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Contributors

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MEDICAL RESEARCH COUNCIL MEMORANDUM
No. 33

AN ANNOTATED CATALOGUE OF THE MUTANT GENES OF THE HOUSE MOUSE

H. GRÜNEBERG

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1956

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PREFACE

TOWARDS the end of 1954 the Medical Research Council appointed a committee to assist them with problems associated with the preservation of pathological mutants in the house mouse, and with the fuller employment of such mutants in medical research. The Council are advised by the Committee that although mutant strains of mice have been utilized in certain pathological research work related to haematology, skeletal and labyrinthine anomalies, and endocrinology, the extent and variety of the material now available and its potential usefulness in various fields of research are not fully appreciated by research workers in general.

Mutant strains of mice characterized by features similar to many of those found in human pathology are now available, and, since their genetic and other determining influences are known, there may be considerable advantage in making use of them in experimental investigations prior to embarking on parallel clinical studies. It is hoped, therefore, by means of this catalogue, to direct the attention of pathologists and of research workers in many fields of biology and medicine to the possibility that new light may be shed on their problems by a study of cognate mutant genes in the mouse.

MEDICAL RESEARCH COUNCIL,
38 Old Queen Street,
London, S.W.1

5th October, 1956

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AN ANNOTATED CATALOGUE OF THE MUTANT GENES OF THE HOUSE MOUSE

by H. GRÜNEBERG, M.D., D.Sc., F.R.S.

I. Introduction

SIGNIFICANCE AND SCOPE OF THE CATALOGUE

Knowledge of the mutant genes of the house mouse is of great potential value for medical research. Yet the workers who might gain by its use know little about this material. This is largely due to the fact that much of the original work has been published in genetical journals unfamiliar to the medical profession. Moreover, the entities are usually referred to by names which have been taken from the vernacular and which convey little meaning to the medical reader; this is inevitable, as at the time of first publication little is generally known about the new mutant except its formal genetics and that affected animals can be recognized, for instance, by their kinky tails or by head shaking. As the original names given to mutant genes are not usually changed, they tend to conceal the fact that much useful knowledge may have been added in the fields of anatomy, embryology, physiology and pathology.

The present annotated catalogue of the mutant genes of the house mouse has been compiled at the request of the Medical Research Council's Committee on the Preservation of Pathological Mutants in the Mouse, in the hope that it will be illuminating to those research workers in medicine who may be able to benefit by the use of this material.

Inclusions and Exclusions

The catalogue includes most of the mutant genes of the mouse which have been published up to the end of 1955, as well as a few in 1956 and others in course of publication. It does not include numerous genes which have been mentioned only in the 'Mouse News Letter', a mimeographed bulletin which is circulated to a limited number of active workers in this field, but which is not a publication in the ordinary sense. The catalogue does not include genes determining antigenic differences (blood group genes, histo-compatibility genes, etc.) nor a few minor coat-colour and spotting genes; nor does it mention certain conditions no longer available for study which have appeared in a number of reports. It includes a few conditions which are probably not due to single-gene differences, but to constellations of genes (anophthalmia, eyelids open at birth, posterior reduplication, post-axial polydactylism, harelip and cleft palate, imperforate vagina); one condition (hydrops) is probably due to a chromosomal aberration. However, peculiarities of inbred strains of mice which are usually genetically complex have not been included. Although many such features are of considerable medical interest, for example differences in structure and function of endocrine glands, malignant tumours, and other diseases of old age, the inclusion of this very large category of conditions would have destroyed the balance of the catalogue; many of them (up to the end of 1949) have been brought together in the second edition of *The Genetics of the Mouse* (Grüneberg, 1952).

As many of the genes of the mouse have manifold effects, they cannot be classified by the structures or organs affected without considerable overlapping. Table 1 (p. 4) has been constructed to enable the reader to trace all the genes with known effects on a particular structure or system.

