proximal to the motor end-plates. In early stages of the disease the structure of the motor nerve terminals and of skeletal muscle fibres appeared to be normal with both light and electron microscopy. With longer survival there was progressive atrophy of skeletal muscle fibres, particularly severe in proximal limb muscles. The histochemical reaction for phosphorylase became progressively weaker. Motor nerves innervating the atrophied muscle fibres showed marked terminal sprouting, the nerve sprouts growing beyond the normal confines of the motor end-plate. The sprouting nerve terminals contained abundant vesicles and mitochondria but the axolemmal-sarcolemmal junctions of these sprouts were deficient in subneural folds. The pathological findings suggest that this hereditary disease is due to progressive failure of neuromuscular transmission causing progressive functional denervation of skeletal muscle.

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**ADDENDUM**

Since this paper was written the results of an investigation of med mice by Zacks, Sheff, Rhodes, and Saito (1969) have been published. These authors report that no abnormalities of the motor end-plate and no atrophy of muscle fibres were found. They conclude that the disease is primarily myopathic in nature. The most likely reason for the failure of Zacks et al. to observe significant pathological changes in the muscles of the med mouse may be that they did not observe that different muscles are affected with varying degrees of severity. Their studies were confined to intercostal and gastrocnemius muscles, which are not uniformly severely affected in this disease.

**REFERENCES**


**GENETIC APPENDIX**

A. G. SEARLE

The med gene arose by spontaneous mutation in a stock homozygous for non-agouti (a), brown (b), chinchilla (c<sup>ch</sup>), pink-eyed dilute (p), dilute (d), short-ear (se), and piebald (s). A technician, Miss Daphne Buck, noticed that a mouse in litter CT/478.1 born 23 October 1958, was making wriggling seal-
like movements instead of running around normally. Some members of later litters from this mating and some progeny from the related matings CT/593 and CT/596 showed the same abnormal symptoms, which gradually increased in severity and caused death at about the time of weaning. Parents were completely normal.

All three affected matings had a common ancestral mating CT/320 on both the maternal and paternal sides. This was two generations back from mating CT/478 and three generations back from the other two matings. Thus it seemed probable that either the male or female member of CT/320 was heterozygous for a recessive gene as a result of mutation in an ancestral germ-cell. The gene was called 'seal' which was later amended to 'motor end-plate disease' (med) after preliminary histological studies suggested that the function of motor nerve terminals was abnormal.

Segregation data have provided further evidence on the mode of inheritance of this character. Out of 3,030 mice classified for it in segregating matings, 730, or 24.1 ± 0.8% were recorded as having the med phenotype. This is not significantly different from the expected 25% for recessive inheritance. Since 2/3 survivors from such matings should be +/med one would expect that 4/9 of intercrosses set up from survivors should be between heterozygotes and should therefore segregate for med. When allowance was made for matings which failed to produce med offspring just by chance, it was found that 98/211 intercross matings were probably between med heterozygotes. This is 46.4% and is in satisfactory agreement with the expected 4/9 (44.4%). It can be concluded that med is a fully penetrant recessive gene with normal transmission, and that homozygotes do not suffer any appreciable extra mortality over normal before the age of classification, which was usually between 12 and 15 days.

Since the med/med phenotype showed some resemblance to that for dystrophia muscularis (dy) although decidedly more severe, known +/med mice were mated to +/dy. None out of 14 offspring were abnormal, so it was concluded that the two genes were not allelic.

Linkage tests were made between med and the recessive genes a, b, c<sup>ch</sup>, p, d, se, and s, which were present in its stock of origin. Around 500 offspring were classified for each segregant phenotype, but none of the recombination frequencies differed significantly from the expected 50% with independent segregation. Linkage test intercrosses were then set up between med and the recessive genes fuzzy (f<sub>2</sub>), leaden (ln), waltzer (v), and pale ears (ep) and over 400 offspring were classified. Again, recombination frequencies did not differ significantly from 50%. Thus no linkage was found between med and genes in linkage groups I, II, III, V, VIII, X, XII, and XIII (see Green, 1966). However, recent tests between med and a linkage stock heterozygous for brachyury (T), caracul (Ca), varitint-waddler (Va), and white (Mi<sup>wh</sup>) have provided evidence for linkage with Ca on group VI. Thus mice of genotype Ca+/+/med crossed to med heterozygotes have given offspring of the following phenotypes:

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Ca+</th>
<th>+med</th>
<th>Ca med</th>
<th>+/+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>26</td>
<td>16</td>
<td>0</td>
<td>9</td>
<td>51</td>
</tr>
<tr>
<td>Expected</td>
<td>19.1</td>
<td>6.4</td>
<td>6.4</td>
<td>19.1</td>
<td>51</td>
</tr>
</tbody>
</table>

The differences between the observed numbers and those expected if the two genes showed independent segregation are clearly highly significant. The absence of Ca med offspring suggests that the two genes are closely linked, although more data will be needed before the recombination frequency can be accurately determined. Intercrosses of the type Ca+/+med should be useful in studying the early effects of med, since nearly all med homozygotes will be non-caracul. The effects of Ca on hair and vibrissae are visible soon after birth, much earlier than the effects of med.

REFERENCE

GENETIC APPENDIX

A. G. Searle

*J Neurol Neurosurg Psychiatry* 1970 33: 249-250
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