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INHERITED NEUROMUSCULAR DISEASES IN THE MOUSE

A REVIEW OF THE LITERATURE

LUIZ FERNANDO BLEGGI TORRES *

SUMMARY — There are several neuromuscular disorders affecting the human being. Most of these are poorly understood and lack an effective treatment. Due to the limitation of experimental manipulation in «anima nobili», inherited neuromuscular diseases in laboratory animals constitute a valuable source of scientific information. Amongst several animal species affected by neuromuscular disorders the house mouse is of particular interest because of its small size, short pregnancy and low costs of maintanence. In the present review 20 murine mutants with diseases affecting peripheral nerves, skeletal muscles and motor end-plates are tabulated. Genetic, clinical and pathological aspects are discussed aiming to provide information about these mutants which might be of great interest as animal models for human neuromuscular diseases.

Doenças neuromusculares hereditárias em camundongos: revisão da literatura

RESUMO — Existem inúmeras doenças neuromusculares que acometem seres humanos. A grande maioria delas é insuficientemente conhecida quanto a mecanismos fisiopatológicos e tratamentos adequados. A limitação na manipulação experimental em «anima nobili» faz-nos procurar meios alternativos para o estudo dessas doenças, tais como animais experimentais com distúrbios neuromusculares geneticamente transmitidos. Estes mutantes constituem fonte inesgotável e valiosa de informações quanto a mecanismos fisiopatogênicos e processos patológicos básicos em doenças neuromusculares. Entre as diversas espécies animais afetadas por distúrbios neuromusculares o camundongo é de particular interesse devido ao seu baixo custo de manutenção, rápida reprodutividade e pequeno tamanho, o que permite amplos estudos morfológicos a custos acessíveis. Nesta revisão analisamos 20 camundongos mutantes com distúrbios afetando nervo periférico, músculo esquelético ou junção neuromuscular. Aspectos genéticos, clínicos e patológicos são discutidos na intenção de oferecer informação atualizada sobre essas mutações animais, muitas das quais de grande interesse como modelos experimentais de doenças neuromusculares humanas.

In recent years the presence of a close relationship and interdependance between skeletal muscle and peripheral nerves became obvious. Several studies exemplified the essential role of the nervous system in the maturation, function and full expression of skeletal muscle fibres [10,21,24,28,43,50,66,100]. There are many inherited human diseases affecting peripheral nerves, skeletal muscles or both. Most of these conditions differ from each other in a number of ways and are classified according to the distribution and characteristics of the wasting process, the pattern of inheritance, age of onset, rate of progression of weakness. However, in most of the situations, there is little understanding of the pathogenesis of the diseases and they lack an effective way of treating or controlling their symptons and evolution. The scarcity of biopsy material and the limitation of experimental manipulation in man make it difficult to study the aetiology and molecular mechanisms of many

* MD,PhD, Neuropathologist, Hospital de Clinicas and Hospital Nossa Senhora das Graças, Curitiba.
Hospital de Clínicas — Rua General Carneiro 181 — 80069 Curitiba PR — Brasil

inherited neuromuscular diseases. It is therefore necessary to consider the possibility of obtaining relevant information from the study of animal mutants with neuromuscular diseases [60]. If features are discovered which are siminar to those expressed in human disease, the mutant might become a useful model for therapeutic trials and experimental investigation which are not possible in man [52]. Apart from man, several animal species are known to be affected by inherited disorders of muscle, motor end-plate and nerve. These include birds (chicken, turkey and duck), small rodents (mouse and hamster) and other larger mammals (goat, pig, horse, cattle, sheep, dog, cat and mink) [48,51,52,60,62,102]. One of the most extensively studied laboratory animals is the mouse due to its small size, short pregnancy and relatively low costs of maintanence. These advantages allow the investigator to employ a wide range of techniques aiming to gain an accurate idea of how the disease begins, the primary sites of pathology and its evolution from the earliest clinical and pathological manifestation through to its full expression. From a survey of recent publications concerning murine mutations (Mouse News Letter, 1986) 20 out of about 1000 genetically determined disorders affect peripheral nerves, neuromuscular junction and/or skeletal muscles (Table 1). The great majority of the mutations listed on table 1 are spontaneous and transmitted as an autosomal recessive trait. In the present tabulation the criteria used for classification were the structures predominantly affected by the mutant gene. The clinical syndromes and pathological abnormalities are distinct in most of these three main groups as will be discussed below. However in a few mutants more than one set of structures might be involved.

