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THE DOMESTICATION OF THE RAT

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The Norway rat (Rattus norvegicus) is a comparatively recent immigrant to Europe and America and at the present time is reproducing in enormous numbers both in a wild state and under domestication. A comparative study of its behavior in the two contrasted states is thus made easy and should throw light on what takes place in a species of mammal when it is brought into captivity and its breeding is controlled by man.

The Norway rat entered western Europe by way of the Norwegian peninsula in the first half of the Eighteenth Century and bears a specific name indicating the route by which it arrived. Its ecological predecessor was the black rat (Rattus rattus) the rat which spread plague in London in 1664–1665. This species was soon afterward replaced in Western Europe by its mortal enemy the newly introduced Norway rat, which promptly made its way on ships to the New World, where the black rat had preceded it but was, as in Europe, promptly supplanted by the Norway rat except in out-lying districts such as northern New Hampshire where Dr. C. C. Little secured for me live examples of Rattus rattus about 1910, and on which Dr. H. W. Feldman made genetic studies. One interesting result of these studies was the demonstration that crosses between the two species, R. rattus and R. norvegicus, are very difficult to obtain: embryos never coming to term alive. So it is easy to see why hybrids do not occur in nature.

At sometime after the introduction of the Norway rat into Western Europe, it is probable that albino mutants made their appearance in the

wild population, as they do in the case of most wild mammals. Albino individuals were probably captured and tamed because of their attractive and distinctive appearance and thus the tame white rat became the earliest domesticated type of rat. Similarly a black (non-agouti) mutation made its appearance, and also a piebald (hooded) mutant appeared, perhaps originally gray-and-white in color, but if mated to black individuals resulting in the production of the double recessive black hooded type. Then if the black hooded type was crossed with albinos, triple recessives would result, albinos homozygous for black and piebald (*cc aa hh*). Keeler has shown that black individuals are in temperament gentler than grays of like ancestry and it seems probable that this made easier the process of taming the mutant strains, since the gentler individuals would be more amenable to handling and confinement and would thus come to predominate in the domesticated race.

At any rate we know that when the first recorded breeding experiments with white rats were undertaken by Crampe about 1880, an albino female which he mated to a wild gray male transmitted as recessives to her gray F_1 offspring the three mutant genes, *c* (albino), *a* (non-agouti), and *h* (hooded). Although Crampe's experiments were made in the pre-Mendelian period, his records as analyzed by Doncaster (1906) fully support this interpretation.

It is clear also that when white rats of European origin were brought to America (by Dr. H. H. Donaldson and others) and were made the foundation of the Wistar Institute race of albinos, these were homozygous for the same three mutant genes (*cc aa hh*) as were Crampe's albino. Albino rats which Dr. Donaldson kindly supplied to me about 1903 were of this genetic constitution.

Dr. Donaldson in 1906 transferred his colony of albino rats from the University of Chicago to the Wistar Institute. Here Dr. Helen Dean King in 1908 became associated with him in a comparative study of the albino rat and its wild gray ancestor. She had the happy thought that it would be interesting to re-enact the domestication of the rat under controlled conditions and thus to observe just what occurs in the process. In this she had the coöperation and support of Dr. Donaldson, with consequences of the highest importance to the science of genetics. In the spring of 1919 Dr. King began rearing in captivity the progeny of wild rats captured in the vicinity of Philadelphia. In 1929 she reported on the life processes observed in the first 10 generations of captive gray rats, Dr. Donaldson at the same time reporting on size of body and organs of the rats. Ten years later, after Dr. Donaldson's death, Dr. King made a further report on life processes as observed in 26 generations of captive rats.

Donaldson in 1929 had summarized as follows the initial differences

between wild gray rats and albinos. "The wild Norway are more excitable and much more savage. They gnaw their cages. The body weight is less for a given body length, hence it is a slighter animal. The skeleton is relatively heavier, also the suprarenals (both sexes) and the testes and ovaries. The thyroid is of like weight, but the hypophysis distinctly lighter in both sexes. On the other hand, the brain and the spinal cord are both heavier than in the Albino."

