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Lethal Action in the Short-Tailed Mutation in the House Mouse.

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Three dominant factors in which the homozygous mutant form does not exist are known in mice, *viz.*, yellow coat color (A^y), black-eyed white (W), and brachyury. In all of these cases crosses *inter se* yield an F_1 of 2 mutants to one normal. Crosses to normals give a 1:1 ratio. These facts are explained by the supposition that the presence of 2 factors for the mutant character has a lethal action at some period during the development. Little and Castle,[1] following Cuénot, first advanced this hypothesis as to yellow mice. Subsequent investigation seems to show that the action takes place very early in embryogeny. Aberle[2] traced the lethal action in black-eyed white mice to an anemic condition. Here the homozygous anemics may survive to birth and live a short time afterwards. The breeding experiments of N. Dobrovalskia-Zavadskia[3] have indicated that a lethal action probably accompanies dominant short-tailedness (brachyury). The length of the tail varies. A few are indistinguishable from normal except for a slight bluntness. Others have no external tail. The latter have a varying number of malformed caudals and a derangement of the sacral and lumbar vertebrae. One or more rigid bends caused by an ankylosis of vertebrae often accompany the shortening. A paralysis of the posterior limbs is occasionally encountered. It seems probable that this latter condition is the result of abnormalities in the sacral and lumbar vertebrae.

My object was to discover the stage at which the lethal action of this gene occurs and to describe its effect on development. In matings of brachyurie × brachyurie embryos are found at the last of the eighth day, while still in the stage of the primary flexure, which show definite abnormalities. From the ratio in which these appear there is no doubt that they represent the missing homozygous type. In the mid-region of the embryo the neural tube, instead of being straight as in the normal condition, is bent from side to side. The ectodermal outer layer of the embryo is thrown into a varying number of blebs or vesicles immediately lateral to the neural tube.

[1] Little and Castle, *Science*, N. S., 1910, **32**, 868.

[2] Aberle, *Am. J. Anat.*, 1927, **40**, 219.

[3] Dobrovalskia-Zavadskia, N., *C. R. Soc. Biol.*, 1927, **97**; 1928, **98**; 1930, **104**; Dobrovalskia-Zavadskia and Kobozieff, *C. R. Ac. d. Sci.*, 1930, **191**, 352.

These give the impression of the puffing out of the tissue layer by the pressure of internal fluids. The complete or partial absence of somites is a third anomalous condition. Although it is uncertain at present whether or not there are vestiges of somites, certainly no regular segmentation of the body similar to that in normal embryos is found.

Homozygous embryos taken from the uterus early in the tenth day show a very marked contrast to their normal litter mates. At this time the normal has about 30 somites and both anterior and posterior limb buds, the latter just perceptible. In both types the heart beats regularly. The homozygote has no somites and the neural tube is bent as in younger embryos. No trace of the dorsal ectodermal blebs is discernible. Other gross deformities are present. The posterior end of the embryo ends abruptly slightly posterior to the anterior limb buds. In normals the tail tapers and turns spirally. The anterior limb buds are the same size as in normals but are distinctly more dorsal in their origin. There are no posterior buds, although in one case an individual with a single median posterior appendage was found. The size of embryos is considerably below that of normal litter mates. This may be interpreted as an indication of approaching death.

Death takes place during the third quarter of the tenth day. The heart does not beat in homozygous embryos taken from the uterus at this time but can sometimes be slightly stimulated by a needle, indicating that the lethal point is very close to this age. Females examined on the eleventh day show embryos already well started toward resorption. Later stages show resorption as in cases of prenatal mortality from other causes.

The ratio of homozygotes to normal embryos for the litters taken from the uterus on the eighth, ninth, and tenth days agrees closely with the expected 1:3. Out of 256 embryos in 29 litters 60 were of the abnormal type designated as homozygous.

Other defects appearing in serial sections of the embryos have not yet been fully studied, nor have the progressive changes in the gross abnormalities. The earliest manifestation of a difference between the homozygote and the normal must be sought in the seventh and eighth days.