1. Mutant mice with disorders of peripheral nerves

a) Those with pathological abnormalities in nerve cells or axonal profiles:

Dystonia musculorum (dt) — This spontaneous mutation is transmitted by an autosomal recessive gene and expressed as a severe and progressive sensory neuropathy. Affected animals, by the end of the first postnatal week, have abnormal posture and muscle spasms. Although no paralysis or tremor are noted there is

1.	*Disorders of the peripheral nerves*
	Abnormalities of neurons or axons:
	dystonia musculorum (dt)
	wobbler (wr)
	Sprawling (Swl)
	cribriform degeneration (cri)
	tortured (tor)
	Abnormalities of myelin sheath:
	Trembler (Tr)
	twitcher (twi)
	quaking (qk)
	Abnormalities not yet fully characterized:
	peroneal muscular atrophy (pma)
	mocha-2J (mh2J)
	muscle deficient (mdf)
	shiverer (shi)
2.	*Disorder of motor end-plate or neuromuscular transmission*
	motor end-plate (med)
	paralyse (par)
3.	*Mutants said to be affected by disorders of muscle*
	dystrophia muscularis (dy)
	muscular dysgenesis (mdg)
	myodystrophy (myd)
	myotonia (mto)
	A2G-adr (adr)
	X-linked muscular dystrophy (mdx)

Table 1 — Mutant mice with disorders of nerve and muscle (gene symbol in brackets).

progressive incoordination of movements and the growth is severely retarded [35,42]. The morphological abnormalities consist of widespread axonal degeneration of the main sensory pathways with degeneration of peripheral nerves and atrophy of the muscle spindles and skeletal muscle fibres [35,53,63]. It has been suggested that a defect in axoplasmic flow with the eventual formation of axonal swellings could be the underlying mechanism of this disorder [53]. However, segmental demyelination probably due to a primary Schwann cell dysfunction occurs prior to any identifiable swelling of the axons [84,85].

Wobbler (wr) — This mutant mouse, initially identified by its abnormal wobbling gait, presents with proximal muscle weakness affecting mainly neck and forelimb musculature. The disease progresses from one to six months of age and may be fatal. The pathological process consists of widespread vacuolation of motor nerve cells in brainstem and most levels of spinal cord, the result of dilatation of rough endoplasmic reticulum [3,4,12,23,36,38,83,87]. Morphological and physiological evidence of denervation of skeletal muscle has been observed. The former is represented by atrophy of fibres and conspicuous branching of preterminal axons [38] and the latter by spontaneous fibrillations, absence of miniature end-plate potentials and increased extra-junctional sensitivity to acetylcholine [57]. Therefore this mutant could be considered as a potential model for human spinal muscular atrophy [30].

Sprawling (Swl) — The sprawling mouse was identified in subsequent generations of mice previously used in irradiation experiments. Affected animals are usually identifiable by 7 to 10 days of age by abnormal resting posture more marked in the hindlimbs. Morphological studies showed that the sensory neurons are the site of primary pathology. Deficiency of myelinated axons in the ascending tracts, spinal roots and peripheral nerves and a reduction in number of muscle spindles were also observed [29]. It seems that a genetically-induced abnormality of ganglia could be responsible for the failure of induction of sensory receptors thus accounting for the marked reduction of peripheral sensory receptors including muscle spindles [33,34,95,96].

In the *cribriform degeneration* [49] and *tortured* [55] mutant mice the morphological changes have not been so extensively studied. They both present clinically with incoordination, ataxia and behaviour abnormalities. Some preliminary observations showed intracellular vacuolar changes in spinal cord and brainstem of the cribriform while in the tortured mutant progressive degeneration of cerebellum, spinal cord and sensory ganglia has been described. In both mutants as might be expected peripheral nerves are also affected [103].

b) Mice with disorders of myelin of peripheral nerves:

Trembler mouse (Tr) — This mutation is transmitted by a autosomal dominant gene and is expressed by spastic paralysis, convulsions and tremor [45]. Preliminary electroencephalographic studies suggested a possible cerebellar malfunction but no morphological confirmation was obtained [19]. It is now accepted that an hereditary demyelinating neuropathy constitutes the major abnormality in the trembler mouse [5,6, 72,73,89]. The electrophysiological consequences of this hypomyelinated neuropathy are the inability to conduct rapid trains of impulse with marked reduction of motor conduction velocities [74,75]. The pathogenesis of this disorder has been initially attributed to a primary defect in the synthesis of myelin [73,74] but elegant nerve grafting experiments demonstrated conclusively that the neuropathy is due to a primary Schwann cell disorder [1,2]. The pathological abnormalities in skeletal muscle and motor end-plates consist of atrophy of fibres, abundant axonal sprouting and electro-physiological evidences of denervation affecting predominantly slow-twitch muscles. It has been suggested that the more severe involvement of slow fibres could be due to its innervation by motor units subjected to prolonged activity and therefore predominantly affected by conduction block [39,46].

Twitcher mouse (twi) — Special interest has been raised since this mutant was described as a morpho-biochemical model for Krabbe's leucodystrophy. Affected animals show arrested development, progressive weakness and tremor due to widespread loss of myelin with the presence of multinucleated cells in central and peripheral nervous system. These abnormalities are due to severe deficiency of galactosylceramidase and lactosylceramidase I, thus similar to human sphingolipidosis [41,65]. In the peripheral nerves enzymatically-deprived Schwann cells fail to complete synthesis of myelin [97,98,99].