After ten generations in captivity Donaldson finds that in captive grays there has been an increase in body weight in relation to body length, i.e., the body has become less slender, more like the albino in conformation. The hypophysis has increased slightly in weight. No change has occurred in the weight of the gonads. Decrease in weight is shown by brain, thyroid and suprarenals. But brain, suprarenals, gonads and bones are still heavier than in the Albino race. "Ten generations of captivity have, by no means, he says, served to give the captive Grays the organ constitution of the Albino." It would seem, accordingly, that a changed and controlled environment had effected little racial change in the course of ten generations.

As regards the changes observed in life processes during 25 generations in captivity Dr. King (1939) notes a gradual increase in the "rate and extent of body growth," i.e., in general body size. "At the last generation growth acceleration (more rapid growth during the adolescent period) was nearly equal to that found in stock albino rats that have been under domestication for a long period of time. At the twenty-fifth generation adult rats of both sexes were, on the average, about 20 per cent heavier than individuals of the first generation."

"Rats attaining an adult weight much above the average for all individuals of like sex in the same generation group appeared in increasing numbers as the generations advanced." The weight increase is ascribed tentatively to genetic mutation rather than to a direct effect of a changed environment.

At the twenty-fifth generation the average length of the reproductive period was nearly 8 months longer than for the first generation. This extension resulted from the earlier breeding of the rats and the persistence of reproduction to a more advanced age.

Fertility of the rats, as measured by litter production increased steadily reaching its maximum at the nineteenth generation where females produced an average of 10.18 litters each, as contrasted to an average of 3.5 litters each for generation one. No significant change in the size of individual litters was observed. Litter size continued at an average of 6.1 throughout generations 2–26. Variability in body size decreased, i.e., the race became more uniform in body size.

On the whole it would seem that in the experiments of Dr. King genetic

differences present in the foundation animals or mutational changes occurring in their descendants will account adequately for the changes observed.

Those changes are (1) accelerated growth rate resulting in increased body size; (2) decreased "nervous tension" resulting in tamableness when the animals were handled frequently in early life; (3) mutations in color or structure of the hair.

In the course of Dr. King's experiments with captive wild gray rats, she observed the new occurrence among them of four mutations previously known, *c*, *a*, *h* and c^d of table 1. Of these *h* was already present as a re-

TABLE 1

MUTATIONS OF THE RAT

DESIGNATION	GENETIC SYMBOL AND LINKAGE GROUP	NATURE	TIME AND PLACE OF ORIGIN	RECORDED BY	NATURE OF POPULATION IN WHICH IT APPEARED
1. Albino	*c* I	Absence of pigment from coat and eyes	17th or 18th Centuries in Western Europe	H. Crampe, 1885	Wild
2. Non-agouti	*a*	Absence of wild coat pattern, uniform black	17th or 18th Centuries in Western Europe	H. Crampe, 1885	Wild
3. Hooded	*h* I	White except head and back stripe	17th or 18th Centuries in Western Europe	H. Crampe, 1885	Wild
4. Pink-eyed yellow	*p* I	Coat yellow, eyes pink	1907, England	Castle	Wild
5. Red-eyed yellow	*r* I	Coat yellow, eyes red	1907, England	Castle	Wild
6. Curly	*Cu* II	Hairs of coat and vibrissae curved	1920–1930 Wistar Institute	Helen Dean King	Captive wild
7. Brown	*b* II	Black pigment of coat and eyes replaced by brown	1920–1930 Wistar Institute	Helen Dean King	Captive wild
8. Stub	*st* IV	Short stubby tail	1939 Wistar Institute	Helen Dean King	Captive wild
9 Ruby-eyed dilute	c^d I	Allele of albino gene, *c*, pigmentation diminished	1918 in wild rats in Phila.; later in captive grays, 1920–1930	Whiting and King 1918, King 1939	Captive wild

