30% incidence of in 175 breeding females kept for 20 months, but 0 noted before 12 months of age.
2. **lung tumors** ~ 15% incidence of in male and female mice

In the Ha(ICR) colony at RPMI, based on gross examination only, [652] 350 breeding females kept up to 28 months had

1. **mammary tumors** ~ 11% incidence
2. **lung tumors** ~ 25% incidence (vs 14% in 100 male up to 26 mo)
3. **lymphoma** ~11% incidence
4. pituitary tumors ~15% incidence

- colony was seropositive for Reo-3 virus, GDVII, MHV, BUT were considered to be SPF bc they were culture negative for salmonellosis (mouse typhoid), and seronegative for Sendai, K virus, mouse adenovirus, pneumonia virus of mice, polyomavirus.

Hematopoietic, pulmonary and hepatic neoplasms also are most common tumors and neoplastic causes of death in more recent chronic studies of CD-1® mice. [11, 633, 658, 660, 661]

1. **Lymphoma** incidences vary from 1 to 50% in females, 2 to 22% in males, and
2. **(histiocytic sarcoma** incidences from 2-18% in females and 1-8% in males, and there are occasional myeloid leukemias.)
3. **Lung tumor** incidences vary from 0-39% in females and 0-43% in males
4. **Liver tumor** incidences vary from 0-18% in females and 0-45% in males.

CFW Swiss mice have had low reported incidence of spontaneous lymphomas and leukemias, [658, 662] but in a study of *M leprae* infection, ~ 60% control and infected mice developed tumors. 85% were lymphomas, most of B-cell origin. All tumors tested expressed ecotropic MuLVs. [663]

Mammary tumors in females are less common in recent studies [11, 633, 658, 661, 664] [660]

- usually adenocarcinomas and may be implicated as a cause or contributor to death.
- Adenoma, adenoacanthoma, carcinosarcoma and fibrosarcoma of the mammary gland also are reported occasionally.

Pituitary tumors are noted with incidences of up to 14% in female mice and up to 3% in male mice in some studies. [11, 633, 658, 661]

Harderian gland tumors, most commonly adenomas in males, are noted in some studies with incidences of up to 14%. [633, 661]

Hemangiomas or hemangiosarcomas of various tissues including spleen, skin, ovary, liver, heart, lymph nodes, bone marrow, are common in some studies, with incidence of up to 18%. [11, 633, 661]

Related strains and stocks

- Swiss derived inbred strains include FVB/N, NOD, NON, SJL/J, SWR.

NOD (non obese diabetic) mice derive from Japanese ICR outbred stock selected for high fasting blood glucose (diabetes) without cataracts.[588]

NON (non-obese non-diabetic) was separated from main NOD diabetic colony at F13,

- one of several strains / stocks used as control animals in studies of NOD mice.

SENCAR outbred mouse stock, named for SENsitivity to CARcinogens, derive from crossing Charles River CD-1® mice with skin-tumor-sensitive (STS) mice then selective breeding for sensitivity to skin tumor induction

- SENCAR mice have a large data base for carcinogens and promoters.
- The order of susceptibility to DMBA initiation/TPA promotion protocol, has been summarized as: SENCAR > DBA/2 > CD-1® > C3H > BALB/c > C57BL/6. [644, 665, 666]
- Compared to BALB/c, SENCAR mice are more susceptible to chemically induced skin tumors, and less susceptible to chemically induced lung, vascular and uterine tumors.[667]
- SENCAR mice seem **not** to be unusually susceptible to spontaneous tumors. 50% of control mice survived past 96 weeks of age. [668]
- most common neoplasms = histiocytic sarcoma, pulmonary adenoma or adenocarcinoma, mammary tumors, follicular center cell lymphoma, and hepatocellular adenoma. [667, 669] Cr:ORL Sencar out bred stock are available from NCI.
- glomerulonephritis = most common non neoplastic condition and inflammatory changes were common also.
- Several inbred lines or strains have been developed from outbred SENCAR mice, including SencarA/PtCr, SENCARB/PtJ and SENCARC/PtJ, have increased sensitivities to various carcinogen protocols compared to outbred SENCAR mice.[389, 670-672]

III.D. Diversity Outbred DO [623]

- Designed to be the most genetically diverse mouse resource
- Developed by random outcross matings of **160 Collaborative Cross RI** lines
- Maintained by continued random matings that avoid sibling crosses to retain widest possible genetic diversity in each individual.
- Useful for
  - high resolution genetic mapping and validation of previously identified quantitative trait loci (QTLs) linked to disease susceptibility, drug resistance or behavioral phenotypes.
  - Toxicogenomic screens
- http://jaxmice.jax.org/strain/009376.html

Table 1a. Mouse Phenome Database (MPD) Tier 1 and 2 Prioritized strains (2007 Revision).
http://phenome.jax.org/pub-cgi/phenome/mpdcgi?rtn=docs/pristrains (accessed June 29, 2009)