A '+' sign in the table means that the effect of a given gene on a given system has been established. Such an effect may be present in all the animals concerned, for example spina bifida in all 'Loop-tail' homozygotes (No. 43); the same malformation is present only in some animals in 'curly-tail' (No. 44). In some cases, part of a syndrome is present in heterozygotes and part in homozygotes; for instance, 'Splotch' heterozygotes (No. 20) have some white spotting, while the 'Splotch' homozygotes show spina bifida, and in this case '+' signs are shown in columns 2, 5 and 8; this last refers to anomalies of the vertebral column secondary to the spina bifida. Another example is 'Varitint-waddler' (No. 63), in which the heterozygotes and the homozygotes show a peculiar type of coat colour with spotting, together with a labyrinthine syndrome; '+' signs are accordingly shown in columns 1, 2, and 6, and the additional '+' sign in column 5 (CNS) refers to epileptiform seizures which occur in *Va*/*Va* homozygotes, but not in *Va*/+ heterozygotes.

In cases of manifold gene effects, the relative importance of the '+' signs cannot be inferred from Table 1. For instance, in 'hydrocephalus-3' (No. 47), the involvement of the skeleton is confined to the calvarium and is thus a comparatively trivial consequence of the enlargement of the cerebral hemispheres. On the other hand, in the case of 'congenital hydrocephalus' (No. 81), there is a generalized anomaly of the skeleton, and the brain is only secondarily involved.

A '—' sign in Table 1 indicates that there is no *known* effect of a gene on a particular system; it does not mean that the gene does not involve that system. For instance, all the genes Nos. 58–63 produce similar degenerations of the labyrinth; for 'waltzer' (No. 58), various cerebral anomalies have also been described, and for 'shaker-1' (No. 59) there is a report concerning the corpus striatum, with a mild internal hydrocephalus; as nothing is known concerning the CNS of the other mutants of this group, '—' signs occur in column 5 for 'shaker-2', 'jerker' and 'pirouette' (Nos. 60–62).

In view of these limitations, Table 1 can serve only for a first orientation of the subject.

Table 1 is followed (p. 7) by brief annotations on the mutant genes listed. These are in no sense to be taken as descriptions of the various conditions. They are merely intended as an elaboration of the tabulated data, and thus as a guide for the research worker to those conditions which may aid him in the solution of his own problems. Remarks on the various conditions sometimes merely take the form of broad indications, and frequently some fairly important aspects of a mutant are not mentioned at all.

In the Annotations, the name of each mutant is followed, in brackets, by the genetical symbol and, where this is known, by the linkage group, expressed in roman numerals; linkage groups I–XIX are autosomal, while XX denotes the sex-linked genes carried in the X-chromosome.

The genetical literature on the house mouse up to the beginning of the year 1950 is surveyed in the second edition of *The Genetics of the Mouse*, which includes an extensive bibliography. Mutants described in that book have been marked with an asterisk (*) in the Annotations, and no references given in the

book are repeated in this catalogue; in some cases, references to more recent papers are given in the catalogue, but these constitute only a very small selection from the recent literature. In the case of the forty-one conditions not included in the book there is a somewhat fuller documentation, although in several this is far from complete.

LABORATORY ANIMALS BUREAU AND 'MOUSE NEWS LETTER'

The laboratories which maintain the various mutant genes listed in Table 1 can be located through the mimeographed 'Mouse News Letter'* which is issued twice yearly. Research workers interested in a particular mutant cannot usually obtain fixed or otherwise preserved material direct from these laboratories; they will often, however, be able to acquire one or two breeding pairs of animals from which they can establish a substrain of their own. It should be pointed out that the maintenance of most of these mutant genes requires the use of certain special genetical techniques; workers unfamiliar with these techniques will therefore do well to ask for expert advice before starting their own colony.

* Obtainable on application to the Laboratory Animals Bureau, Medical Research Council Laboratories, Holly Hill, Hampstead, London, N.W.3.