10.	Curly$_2$	*Cu*$_2$	Coat hairs and vibrissae strongly curved	Davis, Calif., 1935	Blunn and Gregory	Long-Evans captive gray stock
11.	Kinky	*k* IV	Coat hairs and vibrissae strongly curved	Ann Arbor, Michigan, 1935	H. W. Feldman	Domesticated strain
12.	Lethal	*l* I	Skeleton imperfect	England 1939	H. Grüneberg	Domesticated strain
13.	Blue	*d*	Black pigment diluted (clumped) to yield a blue	University of Illinois, 1929	E. Roberts	Domesticated strain
14.	Hairless	*hr* III	Hair lost at about 4 weeks of age	University of Illinois, 1940	E. Roberts	Domesticated strain
15.	Wobbly	*wo* III	Ataxic locomotion	Univ. of Iowa, 1941	Castle, King, and Daniels	Domesticated strain
16.	Waltzing	*w* I	Runs in circles	Wistar Institute, 1936	Helen Dean King	Domesticated strain
17.	Incisorless	*in* II	Incisors lacking	Squibb Labs., New Brunswick, N. J., 1941	R. O. Greep	Domesticated strain
18.	Anemia	*an* II	Young anemic at birth, lack of red blood cells	Cornell Univ., 1939	Smith and Bogart	Domesticated strain
19.	Cataract	*Ca*	Opaque lens visible in unpigmented eyes, pink-eyed or albino	Cornell Univ., 1943	Smith and Barrentine	Domesticated strain
20.	Jaundice	*j*	Skin and hair yellow at birth and later	Univ. of Toronto, 1938	C. H. Gunn	Domesticated strain
21.	Shaggy	*Sh* II	Hair and vibrissae curved, closely linked to curly	Wistar Institute, 1946	Helen Dean King	Domesticated strain

(Table continued on following page)

22.	Silver	*s*	Black coat interspersed with white hairs	Wistar Institute, 1939	Helen Dean King	Domesticated strain
23.	Fawn	*f*	Dilutes black to tawny, blue to fawn	Wistar Institute, 1946	Helen Dean King	Domesticated strain

cessive in one animal of the foundation wild stock. Three previously unknown mutations of the rat made their appearance in the captive stock, curly in generation 17, brown in generation 22, and stub seven generations later.

Castle had reported in 1907 the occurrence in wild rats in England of mutations *p* and *r*. One of these, *r*, made its appearance independently in Wistar Institute stock (not captive gray) as reported by King, 1923.

Meanwhile several other mutations had been observed in domestic laboratory stocks. Roberts in 1924 reported the occurrence of hairless (*hr*), and in 1929 of blue dilutin (*d*). Wilder (1932) observed an independent occurrence of the hairless mutation, and Feldman demonstrated the identity of the two. Gregory and Blunn in 1935 reported the occurrence of a second dominant curly mutation which they designated $Curly_2$, and showed to be distinct from Curly, the two being independent in inheritance, and so obviously borne in different chromosome pairs. In the same year (1935) Feldman discovered a recessive form of curly hair which he named kinky (*k*).

In 1936 King reported the discovery of a recessive gene for waltzing (*w*) in Wistar albino rats, mutants from captive grays. In (1937) Daniels discovered a recessive gene for wobbly, which was described and its linkage relations canvassed by Castle, King, and Daniels. In 1938 Gunn described a recessive gene for jaundice. In 1939 Smith and Bogart reported the discovery of a recessive lethal, anemia (*an*); and Grüneberg reported on a different lethal (*l*) resulting in an abnormal skeleton. This he showed to be carried in the albino chromosome. In 1941 Greep reported the discovery of incisorlers (*in*). In 1943 Smith and Barrentine reported the discovery of a new dominant mutation cataract (*Ca*). King has also discovered three other mutations on which as yet no publication has been made. They are silver, a recessive; fawn, also recessive; and shaggy, a dominant resembling the curly mutations.

Burhoe, studying the blood groups of the rat, has demonstrated the existence of two dominant agglutinogen genes, *Ag* and *M*.

One striking fact concerning the mutations of the rat is that they may occur again independently of an original and earlier occurrence. King has demonstrated this in her own studies for *c*, *a*, *h* and *r*, also for Cu_2 observed

as occurring independently in New Haven, Conn., by Whitney. The blue mutation (*d*) originally observed by Roberts in 1929 was shown to have occurred independently later in New York (Curtis and Dunning, 1940). Curly, as well as $Curly_2$, has made a second independent appearance, at Madison, Wis., (personal communication from Dr. A. B. Chapman).