The *quaking mouse* is another mutant of value for the study of myelin loss in central and peripheral nerves [94,101,108,113]. Several etiological factors have been postulated such as deficiency of mielyn-specific proteins [26], a plasmalemma molecular defect in oligodendrocytes [109] and a Schwann cell dysfunction [1].

c) Peripheral nerve disorders not yet characterized:

The animals described in this group show variable degrees of abnormalities in the peripheral nervous system as part of more complex pleiotropic genetic defects. They lack, however, adequate morphological and developmental studies and will be discussed only briefly. The *peroneal muscular atrophy* shows agenesis of common peroneal nerve which induces secondary atrophy of skeletal muscles of the leg [44]. In other mutations such as the *mocha-2J, muscle deficient* and *shiverer,* peripheral neuropathy and shortening of internodal lengths have been reported [25,68,103].

2. Functional and morphological disorders of motor end-plate:

Both mutants belonging to this group have devastating clinical signs of progressive muscle weakness, paralysis and premature death. In the *motor end-plate* mutant mouse there is striking atrophy of muscle fibres and complex terminal axonal sprouting at motor end-plates [31,37]. It was suggested that these changes were induced by a progressive loss of functional innervation [32,57] but other authors considered that the pathological process in the med mouse is a myopathy [114] or peripheral neuropathy [92,93]. The *paralyse* mutant shows progressive atrophy of motor nerve terminals with a reduction of neuromuscular transmission and eventual denervation of end-plates. The cause of such morphophysiological abnormalities remains uncertain [40].

3. Mutants said to show primary muscle pathology:

Dystrophia muscularis (dy) — The dystrophic mouse presents with progressive weakness of axial and limb muscles and a reduced life-span. It was initially thought to be affected by a primary myopathic disorder [7,9,71,82,88,112]. A few years later McComas et al.[78-81] suggested that muscle degeneration could be the result of a primary disorder of the motor neurons. Furthermore Gallup and Dubowitz [47] demonstrated in tissue culture that motor nerve cells of the dystrophic mouse were unable to support functional regeneration of both normal and dystrophic muscle fibres. These observations suggesting the influence of a neural factor upon muscle degeneration led to more extensive studies of the nervous system of this murine mutant with the eventual characterization of its abnormalities of myelin sheath in roots, cranial and peripheral nerves [13,15,16,17,104]. These abnormalities consist of large clusters of naked axons packed closely together and not invested by Schwann cell cytoplasm, myelin or even basal lamina. Such neural abnormalities are attributed to a genetically-determined impairment of Schwann cell differentiation, proliferation and survival together with a possible disorder in the interaction between axons, Schwann cells and fibroblasts [1,20,100]. Many other abnormalities in the peripheral nerves such as deficiency in basal lamina [76], widening of nodes of Ranvier with retraction of Schwann cell cytoplasm from the paranodal areas [18] and shortening of internodal lengths [11] have been reported. The electrophysiological disturbances originated from this insulation defect of roots and nerves are a possible lateral transmission of action potentials between neighboring bared axons (cross-talk) with a reduction in motor conduction velocities [14,61,67]. It has been suggested that muscle fibres of the dystrophic mouse might be functionally denervated [70,77]. Further studies, however, demonstrated no extra-junctional sensitivity to acetylcholine, no tetrodotoxin-resistant action potentials and normal muscle action potential in response to nerve stimulation in the dystrophic strain. Such observations indicate normal functional innervation of skeletal muscle fibres [56,58,59]. Although some authors point out that the muscle abnormalities in the dy mouse do not seem to be due to neural abnormalities [67,115] at present it is not known whether the neural or muscular changes are the first to appear and whether they are causally related. Until this problem is resolved it would be unwise to use this mutant as a model for primary muscular disease.

The *muscular dysgenesis* mice die at birth because of widespread failure of differentiation of cardiac and skeletal muscles which also induces skeleton malformations [8,86,90,91]. The myopathic involvement in the *myodystrophy* mutant was only recognized a few years after its original identification [69]. Progressive episodes of muscle degeneration followed by regeneration constitute the principal pathology but abnormalities in the spinal roots similar to those observed in the dystrophic mouse

have been reported [55]. The *myotonic* and the *A2G-adr* mutant mice lack comprehensive investigations of the skeletal muscles and nervous system. The first was assessed only electrophysiologically and showed widespread myotonic discharges while the second was reported to have a possible biochemical defect of muscle fibres [110,111].