II. Classified List of the Main Mutant Genes of the House Mouse

TABLE 1

(See p. 2 for the significance of '+' and '—' signs)

Annotation No.	Mutant gene	Structure or organ system affected										
		1 Coat and/or eye colour	2 Spotting	3 Skin and hair structure	4 Endocrine system	5 Central nervous system	6 Labyrinth	7 Eye	8 Skeleton	9 Blood	10 Urogenital system	11 Alimentary canal
1.	a. chinchilla	+	—	—	—	—	—	—	—	—	—	—
	b. extreme dilution	+	—	—	—	—	—	—	—	—	—	—
	c. albino	+	—	—	—	—	—	—	—	—	—	—
2.	a. Yellow	+	+	—	+	—	—	—	—	—	—	—
	b. White-bellied agouti	+	—	—	—	—	—	—	—	—	—	—
	c. Grey-bellied agouti	+	—	—	—	—	—	—	—	—	—	—
	d. black-and-tan	+	—	—	—	—	—	—	—	—	—	—
	e. non-agouti	+	—	—	—	—	—	—	—	—	—	—
3.	a. brown	+	—	—	—	—	—	—	—	—	—	—
	b. cordovan	+	—	—	—	—	—	—	—	—	—	—
4.	Light	+	—	—	—	—	—	—	—	—	—	—
5.	a. maltese dilution	+	—	—	—	—	—	—	—	—	—	—
	b. dilute-lethal	+	—	—	—	+	—	—	—	—	—	—
6.	leaden	+	—	—	—	—	—	—	—	—	—	—
7.	misty	+	+	—	—	—	—	—	—	—	—	—
8.	taupe	+	—	—	—	—	—	—	—	—	—	—
9.	a. pink-eyed dilution	+	—	—	—	—	—	—	—	—	—	—
	b. ruby	+	—	—	—	—	—	—	—	—	—	—
10.	pallid	+	—	—	—	—	+	—	—	—	—	—
11.	ruby-eye	+	—	—	—	—	—	—	—	—	—	—
12.	pearl	+	—	—	—	—	—	—	—	—	—	—
13.	silver	+	—	—	—	—	—	—	—	—	—	—
14.	Tabby	+	—	+	—	—	—	—	+	—	—	—
15.	Mottled	+	—	—	—	—	—	—	—	—	—	—
16.	Brindled	+	—	+	—	—	—	—	—	—	—	—
17.	Tortoiseshell	+	—	+	—	—	—	—	+	—	—	—
18.	piebald	—	+	—	—	—	—	—	—	—	—	—
19.	a. Dominant spotting	—	+	—	—	—	—	—	—	+	+	—
	b. ,, viable allele	+	+	—	—	—	—	—	—	+	+	—
20.	Splotch	—	+	—	—	+	—	—	+	—	—	—
21.	belted	—	+	—	—	—	—	—	—	—	—	—
22.	ruby-spotted	+	+	—	—	—	—	—	—	—	—	—
23.	waved-1	—	—	+	—	—	—	+	—	—	—	—
24.	waved-2	—	—	+	—	—	—	+	—	—	—	—
25.	Caracul	—	—	+	—	—	—	—	—	—	—	—
26.	Rex	—	—	+	—	—	—	—	—	—	—	—
27.	wellhaarig	—	—	+	—	—	—	—	—	—	—	—
28.	fuzzy	—	—	+	—	—	—	—	—	—	—	—

TABLE 1 (*continued*)