Linkage studies made to discover what genes are carried in a common chromosome pair have been made by Roberts and Quisenberry (1936), by Burhoe and by Feldman, but all their findings were negative. The first positive finding was made by Castle and Wright, who showed that the two genes for yellow coat, *p* and *r* are linked with each other. Later it was found by Castle, Dunn and Wachter that they lie in the same chromosome pair as the albino gene. Castle and King found that the gene for waltzing also lies in the albino chromosome, and Grüneberg added a fifth gene, a lethal *l* to this first linkage group. A second linkage group was found by King and Castle to include curly and brown, to which later were added the genes shaggy, anemia and incisorless. A third linkage group was found by Castle, King and Daniels to include the genes wobbly and hairless. A fourth group includes genes kinky and stub, as demonstrated by Castle and King. Conventional linkage maps may be expressed as follows:

I	*p*	*r*	*c*	*l*	*w*
	0	20.5	21	24.3	66.3
II	*Cu*	*Sh*	*an*	*in*	*b*
	0	0.5	10.3	24	45
III	*wo*				*hr*
	0				40.3
IV	*k*				*st*
	0				34.1

For the following genes no linkage has as yet been found, though the investigation is far from complete: *a*, *Ag*, *Ca*, Cu_2, *d*, *h*, *j* and *M*. If all of these should be shown to be independent of the established linkage groups we should have genetic markers for 12 of the 20 autosomal chromosome pairs, no sex-linked gene having as yet been discovered.

By way of summary we may say that the earliest attempts at domestication of the Norway rat followed the discovery in wild populations of conspicuous mutants, albinos, non-agouti blacks and piebalds. These were captured, and intercrossed, resulting in the formation of a race of albinos homozygous for the three mutant genes *c*, *a* and *h*. Such is the genetic constitution of the ordinary laboratory white rat.

Unconscious selection was probably made of the more gentle and tamable individuals for propagation, which also favored increased productiveness in captivity.

Experimental re-enactment of domestication by taking wild gray rats into captivity has resulted in (1) increased body size, (2) decreased savageness (inclination to bite and attempt to escape) and (3) increased fertility.

These may be regarded as consequences of mutations affecting behavior either directly or by way of endocrine changes, rather than as direct effects of a changed environment. At the same time mutations have been observed to occur which affect the structure of the hair or its pigmentation, or the central nervous system (waltzing, wobbly), the eyes or the skeleton (stub tail, lethal *l*). These are not to be regarded as consequences of domestication but purely as sports, spontaneous and without assignable causation.

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Ag is used as the symbol of a gene for agglutinogene A of Burhoe (published herewith) to avoid confusion with *A*, agouti, dominant allele of *a*.

AN EXPRESSION OF HOPF'S INVARIANT AS AN INTEGRAL*

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1. Let $S^2 \subset R^2$ and $S^3 \subset R^4$ be spheres in the sense of Euclidean geometry, S^2 having unit radius, and let $f: S^3 \to S^2$ be a twice differentiable map. Let x^1, x^2, x^3 be local coördinates for S^3, let λ, μ be local coördinates for S^2 and let $\sigma(\lambda, \mu)$ be the area density on S^2. Let

$$u_{ij} = \frac{1}{4\pi}\,\sigma(\lambda, \mu)\,\frac{\partial(\lambda, \mu)}{\partial(x^i, x^j)}\ (i, j = 1, 2\ 3), \tag{1.1}$$

where λ, μ, in (1.1) stand for the functions $\lambda(x^1, x^2, x^3)$, $\mu(x^1, x^2, x^3)$, by means of which f is expressed locally. Then u_{ij} are the components of an alternating tensor in S^3. It may be verified that the divergence of this tensor vanishes. That is to say

$$\partial u_{23}/\partial x^1 + \partial u_{31}/\partial x^2 + \partial u_{12}/\partial x^3 = 0.$$

Hence, by de Rham's theorem[1] there is a covariant vector-field (v_1, v_2, v_3), defined over the whole of S^3, such that

$$\partial v_i/\partial x^j - \partial v_j/\partial x^i = u_{ij}. \tag{1.2}$$