X-linked muscular dystrophy (mdx) — The mdx mutant mouse was first observed during a survey of genetic variations of pyruvate kinase in the mouse [22]. Further studies showed that the gene defect in the mdx mutant is in the X-chromosome in a region similar to human muscular dystrophy of the Duchenne type. Affected mice have high serum levels of this enzyme and although showing little disability they have widespread and severe muscle disease. Preliminary morphological studies were restricted only to the analysis of muscle pathology and showed that muscle necrosis was followed by regeneration with little impairment of function [22,27,64,105]. Recent studies by Torres and Duchen [106,107] demonstrated that significant ultrastructural abnormalities were present in the mdx as early as 1 day of age consisting of streaming of Z-line material followed by segmental necrosis and regeneration. Furthermore the disease was progressive, initially affecting proximal muscle groups but in 2-3 months most muscles were abnormal. At this stage affected muscles showed marked variation in fibre size and diameter with little increase in endomysial connective tissue or fat infiltration. There was no inflammation and the heart and eye muscles were normal. Quantitative and qualitative studies of peripheral nerves showed no abnormalities and the nerve terminals were unaffected but there was a reduction in the number and depth of post-synaptic folds at motor end-plates. These authors concluded that the mdx mouse has a primary muscle disease with a total absence of structural pathology in either central or peripheral nervous systems.

A summary of the main genetic and clinical characteristics of all the murine mutants which have been described above is presented in table 2 while in table 3 their main pathological changes are tabulated.

Mutant	Genetics	Onset	Clinical	Viability
dystonia musculorum	AR	7 d	ataxia	reduced (2)*
wobbler	AR	21 d	weakness	normal
Sprawling	AD	7 d	ataxia	normal
cribriform	AR	17 d	weakness	reduced (3)
tortured	AR	17 d	ataxia	normal
dystrophia muscularis	AR	10 d	weakness	reduced (6)
Trembler	AD	12 d	paralysis	reduced (3)
twitcher	AR	30 d	weakness	reduced (3)
quaking	AR	10 d	tremor	normal
peroneal atrophy	AR	birth	leg malformation	normal
Mocha-2J	AR	—	abnormal behaviour	—
muscle deficient	AR	—	atrophic muscle	—
shiverer	AR	12 d	tremor	reduced (3)
motor endplate	AR	10 d	weakness	reduced (1)
paralyse	AR	8 d	weakness	reduced (1)
muscular dysgenesis	AR	birth	absent movements	none
myodystrophy	AR	12 d	seizures	reduced (4)
myotonic	AR	14 d	myotonia	—
A2G-adr	AR	10 d	myotonia	reduced (9)
MDX	X-linked	—	none	normal

*Table 2 — Genetic and clinical features of murine mutations. * (survival time in months, normal mouse = 15-18 months); AR = autosomal recessive; AD = autosomal dominant.*

Mutant	CNS	Peripheral nerves	Motor endplate	Skeletal muscles
dystonia musculorum	—	sensory neuropathy	—	atrophy
wobbler	abnormal neurons	—	sprouting	atrophy
Sprawling	—	abnormal DRG	—	—
cribriform	abnormal neurons + glia	neuropathy	—	—
tortured	degeneration cerebellum	neuropathy	—	—
dystrophia muscularis	—	abnormal myelin	abnormal sprouting	myopathy
Trembler	—	neuropathy	sprouting	atrophy
Twitcher	abnormal myelin	abnormal myelin	—	—
quaking	abnormal myelin	abnormal myelin	—	—
peroneal atrophy	—	agenesis	—	atrophy
mocha-2J	—	neuropathy	—	—
muscle deficient	—	neuropathy	—	atrophy
shiverer	abnormal myelin	neuropathy	—	—
motor endplate	—	—	sprouting	atrophy
paralyse	—	—	atrophy	—
muscular dysgenesis	—	—	—	failure maturation
myodystrophy	—	—	—	membrane disorder
A2G-adr	—	—	—	biochemical disorder
MDX	—	—	postsyn changes	myopathy

Table 3 — Main pathological abnormalities in murine mutants.

Conclusions — It is relevant to note the wide variability of inherited diseases of skeletal muscle and nerves affecting the house mouse with clinical manifestations, evolution and pathological features in many ways similar to those of human disorders. However it seems unrealistic to look at animal models as exact counterparts of human neuromuscular diseases. A more wise approach would be to study those features of animal models which are shared with inherited human disorders aiming to find a fundamental abnormality at cellular level and to understand the common manifestations that arise from these genetic abnormalities.