Annotation No.	Mutant gene	Structure or organ system affected										
		1 Coat and/or eye colour	2 Spotting	3 Skin and hair structure	4 Endocrine system	5 Central nervous system	6 Labyrinth	7 Eye	8 Skeleton	9 Blood	10 Urogenital system	11 Alimentary canal
29.	rough	−	−	+	−	−	−	−	−	−	−	−
30.	frizzy	−	−	+	−	−	−	−	−	−	−	−
31.	Ragged	+	−	+	−	−	−	−	−	−	−	−
32.	furless	−	−	+	−	−	−	−	−	−	−	−
33.	crinkled	+	−	+	−	−	−	−	+	−	−	−
34.	ichthyosis	−	−	+	−	−	−	−	+	−	+	−
35.	matted	+	−	+	−	−	−	−	−	−	−	−
36.	Alopecia	−	−	+	−	−	−	−	−	−	−	−
37.	a. hairless	−	−	+	−	−	−	−	−	−	−	−
	b. rhino	−	−	+	−	−	−	−	−	−	−	−
	c. bald	−	−	+	−	−	−	−	−	−	−	−
38.	Naked	−	−	+	−	−	−	−	−	−	−	−
39.	hypotrichosis juvenilis	−	−	+	−	−	−	−	−	−	−	−
40.	pituitary dwarfism	−	−	−	+	−	−	−	+	−	+	−
41.	obese	−	−	−	+	−	−	−	−	−	+	−
42.	absence of corpus callosum	−	−	−	−	+	−	−	−	−	−	−
43.	Loop-tail	−	−	−	−	+	−	−	+	−	+	−
44.	curly-tail	−	−	−	−	+	−	−	+	−	−	−
45.	hydrocephalus-1	−	−	−	−	+	−	−	+	−	−	−
46.	hydrocephalus-2	−	−	−	−	+	−	−	+	−	−	−
47.	hydrocephalus-3	−	−	−	−	+	−	−	+	−	−	−
48.	Trembler	−	−	−	−	+	−	−	−	−	−	−
49.	reeler	−	−	−	−	+	−	−	−	−	−	−
50.	jimpy	−	−	−	−	+	−	−	−	−	−	−
51.	ducky	−	−	−	−	+	−	−	−	−	−	−
52.	jittery	−	−	−	−	+	−	−	−	−	−	−
53.	agitans	−	−	−	−	+	−	−	−	−	−	−
54.	ataxia	−	−	−	−	+	−	−	−	−	−	−
55.	Wabbler-lethal	−	−	−	−	+	−	−	−	−	−	−
56.	vacillans	−	−	−	−	+	−	−	−	−	−	−
57.	'myelencephalic' blebs	−	−	+	−	+	−	+	+	−	+	−
58.	waltzer	−	−	−	−	+	+	−	−	−	−	−
59.	shaker-1	−	−	−	−	+	+	−	−	−	−	−
60.	shaker-2	−	−	−	−	−	+	−	−	−	−	−
61.	jerker	−	−	−	−	−	+	−	−	−	−	−
62.	pirouette	−	−	−	−	−	+	−	−	−	−	−
63.	Varitint-waddler	+	+	−	−	+	+	−	−	−	−	−
64.	shaker-short	−	−	−	−	+	+	−	+	−	−	−
65.	kreisler	−	−	−	−	+	+	−	+	−	−	−
66.	fidget	−	−	−	−	+	+	+	+	−	−	−
67.	dreher	−	−	−	−	−	+	−	+	−	−	−
68.	Twirler	−	−	−	−	−	+	−	+	−	−	−
69.	Zigzag	−	−	−	−	−	+	−	+	−	−	−

TABLE 1 (*concluded*)