Current MPD priority group	Former MPD priority group	Name	Type
1. Tier 1	A	**129S1/SvImJ**	INbred
2. Tier 1	A	**A/J**	INbred
3. Tier 1	B	**AKR/J**	INbred
4. Tier 1	A	**BALB/cByJ**	INbred
5. Tier 1	D	**BTBR T^+ tf/J**	INbred
6. Tier 1	A	**C3H/HeJ**	INbred
7. Tier 1	A	**C57BL/6J**	INbred
8. Tier 1	A	**CAST/EiJ**	WILD derived
9. Tier 1	A	**DBA/2J**	INbred
10. Tier 1	A	**FVB/NJ**	INbred
11. Tier 1	C	**KK/HlJ**	INbred
12. Tier 1	B	**MOLF/EiJ**	WILD derived
13. Tier 1	B	**NOD/ShiLtJ**	INbred
14. Tier 1	D	**NZW/LacJ**	INbred
15. Tier 1		**PWD/PhJ**	WILD derived
16. Tier 1	C	**WSB/EiJ**	WILD derived
1. Tier 2	C	BUB/BnJ	INbred
2. Tier 2	C	C57BLKS/J	INbred
3. Tier 2	B	C57L/J	INbred
4. Tier 2	C	CBA/J	INbred
5. Tier 2		DDY/JclSidSeyFrkJ	INbred
6. Tier 2		MRL/MpJ	INbred
7. Tier 2	C	MSM/Ms	WILD derived
8. Tier 2		NZL/LtJ	INbred
9. Tier 2	A	SJL/J	INbred
10. Tier 2	B	SM/J	INbred

Table 2. Laboratory codes – some examples
http://www.informatics.jax.org/mgihome/nomen/index.shtml (accessed June 29, 2009)

Lab code	Investigator	Organization
Cr		NCI, DCTD Animal Production Program; MD USA
Crl		Charles River Laboratories
Hsd		Harlan Laboratories, Inc.
Ola		Harlan UK, Ltd
ICR		Institute for Cancer Research (Fox Chase, PA)
J		The Jackson Laboratory; ME, USA
N		National Institutes of Health; USA
NMRI		
Rik (etc.)		RIKEN Institute of Physical and Chemical Research
Sv	Leroy C. Stevens	Retired code
Tac		Taconic Farms, Inc.
Bom		Formerly M&B A/S, Bomholt, DK

Table 3a. Attributes, Phenotypes of common strains and stocks

	Color	Color Genotype	H2	Some notable features (genotypes, phenotypes)
129	Agouti etc.	Variable; A^{W}+/- *p, d*	Var b bc	ES cell source; substrain variable features: +/- *Ahl*, hypocallosity/acallosity, teratoma, hyalinosis, acidophilic macrophage pneumonia, etc.
A	Albino	*a/a Tyrp1*^{b}/*Tyrp1*^{b} *Tyr*^{c}/ *Tyr*^{c}	a	*Ah1; ApoAII*^{c}; Cleft lip/ palate; lung tumors; teratogen susceptibility; Helicobacter susceptibility; *Dysf*^{prmd} muscular dystrophy in A/J *Hc*^{0} → C5 deficient- A/J, A/HeJ
AKR	Albino	*a/a* *Tyr*^{c}/ *Tyr*^{c} *Hc*$^{0/}$ *Hc*^{0}	a	*ApoAII*^{a}; thymic precursor T cell lymphoma *Hc*^{0} → C5 deficient
BALB/c	Albino	*A/A Tyrp1*^{b}/*Tyrp1*^{b} *Tyr*^{c}/ *Tyr*^{c}	d	hypocallosity; cardiac calcinosis; myoepitheliomas; Harderian tumors, induced plasmacytomas
C3H	Agouti	*A/A*	k	*rd1;* cardiac calcinosis; alopecia areata; mammary tumors in F; liver tumors M>F *Tlr4*^{lps} in C3H/HeJ
C57BL/6	Black	*a/a*	b	*Ah1; ApoAII*^{a}; microphthalmia; hydrocephalus; barbering/dermatitis F>M; amyloidosis; acidophilic macrophage pneumonia; lymphoma F>M; histiocytic sarcoma, pituitary tt F>M
DBA/2	Dilute brown	*Myo5a*^{d}/*Myo5a*^{d} *Tyrp1*^{b}/*Tyrp1*^{b} *a/a*	d	*Ah1; ApoAII*^{a}; cardiac calcinosis; glaucoma *Hc*^{0} → C5 deficient
FVB/N	Albino	*A/A* *Tyr*^{c}/ *Tyr*^{c}	q	*rd1; Fv1*^{b} (susceptible to Friend LV type B); large pronuclei; seizures; mammary hyperplasia *Hc*^{0} → C5 deficient – FVB/NJ, FVB/NMob
SJL/J	Albino	*p/p* *Tyr*^{c}/*Tyr*^{c}	s	*rd1; ApoAII*^{c}; *Dysf*^{im} muscular dystrophy; lymphoma; aggressive males
B6;129	Variable	Variable	Var	variable - cf B6, 129, e.g. hyalinosis, acidophilic macrophage pneumonia; lymphoma
B6C3F1	Agouti (dark)	*A/a*	b/k	robust → tox; liver tumors M>F; lymphoma F>M, lung tumors, pituitary tumors F>M ; Harderian gl tumors
Swiss	Albino	*Tyr*^{c}/*Tyr*^{c} *etc.*	Var	robust → tox; stock/source variable features, e.g. +/- *rd1*; amyloid; lymphoma; lung tumor; liver tumor; etc. *Hc*^{0} ?→ C5 deficient ?