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REFERENCES

1. Aguayo AJ, Bray GM, Perkins SC — Axon-Schwann cell relationships in neuropathies of mutant mice. **Ann New York Acad Sci** 317:512, 1979.
2. Aguayo AJ, Attiwell M, et al — Abnormal myelination in transplanted mouse Schwann cells. Nature (Lond) 265:73, 1977.
3. Andrews JM — The fine structure of the cervical spinal cord, ventral root and brachial nerves in the wobbler (wr) mouse. **J Neuropathol Exper Neurol** 34:12, 1975.
4. Andrews JM, Maxwell DS — Ultrastructural features of anterior horn cell degeneration in wobbler (wr) mouse. **Anat Records** 157:206, 1967.
5. Ayers MM, Anderson R McD — Onion bulb neuropathy in the trembler mouse: a model for hypertrophic interstitial neuropathy (Dejerine-Sottas) in man. **Acta Neuropathol** (Berlin) 25:54, 1973.
6. Ayers MM, Anderson R McD — Development of onion bulb neuropathy in the trembler mouse — comparison with normal nerve maturation. **Acta Neuropathol** (Berlin) 32: 43, 1975.
7. Banker BQ — A phase and electron microscopic study of dystrophic muscle: II. The pathological changes in the newborn Bar Harbor 129 dystrophic mouse. **J Neuropathol Exper Neurol** 27:183, 1968.
8. Banker BQ — Muscular dysgenesis in the mouse (mdg/mdg): I. Ultrastructural study of skeletal and cardiac muscle. **J Neuropathol Exper Neurol** 36:100, 1977.
9. Banker BQ, Denny-Brown D — A study of denervated muscle in normal and dystrophic mice. **J Neuropathol Exper Neurol** 18:517, 1959.
10. Bennett MR — Development of neuromuscular synapses. **Physiological Rev** 63:915, 1983.
11. Beuche W, Friede RL — A quantitative assessment of myelin sheaths in the peripheral nerves of Dystrophic, Quaking and Trember mutants. **Acta Neuropathol** (Berlin) 66:29, 1985.
12. Bird MT, Shuttleworth EC, Koestner A, Reinglass J — The wobbler mouse mutant: an animal model of hereditary motor system disease. **Acta Neuropathol** (Berlin) 19:39, 1971.
13. Biscoe TJ, Caddy K, Pallot DJ, Pehrson UMM — Investigation of cranial and other nerves in the mouse with muscular dystrophy. **J Neurol Neurosurg Psychiat** 38:391, 1975.
14. Biscoe TJ, Headley PM, Martin MR, Stirling CA — Electrophysiological observations on the spinal cord of normal and dystrophic mouse. **J Neurol Sci** 31:51, 1977.
15. Biscoe TJ, Caddy K, Pallot D, Pehrson M, Stirling CA — The neurological lesion in the dystrophic mouse. **Brain Res** 76:534, 1974.
16. Bradley WG, Jenkison M — Abnormalities of peripheral nerves in murine muscular dystrophy. **J Neurol Sci** 18:227, 1973.
17. Bradley WG, Jenkison M — Neural abnormalities in the dystrophic mouse. **J Neurol Sci** 25:249, 1975.
18. Bradley WG, Jaros E, Jenkison M — The nodes of Ranvier in the nerves of mice with muscular dystrophy. **J Neuropathol Exper Neurol** 36:797, 1977.
19. Braverman IM — Neurological actions caused by the mutant gene «trembler» in the house mouse. **J Neuropathol Exper Neurol** 12:64, 1953.
20. Bray G, Perkins S, Peterson AC, Aguayo AJ — Schwann cell multiplication deficit in nerve roots of newborn dystrophic mice. **J Neurol Sci** 32:203, 1977.
21. Buchthal F, Schmalbruch H — Motor unit of mammalian muscle. **Physiological Rev** 60:90, 1980.
22. Bulfield G, Siller WG, Wight PA, Karen JM — X-chromosomelinked muscular dystrophy (mdx) in the mouse. **Proc Nat Acad Sci** 81:1189, 1984.
23. Campbell MJ — Ultrastructural observations on the wobbler mouse. **J Neuropathol Exper Neurol** 31:190, 1972.
24. Carlson BM, Gutman E — Contractile and histochemical properties of sliced muscle grafts regenerating in normal and denervated rat limbs. **Exper Neurol** 50:319, 1976.
25. Chernoff GF — Shiverer: an autosomal recessive mutant mouse with myelin deficiency. **J Hereditary** 72:128, 1981.
26. Constantino-Ceccarini E, Morell P — Quaking mouse: in vitro studies of brain sphingolipid biosynthesis. **Brain Res** 29:75, 1971.
27. Dangain J, Vrbova G — Muscle development in mdx mutant mice. **Muscle and Nerve** 7:700, 1984.
28. Dubowitz V — Pathology of experimentally re-innervated skeletal muscle. **J Neurol Neurosurg Psychiat** 30:99, 1967.