Annotation No.	Mutant gene	Structure or organ system affected										
		1 Coat and/or eye colour	2 Spotting	3 Skin and hair structure	4 Endocrine system	5 Central nervous system	6 Labyrinth	7 Eye	8 Skeleton	9 Blood	10 Urogenital system	11 Alimentary canal
70.	shaker with syndactylism ..	−	−	−	−	−	+	−	+	−	−	−
71.	deaf	−	−	−	−	−	+	−	−	−	−	−
72.	anophthalmia	−	−	−	−	−	−	+	−	−	−	−
73.	rodless retina	−	−	−	−	−	−	+	−	−	−	−
74.	retinal degeneration	−	−	−	−	−	−	+	−	−	−	−
75.	lens rupture	−	−	−	−	−	−	+	−	−	−	−
76.	cataracta subcapsularis ..	−	−	−	−	−	−	+	−	−	−	−
77.	eyelids open at birth ..	−	−	−	−	−	−	+	−	−	−	−
78.	dystrophia muscularis ..	−	−	−	−	−	−	−	−	−	−	−
79.	grey-lethal	+	+	−	−	−	−	−	+	−	−	+
80.	a. microphthalmia	+	+	−	−	−	−	+	+	−	−	+
	b. White	+	+	−	−	−	−	+	−	−	−	−
81.	congenital hydrocephalus ..	−	−	+	−	+	−	−	+	−	−	−
82.	short-ear	−	−	−	−	−	−	−	+	−	+	−
83.	pygmy	−	−	−	−	−	−	−	+	−	−	−
84.	undulated	−	−	−	−	−	−	−	+	−	−	−
85.	tail-kinks	−	−	−	−	−	−	−	+	−	−	−
86.	Bent-tail	−	−	−	−	−	−	−	+	−	−	−
87.	vestigial-tail	−	−	−	−	−	−	−	+	−	−	−
88.	Crooked-tail	−	−	+	−	+	−	+	+	−	−	+
89.	Tail-short	−	+	−	−	+	−	−	+	−	−	−
90.	Pintail	−	−	−	−	−	−	−	+	−	−	+
91.	Hook	−	−	−	−	−	−	−	+	−	−	+
92.	Brachyury	−	−	−	−	+	−	−	+	−	−	+
93.	a. Fused	−	−	−	−	+	+	−	+	−	+	+
	b. Kinky-tail	−	−	−	−	−	+	−	+	−	−	−
94.	screw-tail	−	−	−	−	−	−	−	+	−	−	+
95.	posterior reduplication ..	−	−	−	−	−	−	−	+	−	+	+
96.	hemimelia tibiae (luxate) ..	−	−	−	−	−	−	−	+	−	+	−
97.	luxoid	−	−	−	−	−	−	−	+	−	−	−
98.	brachypodism	−	−	−	−	−	−	−	+	−	−	−
99.	syndactylism	−	−	−	−	−	−	−	+	−	−	−
100.	Oligosyndactylism	−	−	−	−	−	−	−	+	−	−	−
101.	oligodactylism	−	−	−	−	−	−	−	+	−	+	−
102.	preaxial polydactylism ..	−	−	−	−	−	−	−	+	−	−	−
103.	postaxial polydactylism ..	−	−	−	−	−	−	−	+	−	−	−
104.	siderocyte anaemia (flexed)	−	+	−	−	−	−	−	+	+	−	−
105.	another anaemia	−	−	−	−	−	−	−	−	+	−	−
106.	Danforth's short-tail ..	−	−	−	−	−	−	−	+	−	+	+
107.	uro-recto-caudal syndrome	−	−	−	−	−	−	−	+	−	+	+
108.	imperforate vagina	−	−	−	−	−	−	−	−	−	+	−
109.	harelip and cleft palate ..	−	−	−	−	−	−	−	+	−	−	+
110.	Hydrops	−	−	−	−	+	−	−	+	−	−	−

III. Annotations

1. *Chinchilla*, extreme dilution* and albinism** (c^{ch}, c^e, c; I)

The three members of the albino series, all recessive to full colour (*C*) but intermediate in the compounds c^{ch}/c^e, c^{ch}/c and c^e/c, dilute both the black and brown eumelanins and the yellow phaeomelanin pigment. 'Chinchilla' removes most of the yellow and a little of the black pigment; 'extreme dilution' removes all the yellow and a large part of the black pigment; 'albinos' are snow-white with pink eyes.

2. *The agouti series** (A^y, A^w, A, a^t, a; V)

The hairs of the coat of the normal mouse show a banded or 'agouti' pattern, so called after a South American rodent which shows it particularly clearly. Each individual hair has a black (eumelanin) tip, a yellow (phaeomelanin) sub-apical band and a dark (eumelanin) base. The members of this series of multiple alleles do not affect the total quantity of pigment formed, but determine its nature, whether phaeomelanin, or eumelanin, or a rhythmical alternation between the two. In 'Yellow' (A^y), all the pigment formed, except in the eyes, is phaeomelanin; the next two genes show the typical agouti pattern, A^w with a light and *A* with a dark belly; a^t or 'black-and-tan' has a glossy black back (eumelanin only) but a cream-coloured belly; and *a* or 'non-agouti' has black eumelanin only on the back and belly. The genes are dominant over each other in the order given, A^y being the top dominant and *a* the bottom recessive.