Table 3b. Mouse Strains and some phenotype-relevant genotypes
(From MGI gene, Jax mice data, etc references)

Strains	*Gene*^{allele}	Gene allele information	System or phenotype
129	*A^{W}* *+/- p, d,ch*	White bellied agouti +/- Pink eye, dilute, chinchilla	**Coat Color**
129 P1, P3, P4, S1, T2	*H2* ^{b}	b MHC haplotype	Immunity
129 X1, P3J	*H2* ^{bc}	bc MHC haplotype	
129 (P,S, T, X)	*Disc1*^{del}	disrupted in schizophrenia 1, delta 6 allele (deletion)	Behavior
129P1- *Lama2*^{dy}	Lama2dy	laminin, alpha 2; dystrophia muscularis	Muscle
129P3	*Ahr*^{d}	aryl-hydrocarbon receptor d variant (NON responsive allele)	Toxin response
129X1	*Cdh23*^{ahl}	age related hearing loss 1	Deafness
Previous 129	*Kitl*$^{Sl\text{-}J}$	Kit ligand (mast cell growth factor) Steel Jackson allel	Immunity mast cells
Previous 129	*Dnd1*^{Ter}	dead end homolog 1 (zebrafish); teratoma	Testicular teratoma
A/	***c/c***	***a/a Tyrp1*^{b}*/Tyrp1*^{b} *Tyr*^{c}*/Tyr*^{c}**	**albino**
A/	*H2* ^{o}	haplotype	Immunity
A/J, A/HeJ A/WySnJ	*Cdh23*^{ahl}	age related hearing loss 1	Deafness
A/J	*Ahl*^{4}	age related hearing loss 4	Deafness
A/J, A/HeJ	*Ahr*$^{b\text{-}2}$	aryl-hydrocarbon receptor, b-2 variant	Toxin responses
A/J	*Apoa2*^{c}	Apolipoprotein A2 c allele – early onset	Senile amyloid
A/J A/WySnJ	*Cdh23*^{ahl}	cadherin 23 (otocadherin) age related hearing loss 1	Deafness
A/J	*Dysf*^{prmd}	Dysferlin , progressive muscular dystrophy	Muscular dystrophy
A/J, A/HeJ A/WySnJ	*Hc*^{0}	hemolytic complement (C5) deficient	Immunity
A/J, A/HeJ A/WySnJ	*Il3ra*^{m1}	interleukin 3 receptor, alpha chain	Immunity
A/J	*Rmcf*^{s}	Sensitive to MCF virus	Immunity
A/WySnJ	*Tnfrsf13c* *Bcmd1-A*	tumor necrosis factor receptor superfamily, member 13c	Immunity - B-cell maturation defect 1