29. Duchen LW — «Sprawling»: a new mutant mouse with failure of myelination of sensory axons and a deficiency of muscle spindles. **Neuropathol Appl Neurobiol** 1:89, 1975.
30. Duchen LW — Motor neuron diseases in man and animals. **Invest Cell Pathol** 1:249, 1978.
31. Duchen LW, Searle AG — Hereditary motor end-plate disease in the mouse: light and electron microscopic studies. **J Neurol Neurosurg Psych** 33:238, 1970.
32. Duchen LW, Stefani E — Electrophysiological studies of neuromuscular transmission in hereditary motor end-plate disease of the mouse. **J Physiology** 212:535, 1971.
33. Duchen LW, Scaravilli F — The structure and composition of peripheral nerves and nerve roots in the Sprawling mouse. **J Anatomy** 123:763, 1977.
34. Duchen LW, Scaravilli F — Quantitative and electron microscopic studies of sensory ganglion cells of the Sprawling mouse. **J Neurocytol** 6:465, 1977.
35. Duchen LW, Strich SJ, Falconer DS — Clinical and pathological studies of an hereditary neuropathy in mice (Dystonia musculorum). **Brain** 87:367, 1964.
36. Duchen LW, Falconer DS, Strich SJ — Hereditary progressive neurogenic muscular atrophy in the mouse. **J Physiology** 183:53, 1966.
37. Duchen LW, Searle AG, Strich SJ — An hereditary motor end-plate disease in the mouse. **J Physiology** 189:4, 1967.
38. Duchen LW, Strich SJ, Falconer DS — An hereditary motor neurone disease with progressive denervation of muscle in the mouse: the mutant «woobler». **J Neurol Neurosurg Psychiat** 31:535, 1968.
39. Duchen LW, Gale AN, Gomez S — Motor end-plate morphology and neuromuscular transmission in the mutant Trembler mouse. **J Physiology** 308:18, 1980.
40. Duchen LW, Gomez S, Guenet J-L, Love S — Paralyse: a new neurological mutant mouse with progressive atrophy and loss of nerve terminals. **J Physiology** 345:166P, 1983.
41. Duchen LW, Eicher EM, Jacobs JM et al — Hereditary leucodystrophy in the mouse: the new mutant twitcher. **Brain** 103:695, 1980.
42. Eldridge R, Fahn S — Advances in Neurology. Raven Press, New York, 1976.
43. Engel WK, Karpati G — Impaired skeletal muscle maturation following neonatal neurectomy. **Develop Biol** 17:713, 1968.
44. Esaki K, Yasuda Y, Nakamura M et al — A new mutant in the mouse: peroneal muscular atrophy. **Exper Animals** 30:151, 1981.
45. Falconer DS — Two new mutants «Trembler» and «Reeler» with neurological actions in the house mouse (Mus musculus L). **J Genetics** 50:192, 1951.
46. Gale AN, Gomez S, Duchen LW — Changes produced by a hypomyelinating neuropathy in muscle and its innervation. Morphological and physiological studies in the Trembler mouse. **Brain** 105:373, 1982.
47. Gallup B, Dubowitz V — Failure of «dystrophic» neurons to support functional regeneration of normal and dystrophic muscle in culture. Nature (London) 243:287, 1973.
48. Green EL — Biology of the Laboratory Mouse. Mc Graw Hill, New York, 1966.
49. Green MC, Sidman RL, Pivetta O — Cribriform degeneration (cri): a new recessive neurological mutation in the mouse. **Science** 176:800, 1972.
50. Grinnell AD, Herrera A — Specificity and plasticity of neuromuscular connections: long-term regulation of motor neuron function. **Progress in Neurobiology** 17:203, 1981.
51. Gruneberg H — The Genetics of the Mouse. Martinus Nijhoff, The Hague, 1952.
52. Gruneberg H — An annotated catalogue of the mutant genes of the house mouse. HMSO, London, 1956.
53. Hanker JS, Peach R — Histochemical and ultrastructural studies of primary sensory neurons in mice with dystonia musculorum: I. Acetylcholinesterase and lysosomal hydrolases. **Neuropathol Appl Neurobiol** 2:79, 1976.
54. Harris AJ — Embryonic growth and innervation of rat skeletal muscles. **Philosophical Trans Roy Soc London** 293:257, 1981.
55. Harris JB — Muscular dystrophy and other inherited diseases of skeletal muscle in animals. New York Academy of Sciences, New York, 1979.
56. Harris JB, Marshall M — A study of action potential generation in murine dystrophy with reference to functional denervation. **Exper Neurol** 41:331, 1973.
57. Harris JB, Ward MR — A comparative study of denervation in muscles from mice with inherited progressive neuromuscular disorders. **Exper Neurol** 42:169, 1974.
58. Harris JB, Montgomery A — Some mechanisms and electrical properties of distal hind limb muscles of genetically dystrophic mice (C75B1/6J dy2j/dy2j). **Exper Neurol** 48:568, 1975.
59. Harris JB, Ribchester R — Muscular dystrophy in the mouse: neuromuscular transmission and the concept of functional denervation. **Ann New York Acad Sci** 317:152, 1979.

