CHAPTER 1

THE BEGINNINGS: ODE TO A WEE MOUSE

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1. Introduction

This chapter provides a brief overview and historical perspective of how the mouse came to be an important animal model in mammalian genetics research. More detailed reviews can be found in several sources.[1–5] Kenneth Paigen has recently published an excellent review of the first one hundred years of mouse genetics from 1902 to 2002.[6,7]

The house mouse became a well-recognized pest to humans with the introduction of plant and animal domestication. The transition of humans from hunter-gatherers to farmers began about 8,500 B.C. in the region of Southwest Asia called the Fertile Crescent.[8] The mouse found itself in a luxuriant environment with unlimited food in the form of stored grains and other food morsels in dwellings of the sedentary human population of this area.[5] Thus began the never-ending struggle of people to protect their stored food from what might be called the *bad mouse.* It is not surprising that the word *mouse* comes originally from the Sanskrit *mush* meaning to steal, which became *mus* in Latin and *mys* in Greek.[1] It has been suggested that the ancient Egyptians deified the cat because of its ability to control the mouse population. The mouse even receives some harsh treatment in the book of Leviticus:

> There also shall be an abomination to you among the creeping things that creep upon the earth: the weasel and the *mouse,* and the tortoise after his kind…. These are unclean to you among all that creep; whosoever doth touch them, when they be dead, shall be unclean until even.

At various times the Greeks and Romans worshipped mice, and physicians used mice in their medicinal formulas. The clergy of the Middle Ages in Europe considered mice as lustful creatures and instruments of the devil,[1] but the mouse had a more positive status in Asia.

The use of mice in pharmaceutical concoctions continued well into the 17th century and later in parts of Europe.[3] The Chinese and Japanese became enamored of mice.[1,3] Positive mouse symbolism in Asia became wide spread. In Japan, the mouse was given the special status as messenger of Daikoku, the God of Wealth.[9] In many parts of Asia, the mouse is recognized in several ways: a) one of every twelve years is known as the year of the mouse; b) the hours of the day between 11:00AM and 1:00PM are designated as the hours of the mouse; and c) multiplications by serial 2's are known as mouse numbers.[3]

Robert Burns, the great 18th century Scottish poet, immortalized the intimate relationship between the farmer and the mouse and their struggle for survival in his famous ode *To a Mouse.*

ON TURNING HER UP IN HER NEST, WITH THE PLOUGH, NOVEMBER 1785

Wee, sleekit, cowrin, tim'rous beastie,
O, what a panic's in thy breastie!
Thou need na start awa sae hasty,
Wi' bickering brattle!
I wad be laith to rin an' chase thee,
Wi' murd'ring pattle!

I'm truly sorry Man's dominion
Has broken Nature's social union,
An' justifies that ill opinion,
Which makes thee startle,
At me, thy poor, earth-born companion,
An' fellow-mortal!…

…But, Mousie, thou art no thy lane,
In proving foresight may be vain:
The best-laid schemes o' mice an' men
Gang aft a-gley,
An' lea'e us nought but grief an' pain,
For promis'd joy!

Still though are blest, compar'd wi' me!
The present only toucheth thee:
But, Och! I backward cast my e'e

On prospects drear!
An' forward, tho' I canna see,
I guess an' fear!

2. Mouse Domestication

The Chinese and Japanese are believed to have been the first to domesticate mice.[3] They were the first to raise unusual mice, particularly with regard to coat color and waltzing mutants. The spotted mouse is mentioned in the Eh Yah lexicon in 1100 B.C., and the waltzing mouse is described as early as 80 B.C. in the annals of the Han Dynasty.[1,9]

The *mouse trade* brought fancy mice to Europe, so that by the 19th century the house mouse hobby became popular there and spread to the United States by the beginning of the 20th century.[5] One of these mouse fanciers, Ms. Abbie Lathrop, a retired schoolteacher, became the link between hobby and science for the house mouse. A detailed description of Abbie Lathrop's mouse breeding business in Granby, Massachusetts, USA from about 1900 until her death in 1918 at age 50, showed that she interacted with biologists of the day as well as mouse fanciers.[2] She first sold mice to hobbyists, but soon she received orders for mice from research laboratories, including the Bussey Institute at Harvard University. Many inbred mouse lines were derived from mice originally obtained from Lathrop's farm.[2] Thus, the wee mouse had come full circle from the *bad mouse*, a nemesis to humans, to the *good mouse*, an important biological model for biomedical research.

3. The Birth of Mouse Genetics

But for the intervention of a conservative bishop who forbade Gregor Mendel from continuing to study inheritance of coat color traits of mice,[10] mouse genetics may have had its beginnings in 1866 instead of 1902. The bishop in Mendel's district felt it was inappropriate for the monk to share his living quarters with critters that had sexual intercourse, and so Mendel was forced to turn his attention to making experimental crosses with the garden pea. Fortunately for Mendel, the bishop was apparently unaware that plants also had sex.