Strains	*Gene*^{allele}	Gene allele information	System or phenotype
AKR/J	***c/c***	***a/a Tyr^{c}/Tyr^{c}***	**albino**
AKR/J	***H2*** ^{k}	**MHC haplotype**	Immunity
AKR/J	*Ahr*^{d}	aryl-hydrocarbon receptor d variant (non responsive allele)	Toxin Response
AKR/J	*Hc*^{0}	hemolytic complement (C5) deficient	Immunity
AKR/J	*Hid*	Hair interior defect (Microscopic)	hair
AKR/J	*Il3ra*^{m1}	interleukin 3 receptor, alpha chain	Immunity
AKR/J	*Rmcf*^{s}	Sensitive to MCF virus	Immunity
AKR/J	*Soat1*^{ald}	sterol O-acyltransferase 1 Adrenocortical lipid depletion	Adrenal
AKR/J	*Apoa2*^{a}	Apolipoprotein A2 a allele	Lower? Senile amyloid
BALB/cByJ BALB/c	***c/c***	***A/A Tyrp1b/Tyrp1b Tyrc/Tyrc***	**albino**
	H2 ^{d}	MHC haplotype	immune
	Hld	hippocampal lamination defect	Brain
	Apoa2^{b}	Apolipoprotein A2 – b variant (Hdlq5)	Hier HDL
BALB/cByJ	*Acads*$^{del-J}$	acyl-Coenzyme A dehydrogenase deficiency	organic aciduria
BALB/cByJ	*Ahr*$^{b-2}$	aryl-hydrocarbon receptor, b-2 variant	Toxin responses
BALB/cByJ	*Cdh23*^{ahl}	cadherin 23 (otocadherin) age related hearing loss 1	Hearing
BALB/cByJ	*Mdmg1*	mandibular morphogenesis 1 longer dorsal edge	Skeletal
C3H/HeJ	***A/A***	***A/A***	**Agouti**
C3H/HeJ	*H2b-2*	MHC haplotype	
C3H/HeJ	*Ahr*$^{b-2}$	aryl-hydrocarbon receptor, b-2 variant	Toxin responses
C3H/HeJ	*Pde6b*^{rd1}	Retinal degeneration 1 phosphodiesterase 6B, cGMP, rod receptor, beta polypeptide	Vision
C3H/HeJ	*Tlr4*$^{Lps-d}$	toll-like receptor 4 - defective lipopolysaccharide response - Endotoxin resistant	Immunity
C3H/HeJ	*Dyscalc (1-4)*	dystrophic cardiac calcinosis QTL's Chr 7,4,12,14 (*Dyscalc1 = Abcc6*)	Cardiac etc Dystrophic calcification
C3H/HeJ	*Apoa2*^{b}	Apolipoprotein A2 – b variant (Hdlq5)	Hier HDL
C57BL/6J	***a/a***	***a/a***	**Black non agouti**

Strains	*Gene*^{allele}	Gene allele information	System or phenotype
C57BL/6N	*H2 b*	MHC haplotype	
C57BL/6	*Ahr*$^{b-1}$	aryl-hydrocarbon receptor, b-1 variant	Toxin responses
C57BL/6J	*Apoa2*^{a}	Apolipoprotein A2 a allele	Less? Senile amyloid
C57BL/6J	*Cdh23*^{ahl}	cadherin 23 (otocadherin) age related hearing loss 1	Hearing
C57BL/6J	*Fbrwt1*$^{C57BL/6J}$	Hi forebrain weight (QTL) vs DBA/2J	brain
C57BL/6J	*Nnt*$^{C57BL/6J}$	nicotinamide nucleotide transhydrogenase deficient (deletion) (+/+ in N strains)	Gluc Metabolism
C57BL/6N	*Nnt*$^{+/+}$	NNT Wild type (+/+ In all? C57BL/6N strains)	Gluc Metabolism
C57BL/6N	*Crb1*^{rd8}	crumbs homolog 1 (Drosophila); retinal degeneration 8 – mild rd	vision
DBA/1J DBA/2J	*d/d b/b a/a*	*Myo5a*^{d}*/ Myo5a*^{d} *Tyrp1*^{b}*/Tyrp1*^{b} *a/a* *Myo5a*^{d}*/ Myo5a*^{d} *Tyrp1*^{isa}*/Tyrp1*^{isa} *a/a*	Dilute brown, non agouti
	Cdh23^{ahl}	cadherin 23 (otocadherin) age related hearing loss 1	Hearing
	Rmcf^{r}	resistance to MCF virus	Immunity
DBA/1J	*H2 q*	MHC haplotype	
DBA/2J	*H2 d*	MHC haplotype	
DBA/2J	*Ahl8*$^{DBA?2J}$	age related hearing loss 8	Hearing
DBA/2J	*Ahr*^{d}	aryl-hydrocarbon receptor d variant (NON responsive allele)	Toxin response
DBA/2J	*Asp*^{2}	Audiogenic seizure prone 2	Seizures
DBA/2J	*Gpnmb*^{ipd}	iris pigment dispersion	Vision
DBA/2J	*Hc*^{0}	C5, hemolytic complement deficient	immunity
DBA/2J	*Klrd1*	killer cell lectin-like receptor, subfamily D, member 1 mutation → cd94 deficient	Immunity
DBA/2J	*Tyrp1*^{isa}	Trp1, iris stromal atrophy	Vision

FVB/NJ	***c/c***	**A/A Tyrc/Tyrc**	**Albino**
FVB/NJ	*H2q*	MHC haplotype	
FVB/NJ	*Ahrb-2*	aryl-hydrocarbon receptor B2 variant	Toxin responses