60. Harris JB, Slater C — Animal models: what is their relevance to the pathogenesis of human muscular dystrophy? **Brit Med Bull** 36:193, 1980.
61. Huizar P, Kuno M, Miyata Y — Electrophysiological properties of spinal motorneurones of normal and dystrophic mice. **J Physiology** 248:231, 1975.
62. Innes JR — Myopathies in animals. **Brit Veterinary J** 107:131, 1951.
63. Janota I — Ultrastructural studies of an hereditary sensory neuropathy in mice (Dystonia musculorum). **Brain** 95:529, 1972.
64. Karpati G, Carpenter S, Prescott S — Small-caliber skeletal muscle fibres do not suffer necrosis in X-linked Muscular Dystrophy (MDX) of mice. **Neurology** 36:240, 1986.
65. Kobayashi T, Yamanaka T, Jacobs JM et al — The twitcher mouse: an enzymatically authentic model of human globoid cell leucodystrophy (Krabbe disease). **Brain Res** 202:479, 1980.
66. Kugelberg E — Adaptive transformation of rat soleus motor units during growth. Histochemistry and contraction speed. **J Neurol Sci** 27:269, 1976.
67. Kuno M — Physiologic consequences of neural abnormalities in murine dystrophy. **Ann New York Acad Sci** 317:143, 1979.
68. Lane PW, Deol M — Mocha, a new coat color and behaviour mutation on chromosome 10 of the mouse. **J Hereditary** 65:362, 1974.
69. Lane PW, Beamer TC, Myers D — Myodystrophy, a new myopathy on chromosome 8 of the mouse. **J Heredity** 67:135, 1976.
70. Law P, Atwood H, McComas AJ — Functional denervation in the soleus muscle of dystrophic mice. **Exper Neurol** 51:434, 1976.
71. Locke S — Modern Neurology. Little-Brown, Boston, 1969.
72. Low PA — Hereditary hypertrophic neuropathy in the trembler mouse: 1. Histopathological studies: light microscopy. **J Neurol Sci** 30:327, 1976.
73. Low PA — Hereditary hypertrophic neuropathy in the trembler mouse: 2. Histopathological studies: electron microscopy. **J Neurol Sci** 30:343, 1976.
74. Low PA, McLeod JG — Hereditary demyelinating neuropathy in the trembler mouse. **J Neurol Sci** 26:565, 1975.
75. Low PA, McLeod JG — Refractory period, conduction of trains of impulses and effect of temperature on conduction in chronic hypertrophic neuropathy: electrophysiological studies on the trembler mouse. **J Neurol Neurosurg Psychiat** 40:434, 1977.
76. Madrid RE, Jaros E, Cullen MJ et al — Genetically determined defect of Schwann cell basement membrane in dystrophic mouse. **Nature** (London) 257:319, 1975.
77. McComas AJ, Mrozek K — Denervated muscle fibres in hereditary mouse dystrophy. **J Neurol Neurosurg Psychiat** 30:526, 1967.
78. McComas AJ, Sica RE — Muscular dystrophy: myopathy or neuropathy? **Lancet** 1:1119, 1970.
79. McComas AJ, Sica RE, Currie S — Muscular dystrophy: evidence for a neural factor. **Nature** (London) 226:1263, 1970.
80. McComas AJ, Sica RE, Campbell MJ — «Sick motoneurones»: a unifying concept of muscle disease. **Lancet** 1:321, 1971.
81. McComas AJ, Sica RE, Currie S — An electrophysiological study of Duchenne dystrophy. **J Neurol Neurosurg Psychiat** 34:461, 1971.
82. Michelson AM, Russell ES, Harman PJ — Dystrophia muscularis: a hereditary primary myopathy in the house mouse. **Proc Nat Acad Sci** 41:1079, 1955.
83. Mitsumoto H et al — Vacuolated anterior horn cells in wobbler mouse motor neuron disease: peripheral axons and regenerative capacity. **J Neuropathol Exper Neurol** 46:214, 1987.
84. Moss TH — Segmental demyelination in the peripheral nerves of mice affected by a hereditary neuropathy (Dystonia musculorum). **Acta Neuropathol** (Berlin) 53:51, 1981.
85. Moss TH — Schwann cell involvement in the neurological lesion of the dystonic mutant mouse. **J Neurol Sci** 49:207, 1981.
86. Pai AC — Developmental genetics of a lethal mutation, muscular dysgenesis (mdg) in the mouse. **Develop Biol** 11:82, 1965.
87. Papapetroupolos TA, Bradley WG — Spinal motor neurons in murine muscular dystrophy and spinal muscular atrophy. **J Neurol Neurosurg Psychiat** 35:60, 1972.
88. Pearce GW, Walton JN — A histological study of muscle from the Bar Harbor strain of dystrophic mice. **J Pathol Bacteriol** 86:25, 1963.
89. Perkins S, Mizuno K, Aguayo AJ et al — Increased Schwann cell proliferation in trembler mouse nerves — quantitative microscopy and radioautography. **Neurology** 27:377, 1977.
90. Platzer A — Embryology of two murine muscle diseases: muscular dystrophy and muscular dysgenesis. **Ann New York Acad Sci** 317:94, 1979.