Upon the rediscovery of Mendel's laws in 1900 by Correns, De Vries and Tschermak working independently with plants, there was a question of whether the laws applied to animals as well.[6] In 1902 Lucien Cuénot in France demonstrated independent segregation of albino *vs* color and of yellow *vs* black

coat color,[11] and in 1903 William Castle in the United States established segregation and independent assortment of albino *vs* colored, spotted *vs* solid colored, black *vs* brown, and yellow *vs* nonyellow.[12] Castle, together with a bright Harvard undergraduate, Clarence Cook Little, established nine genetic coat color loci.[13,14] As chronicled by Paigen,[6] Cuénot described the first lethal mutation, the A^y allele of the agouti locus,[15] which was verified in 1910 by Castle and Little.[14] The first genetic linkage group for mice was established by Haldane and co-workers in 1915.[16]

William Castle was the first co-director of the Bussey Institute at Harvard University, which opened in 1908. Castle was a catalyst for promoting research in mouse genetics. He attracted a covey of outstanding Ph.D. students to the Institute. Although only 13 of Castle's 246 publications were concerned primarily with mice, he had a pervasive influence on mouse genetics.[2] Most of the early American mouse and mammalian geneticists started out with Castle at the Bussey.[4] Numbered among Castle's students were Clarence Little (1914), developer of the first inbred mouse line; Sewell Wright (1915), co-founder of the field of population genetics; L. C. Dunn (1920), eminent developmental geneticist; and George Snell (1930), developer of coisogenic strains used to study histocompatability loci and recipient of the 1980 Nobel Prize in Physiology or Medicine.

Despite early indications that some human diseases might be mimicked by certain mouse mutants, progress in defining new genetic variants was slow.[3] In fact, Little and Bagg wrote in 1924 that "mice and rats are singularly free of morphologic variations."[17] We know that Little certainly did not heed his own advice. He went on to become the first director of the Jackson Laboratory in Bar Harbor, Maine in 1929, which eventually became the pre-eminent mouse research facility in the world.[18] Also, according to a personal communication to Morse[3] from C.E. Keeler, one of Castle's Ph.D. students, Castle had suggested to Keeler that "some species besides mice should occupy his time in the future as there were no new mutations to be discovered." Now here is a case where not paying attention to one's mentor was a smart decision. Of course, it is possible that Castle was simply trying to challenge Keeler.

The origin of mouse genetics research was, from its inception at the beginning of the 20th century, aimed at queries in human medicine.[4,18] The earliest of these studies involved the use of the first inbred line (DBA, denoting the coat color genes *d*, dilute; *b*, brown; and *a*, nonagouti) developed by Little while still an undergraduate at Harvard. In elegant tumor transplant experiments involving DBA and Japanese waltzing mice, Little and E.E. Tyzzer demonstrated that transplant acceptance depends upon polygenic inheritance; the successful

recipient must carry the dominant gene at each histocompatibility locus carried by the donor tissue.[19] This research also demonstrated the value of the genetic uniformity of an inbred line and perhaps was the impetus for researchers to develop many more inbred lines for biomedical research.[2] The original inbred lines are thought to consist of a combination of four *Mus* species, *Mus musculus domesticus, M. m. musculus, M. m. castaneus and M. m. bactrianus*,[20] and are conventionally identified as *Mus musculus.*[5]

At the other end of the spectrum of early mouse genetics research was the interest by evolutionary biologists and animal breeders concerning the nature of genetic variation. The first experimental approach was to select for a specific quantitative trait and simply to see how far artificial selection could change a trait and how many generations were needed to reach a limit, if indeed there would be a limit. To insure maximum genetic variation, selection was initiated in a randombred strain or after crossing two or more inbred lines. The earliest experiments of this nature were by Goodale in 1931 for white hair on the face[20,21] and by Goodale in 1930 and MacArthur in 1939 for 60-day body weight.[22–26] The first modern selection experiments with the mouse, analyzed and interpreted by conventional quantitative genetics methods, were reported by Falconer at the University of Edinburgh.[27]

4. Conclusions

The relationship between the house mouse and humans became firmly established with the introduction of agriculture in the Fertile Crescent about 10,000 years ago. The mouse was well adapted to *steal* food from granaries following the harvest. As farming spread through Eurasia, the major defense against the insurgent mice was the use of cats, which may have led to deification of cats in Egypt. The mouse itself enjoyed periods of being protected and worshipped during the Greek and Roman eras, where they were also used as augurs. During these periods and at different times well into the 17th century, the mouse was employed in various pharmaceutical remedies. However, the mouse was scorned by the Catholic clergy as being libidinous and an instrument of the devil.

The domestication of the house mouse probably originated in China and Japan where the first mutant mice were maintained. Mouse fanciers from Asia brought their hobby to Europe in the 19th century, and fancy mice eventually reached the United States toward the latter part of the 19th century. At the beginning of the 20th century Ms. Abbie Lathrop started a mouse breeding

business in Massachusetts, which supplied mice to mouse fanciers and later to laboratories for genetics research.

The rediscovery of Mendel's laws in 1900 launched a rush to verify these genetic principles in other organisms. Use of the mouse was a logical choice in studying mammalian genetics, the initial experiments being conducted by Cuénot in France and Castle in the United States. Early research efforts in mouse genetics were directed toward problems in human medicine, but were also applied to questions in evolutionary biology and breeding. Even more exciting mammalian genetics research was to be conducted with the wee mouse as it entered the world of genetic maps, transgenics, knockouts, positional cloning of mutants and quantitative trait loci affecting complex traits. A crowning milestone in mouse genetics was publication of the sequence of the mouse genome in *Nature* in December 2002.[28] We can only wonder what Castle, Little, Cuénot and the other pioneers in mouse genetics would have made of all this.

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