Strains	*Gene*^{allele}	Gene allele information	System or phenotype
FVB/NJ	*Disc1*^{del}	disrupted in schizophrenia 1, delta 6 allele (deletion)	Behavior
FVB/NJ	*Fv*^{1}	Friend virus susceptibility 1	
FVB/NJ	*Hc*^{0}	C5, hemolytic complement deficient	immunity
FVB/NJ	*Pde6b*^{rd1}	Retinal degeneration 1 phosphodiesterase 6B, cGMP, rod receptor, beta polypeptide	Vision
FVB/NJ	*Apoa2*^{b}	Apolipoprotein A2 – b variant (Hdlq5)	Hier HDL
NOD/shiLtJ	***c/c***	***A/A Tyrc/Tyrc***	**Albino**
NOD/shiLtJ	*H2*^{g7}	MHC haplotype Kd, Aad, Abg7, Enull, Db	Immunity
NOD/shiLtJ	*Cdh23*^{ahl1}	Otocadherin age related hearing loss 1	Immunity
NOD/shiLtJ	*Hc*^{0}	C5, hemolytic complement deficient	immunity
NOD/shiLtJ	*Il2*^{m1}	Interleukin2 hypoactive polymorphism	Vision
SJL/J	***c/c***	***Tyrc/Tyrc A/A***	**Albino**
SJL/J	*H2*^{s}	MHC haplotype	
SJL/J	*Ahr*^{d}	aryl-hydrocarbon receptor d variant (NON responsive allele)	Toxin response
SJL/J	*Apoa2*^{c}	Apolipoprotein A2 c allele – early onset	Senile amyloid
SJL/J	*Ceacam1*$^{Hv2\text{-}r}$	carcinoembryonic antigen-related cell adhesion molecule 1; hepatitis virus (MHV-4) resistance	immunity
SJL/J	*Disc1*^{del}	disrupted in schizophrenia 1, delta 6 allele (deletion)	Behavior
SJL/J	*Dysf*^{im}	Dysferlin Inflammatory myopathy – muscular dystrophy	muscle
SJL/J	*Il2*^{m1}	Interleukin 2 hypOactive polymorphism	immunity
SJL/J	*Pde6b*^{rd1}	Retinal degeneration 1 phosphodiesterase 6B, cGMP, rod receptor, beta polypeptide	Vision
SJL/J	*Rmcf*^{s}	Sensitive to MCF virus	Immunity

Table 4. 129 substrains (16) and nomenclature summary from [155]

More common/available strains are bolded

Abbreviated designation	Full designation	Former designation	Coat Color	Coat Color Genotype
1. 129P1-*Lama2^{dy}*	129P1/Re-*Lama2^{dy}*	129/Re-*Lama2^{dy}*	pink-eyed chinchilla	*A^{w}/A^{w} p Tyr$^{c\text{-}ch}$ /p Tyr$^{c\text{-}ch}$ Lama2^{dy}/Lama2^{dy}*
2. 129P1	129P1/ReJ	129/ReJ	pink-eyed chinchilla	*A^{w}/A^{w} p Tyr$^{c\text{-}ch}$/p Tyr$^{c\text{-}ch}$*
3. 129P2	**129P2/OlaHsd**	**129/OlaHsd**	**pink-eyed chinchilla**	***A^{w}/A^{w} p Tyr$^{c\text{-}ch}$/p Tyr$^{c\text{-}ch}$***
4. 129P3	129P3/J	129/J	pink-eyed light chinchilla or albino	*A^{w}/A^{w} p Tyr$^{c\text{-}ch}$/p Tyr^{c} A^{w}/A^{w} p Tyr^{c}/p Tyr^{c}*
5. 129X1	129X1/SvJ	129/SvJ	pink-eyed light chinchilla or albino	*A^{w}/A^{w} p Tyr$^{c\text{-}ch}$/p Tyr^{c} A^{w}/A^{w} p Tyr^{c}/p Tyr^{c}*
6. 129S1	129S1/Sv-p^{+}Tyr^{+} Kitl$^{Sl\text{-}J}$/+	129/Sv-p^{+}*Tyr^{+}Kitl$^{Sl\text{-}J}$/+*	white-bellied agouti	*A^{w}/A^{w}*
7. 129S1	**129S1/SvImJ**	**129/Sv-p^{+}Tyr^{+}Kitl^{+}/J**	**white-bellied agouti**	***A^{w}/A^{w}***
8. 129S2	129S2/SvPas	129/SvPas	white-bellied agouti	*A^{w}/A^{w}*
9. 129S4	129S4/SvJae	129/SvJae	white-bellied agouti	*A^{w}/A^{w}*
10. 129S5	**129S5/SvEvBrd**	**129/SvEvBrd**	**white-bellied agouti**	***A^{w}/A^{w}***
11. 129S6	**129S6/SvEvTac**	**129/SvEvTac**	**white-bellied agouti**	***A^{w}/A^{w}***
12. 129S7	129S7/SvEvBrd-*Hprt$^{b\text{-}m2}$*	129/SvEvBrd-*Hprt$^{b\text{-}m2}$*	white-bellied agouti	*A^{w}/A^{w}*
13. 129S8	129S8/SvEv-*Gpi1^{c} Hprt$^{b\text{-}m2}$@J*	129/SvEv-*Gpi1^{c} Hprt$^{b\text{-}m2}$@J*	white-bellied agouti	*A^{w}/A^{w}*
14. 129T1	129T1/Sv-p^{+} *Tyr$^{c\text{-}ch}$ Ter/+@Na*	129/Sv-p^{+} *Tyr$^{c\text{-}ch}$ Ter/+@Na*	white-bellied agouti chinchilla	*A^{w}/A^{w} Tyr$^{c\text{-}ch}$/Tyr$^{c\text{-}ch}$*
15. 129T2	129T2/SvEms	129/SvEms-Ter^{+}?	white-bellied agouti chinchilla	*A^{w}/A^{w} Tyr$^{c\text{-}ch}$/Tyr$^{c\text{-}ch}$*
16. 129T2	129T2/SvEmsJ	129/SvEms-Ter^{+}?/J	white-bellied agouti chinchilla	*A^{w}/A^{w} Tyr$^{c\text{-}ch}$/Tyr$^{c\text{-}}$*