91. Platzer A, Gluecksohn-Waelsch S — Fine structure of mutant (Muscular dysgenesis) embryonic mouse muscle. **Develop Biol** 28:242, 1971.
92. Rieger F, Pincon-Raymond M — The motor innervation in motor end-plate disease (med) in the mouse: evidence for nerve abnormalities, prior to muscle damage. **Inserm Symposium** 14:163, 1980.
93. Rieger F, Pincon-Raymond M et al — Paranodal dysmyelination and increase in tetrodotoxin binding sites in the sciatic nerve of the motor end-plate disease (med/med) mouse during postnatal development. **Develop Biol** 101:401, 1984.
94. Samorajski T, Friede RL, Reimer PR — Hypomyelination in the quaking mouse: a model for the analysis of disturbed myelin formation. **J Neuropathol Exper Neurol** 29:507, 1970.
95. Scaravilli F, Duchen LW — The development of sensory ganglion cells in normal and Sprawling mutant mice. **J Neurocytol** 9:363, 1980.
96. Scaravilli F, Duchen LW — Electron microscopic and quantitative studies of cell necrosis in developing sensory ganglia in normal and Sprawling mutant mice. **J Neurocytol** 9:373, 1980.
97. Scaravilli F, Jacobs JM — Peripheral nerve grafts in hereditary leukodystrophy mutant mice (twitcher). **Nature** (London) 290:56, 1981.
98. Scaravilli F, Jacobs JM — Improved myelination in nerve grafts from the leucodystrophy twitcher into trembler mice: evidence for enzyme replacement. **Brain Res** 237:163, 1982.
99. Scaravilli F, Suzuki K — Enzyme replacement in grafted nerve of twitcher mouse. **Nature** (London) 305:713, 1983.
100. Schotland DL — Disorders of the Motor Unit. Wiley Medical, New York, 1982.
101. Sidman RL, Dickie MM, Appel SH — Mutant mice (quaking and jimpy) with deficient myelination in the central nervous system. **Science** 144:309, 1964.
102. Sidman RL, Green MC, Appel SH — Catalog of the Neurological Mutants of the Mouse. Harvard University Press, Massachussetts, 1965.
103. Sidman RL, Cowen JS, Eicher EM — Inherited muscle and nerve diseases in mice: a tabulation with commentary. **Ann New York Acad Sci** 317:497, 1979.
104. Stirling CA — Abnormalities in Schwann cell sheaths in spinal nerve roots of dystrophic mice. **J Anatomy** 119:169, 1975.
105. Tanabe Y, Esaki K, Nomura T — Skeletal muscle pathology in X-chromosome linked Muscular Dystrophy (mdx) Mouse. **Acta Neuropathol** (Berlin) 69:91, 1986.
106. Torres LFB — Muscle, motor end-plate and nerve in hereditary and experimental myopathies in the mouse. PhD Thesis, University of London, London, 1986.
107. Torres LFB, Duchen LW — The mutant mdx: inherited myopathy in the mouse: morphological studies of nerves, muscles and end-plates. **Brain** 110:269, 1987.
108. Valsamis P, Wisniewski H, Morell P — Dysmyelogenesis in the quaking mouse: an ultrastructural study. **J Neuropathol Exper Neurol** 31:190, 1972.
109. Watanabe I, Bingle GJ — Dysmyelination in «quaking» mouse: electron microscopic study. **J Neuropath Exper Neurol** 31:352, 1972.
110. Watkins J, Watts DC — Biological features of the new A2G-adr mouse mutant with abnormal muscle function. **Laborat Animals** 18:1, 1984.
111. Watkins J, Watts RL, Watts D — Deficiency of fructose 1,6-biphosphate aldolase in type 2 muscle fibres of the A2G-adr mouse mutant with abnormal muscle function. **Biochemical Soc Trans** 7:907, 1979.
112. West WT, Murphy ED — Histopathology of hereditary progressive muscular dystrophy in inbred strain 129 mice. **Anatomical Rec** 137:279, 1960.
113. Wisniewski H, Morell P — Quaking mouse: ultrastructural evidence for arrest of myelinogenesis. **Brain Res** 29:63, 1971.
114. Zacks I, Sheff M, Rhodes M et al — MED myopathy: a new hereditary myopathy of mice. **Laboratory Invest** 21:143, 1979.
115. Zeman RJ, Sandow A — Denervation effects on dystrophic and normal muscles and the etiology of dystrophy. **Ann New York Acad Sci** 317:171, 1979.