Table 6. Parental ESC lines and mouse strains of origin

(ftp://ftp.informatics.jax.org/pub/datasets/es_cell_lines.html accessed June 29, 2009)

ES Cell Line	*Strain/stock of origin*	*ES Cell Line*	*Strain/stock of origin*
A3-1	**129X1/SvJ**	IDG3.2	(C57BL/6J x 129S6/SvEvTac)F1
AB1	**129S7/SvEvBrd-Hprt1<+>**	**iTL1**	**129S6/SvEvTac**
AB2.1 AB2.2	**129S7/SvEvBrd-Hprt1<b-m2>**	**J1**	**129S4/SvJae**
AC1	**129/Sv**	**JH1**	**129S7/SvEvBrd**
AK18.1	**129S4/SvJaeSor**	**JM-1**	**129X1/SvJ**
AK7 AK7.1	**129S4/SvJaeSor**	JM8 JM8F6 JM8N4	C57BL/6N
alphaR2	**129S4/SvJae**	JM8A1 JM8A1.N3 JM8A3	C57BL/6N-A
ART4.12	(C57BL/6 x 129S6/SvEvTac)F1	KAB6	B6(Cg)-Tyr<c-2J>/J
AT1	**129S2/SvPasCrl**	**KG1/KG-1**	**129S6/SvEvTac**
ATOM1	(C57BL/6 x 129)F1	KMB6-6	C57BL/6
AV3	**129X1/SvJ**	KTPU8 KTPU10	(C57BL/6 x CBA)F1
B6-Jj	C57BL/6	**Lex-1 Lex-2**	**129S5/SvEvBrd**
BALB/c-I	BALB/cJ	Lex3.13	C57BL/6N
BK4	**129P2/OlaHsd**	**LSW1**	**129X1/SvJ**
BL/6-III	C57BL/6 (N or J?)	**LW1**	**129S4/SvJae**
Bruce 4	C57BL/6 (N or J?)	**MC1 MC3 MC50**	**129S6/SvEvTac**
C1 C13	**129X1/SvJ**	mEMS1204	(B6.129P2-Hprt1<b-m3>/J x 129S-Gt(ROSA)26Sor<tm1Sor>/J)F1
C1368	**129T2/SvEms**	**mEMS128 mEMS21**	**129S1/SvImJ**
C2 (Nagy)	C57BL/6N	**mEMS32**	**129P3/JEmsJ**
C4R8	**129P2/OlaHsd**	**MESC 20**	**129P2/OlaHsd**
C57BL/6Hprt	B6.129P2-Hprt1<b-m3>	**MM13**	**129S/SvEv**
CB1-4	C57BL/6J x (Rb(11.16)2H x Rb(16.17)32Lub)F1	MPI 65-3	B6.129P2-Hprt1<b-m3>
CBA	CBA/CaOlaHsd	**MPI-12D MPI-12G MPI-17A MPI-17E**	**129S6/SvEvTac**
CC1.2	**129S7/SvEvBrd**	MPI-48.1 MPI-71.6	B6.129P2-Hprt1<b-m3>
CCB	**129S/SvEv-Gpi1<c>**	**MPI-II**	**129/Sv**
CCE/EK.CCE	**129S/SvEv-Gpi1<c>**	MPI53.1 MPI76.11	B6.129P2-Hprt1<b-m3>
CGR8	**129P2/OlaHsd**	MRL-+/+ 3	MRL/MpJ
CJ7	**129S1/Sv-Oca2<+> Tyr<+> Kitl<+>**	MS12	C57BL/6 (N or J?)
CK35	**129S2/SvPas**	N1	C57BL/6 (N or J?)
CMTI-1	**129S/SvEv**	**P1**	**129S2/SvPas**
CMTI-2	C57BL/6J	**Pat5**	**129X1/SvJ**
CP-1	**129S6/SvEvTac**	**PC3**	**129S4/SvJae**
CSL3	**129S6/SvEvTac**	**PJ1-5 PJ5**	**129X1/SvJ**
CT129	**129/Sv**		**129X1/SvJ**
D1	(129S6/SvEvTac x C57BL/6J)F1	R1	(129X1/SvJ x 129S1/Sv)F1-Kitl<+>
D3 D3a1 D3a2 D3H	**129S2/SvPas**	**REK1 REK2 REK3 REK4**	**129X1/SvJ**
D4	**129/Sv**	**RF8**	**129S4/SvJae**
DBA-252	DBA/1LacJ	**RW1 RW-4**	**129X1/SvJ**
E	**129S4/SvJae**	**SCC10**	**129X1/SvJ**
E14 E14.1 E14K, TG etc	**129P2/OlaHsd**	**SM1**	**129S6/SvEvTac**
EC7.1	C57BL/6 x 129X1/SvJ	**TBV2**	**129S2/SvPas**
EF1	**129S/SvEv and C57BL/6**	**TC TC-1**	**129S6/SvEvTac**
ENS	**129/Sv**	**TG3 TG4 TG6**	**129S6/SvEvTac**
ESF 116 ESF 122	CBA	**TL1/TL-1**	**129S6/SvEvTac**
ESF48/1 ESF55 ESF58/2	**129P2/Ola**	TT2 TT2F	(C57BL/6 x CBA)F1
ESVJ ESVJ-1182 ESVJ-1183	**129X1/SvJ**	v17.2	(BALB/cJ x 129S4/SvJae)F1
F1H4	(129 x C57BL/6)F1	V26.2,ES-MK	C57BL/6 (N or J?)
G4	(129S6/SvEvTac x C57BL/6NCr)F1	v6.4 v6.5	(C57BL/6J x 129S4/SvJae)F1
GK129	**129P2/OlaHsd**	VGB6	C57BL/6NTac
GS1	**129/Sv**	**W12 W2 W3 W4 W5**	**129S6/SvEvTac**
GSI-1	**129X1/SvJ**	W9.5/W95	129S1/Sv-Oca2<+> Tyr<+> Kitl<+>
GSIB-1	C57BL/6 (N or J?)	WB6a WB6b	C57BL/6 (N or J?)
H1	**129S2/SvPas**	WB6d	C57BL/6NTac
HM-1	**129P2/OlaHsd-Hprt1<b-m3>**	WW6	STOCK 129/Sv and C57BL/6J and SJL/J
IB10/E14IB10	**129P2/OlaHsd**	**ZX3**	**129/Sv**

Table 6. Sources and origins of some Swiss derived and non-Swiss mice

Name [common names, abbreviations][1]	Source or Vendor	Rd[2]	Inbred/ Non-inbred	History
Crl:CD1(ICR) [CD-1®, ICR, Swiss]	Charles River Laboratories	0/60	Non-inbred	Swiss mice, from Lynch at Rockefeller, to various sources, to Landis, to Hauschka, ICR (Ha/ICR) in 1948; to Mirand at RPMI (HaM/ICR) to CRL in 1959; Cesarean derived (CD); BR = barrier reared ~12 closed barrier production colonies in 7 countries. Charles River Website, 2004, 2006; [652, 673, 674]
Crl:CFW(SW) [CFW®, Swiss Webster]	Charles River Laboratories	59/60	Non-inbred	Swiss mice, from Lynch, inbred by Webster at Rockefeller; then outbred from a single pair by Carworth Farm (CF) as CFW stock; CD in 1974 by CRL "from a representative cross section of the Carworth CFW colony."[648]
CRL:CF1 [CF-1®]	Charles River Laboratories	1/60	Non-inbred	**Non-Swiss mice**, probably of wild albino origin, from a Missouri laboratory; inbred by Carworth Farms (CF) > 20 generations, outbred from a single pair as CF-1 stock stock; cesarean derived (CD)3 in 1974 by CRL "from a representative cross section of the Carworth CF-1 colony." [ ]
Hsd:ICR(CD-1®) [ICR]	Harlan	27/60	Non-inbred	Swiss mice descended from (ICR-derived) Crl:CD1(ICR) stock obtained from CRL before 1980. [675]
Hsd:ND4 [ND4, Swiss Webster]	Harlan		Non-inbred	Swiss mice descended from Swiss Webster stock rederived by the University of Notre Dame; obtained by Harlan before 1980. [675]
Hsd:NIHS [NIH Swiss]	Harlan	*rd1/rd1*	Non-inbred	Swiss mice derived from NIH Swiss N:NIH(S) nucleus colony (see below) [675, 676]
Hsd:NSA™(CF-1®) [NSA™, Non-Swiss Albino]	Harlan	0/60	Non-inbred	**Non-Swiss mice** descended from CRL:CF1 stock obtained before 1980. [675]
FVB/N	NIH/NCI (→ Crl, Hsd, J, Tac etc.)	*rd1/rd1*	Inbred	Inbred Swiss origin mice derived from NIH Swiss N:NIH(S) selectively bred for HSFS/N ~1966; then selected for susceptibility to Friend Leukemia virus B strain; inbred from 1975 at NIH; transferred to various suppliers. [7, 653] *Hc*^{0} → C5 deficient-

[1] For non-inbred stocks, abbreviations are those listed by the primary breeder or source. Similarities among these designations are substantial. CD-1®, CF-1®, CFW® are registered trademarks of Charles River Laboratories, Inc. NSA^{tm} is a registered trademark of Harlan.

[2] Ratios in this column refer to numbers of mice evaluated that had retinal degeneration compatible with homozygosity for *Pde6b*^{rd1} per Serfilippi et al. 2004. *rd1/rd1* indicates that the strain is known to be homozygous for *Pde6b*^{rd1}, or that the stock (Hsd:NIHS, NTac:NIHBS) was found to be homozygous at *Pde6b*^{rd1} by Clapcote et al. (2005).

Name [common names, abbreviations][4]	Source or Vendor	Rd5	Inbred/ Non-inbred	History
SJL/J	The Jackson Laboratory	*rd1/rd1*	Inbred	Inbred Swiss origin mice descended from 3 sources of Swiss Webster mice brought to TJL between 1938 and 1943; pen bred until 1955; then inbred by J Lambert; TJL. [69]
SWR/J	The Jackson Laboratory	*rd1/rd1*	Inbred	Swiss mice Inbred by Lynch at Rockefeller; to Parker, University of Toronto 1926; to TJL 1947 at F28+. [69] Hc^0 → C5 deficient-
Cr:NGP(S) [NIH general purpose]	NIH/NCI		Non-inbred	Swiss mice from Lynch or Webster at Rockefeller; to NIH, outbred as N:GP(S); closed colony since 1935 [7, 653, 677]
Cr:NIH(S) [NIH Swiss]	NIH/NCI		Non-inbred	Swiss mice derived from NIH N:GP(S) as N:NIH(S) in 1936; [7, 653, 677]
Cr:NIH-BL(S) [NIH Black Swiss]	NIH/NCI		Non-inbred	Developed at NIH by Dr. Carl Hansen. N:NIH Swiss outbred mice were crossed to C57BL/6N mice to generate hybrid black mouse heterozygous for (non)agouti loci; 'agouti gene was eliminated' via test matings and backcrosses (N10) to N:NIH(S). [677]
Cr:SW [Swiss Webster]	NIH/NCI		Non-inbred	From Crl:CFW, unspec date [677]
TacBom:NMRI [NMRI]	Taconic EU		Non-inbred	Swiss mice from Lynch or Webster, Rockefeller to Poiley NIH 1937; inbred by Poiley as NIH/Pl; to US naval Medical Research Institute (NMRI) in 1951.[7, 653] Random bred at Zentralinstitut für Versuchstierzucht, Hannover; to M&B A/S, Bomholt (lab code Bom) in 1961, 1985. [678, 679]
IcrTac:ICR [ICR]	Taconic	48/60	Non-inbred	Swiss mice from Lynch, Rockefeller; transferred to Hauschka, ICR (Ha/ICR) in 1948; reconstituted from RPMI Ha/ICR stock ~1959; Fox Chase (ICR) to Taconic 1993. [652, 678, 679]
NTac:NIHBS [Black Swiss]	Taconic	*rd1/rd1*	Non-inbred	From NIH Black Swiss stock (Cf Cr:NIH-BL(S)) → N:NIHS-B6? to Taconic in 1991, CD in 1992. [676, 678, 679]
Tac:(SW) [Swiss Webster]	Taconic	47/60	Non-inbred	Descended from Swiss Webster original stock from the Rockefeller Institute through Rockland Farms, Inc. to Taconic in 1940. [678, 679]

[4] For non-inbred stocks, abbreviations are those listed by the primary breeder or source. Similarities among these designations are substantial. CD-1®, CF-1®, CFW® are registered trademarks of Charles River Laboratories, Inc. NSA[tm] is a registered trademark of Harlan.

[5] Ratios in this column refer to numbers of mice evaluated that had retinal degeneration compatible with homozygosity for *Pde6b*^{rd1} per Serfilippi et al. 2004. *rd1/rd1* indicates that the strain is known to be homozygous for *Pde6b*^{rd1}, or that the stock (Hsd:NIHS, NTac:NIHBS) was found to be homozygous at *Pde6b*^{rd1} by Clapcote et al. (2005).

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