'Yellow' heterozygotes (A^y/A^w, A^y/A, A^y/a^t, A^y/a) tend to become very obese in middle life and sometimes show signs of early sterility; while this suggests involvement of the endocrine system, there is little histological evidence in that direction (Mayer, 1953). 'Yellow' homozygotes (A^y/A^y) are inviable; they die as early embryos at about the time of implantation in the uterine mucosa and are subsequently absorbed.

3. *Brown* and cordovan* (b, b^c; VIII)

'Brown' is a recessive gene for brown rather than black eumelanin. The recently described allele for 'cordovan' (Miller and Potas, 1955) produces a rich deep brown colour; it is recessive to black, but dominant over 'brown'.

4. *Light** (*Lt*; VIII)

The homozygote *Lt*/*Lt* has almost white hair, except for the hair tips which are 'hair brown'; the *Lt*/+ heterozygotes have darker tips known as 'chaetura drab' (both on the Ridgway colour scale), the pigment extends farther down the hair, and the lower part of the hair is very light grey. *Lt* is closely linked to *b* (No. 3) and may be an allele of that gene.

5. *Maltese dilution* and dilute lethal* (d, d^l; II)

The 'blue' dilution produced by these recessive genes is due to clumping of melanin pigment into a few large lumps, some of them near the hair roots; the actual quantity is slightly increased rather than reduced. The original allele of the Mouse Fancy (*d*) is fully viable. 'Dilute lethal' (d^l) from the age of about 10 days onwards shows a neurological syndrome including clonic convulsions with opisthotonus which proves fatal at the age of about three weeks (Searle, 1952).

6. *Leaden** (*ln*; XIII)

This recessive gene is a close mimic of 'Maltese dilution' (No. 5), even as regards the clumping of hair pigment.

---

* See Grüneberg (1952) for a description of this gene.

7. *Misty** (*m*; VIII)

'Misty' is a recessive gene producing a rather slight dilution of fur colour. A possible effect in the heterozygous condition is slight spotting (white tail tip and an occasional white belly spot).

8. *Taupe* (*tp*; I)

'Taupe' is a recessive gene diluting black to grey or sepia colour; it is similar in appearance to 'ruby-eye' (No. 11), but without dilution of eye colour (Fielder, 1952). While the mammary gland tissue is normal, the nipples seem to be defective.

9. *Pink-eyed dilution* and ruby** (*p*, p^r; I)

The recessive gene for 'pink-eyed dilution' (*p*) drastically reduces black and brown eumelanin pigment, but has little effect on the yellow phaeomelanin. The eye colour is pink. The effect of the gene for 'ruby' (p^r) on coat colour is similar to that of *p*, but less extreme. The eye colour varies from pink through ruby to almost black, and is often asymmetrical in the two eyes (heterochromia iridis).

10. *Pallid** (*pa*; V)

The recessive gene for 'pallid' reduces both eumelanin and phaeomelanin pigment; the coat is therefore rather paler than in 'pink-eyed dilution' (No. 9); the eyes are pink. 'Pallid' mice tend to lack otoliths of the sacculus or the utriculus or both (Lyon, 1953, 1955a).

11. *Ruby-eye** (*ru*; XII)

This recessive gene dilutes black to a sepia colour. The eyes are almost unpigmented at birth like those of an albino, but darken later to a ruby colour.

12. *Pearl* (*pe*)

On a black background the fur looks rather like that of 'ruby-eye' (No. 11), but has a much lighter under-fur which becomes visible on blowing. Yellow pigment is diluted to a cream colour. The eye colour is little affected except in combination with brown, when the eyes have a ruby tint (Sarvella, 1954).

13. *Silver** (*si*; IV)

'Silver' is a recessive gene causing an admixture of white hairs in the fur. In some combinations the under-fur is almost white.

14. *Tabby* (*Ta*; XX)

This sex-linked semi-dominant gene (Falconer, 1953) shows the same effect in hemizygous (*Ta*/–) males and in homozygous (*Ta*/*Ta*) females; the effects are manifold, and remarkable in that they are an exact replica of the effects of the autosomal recessive gene for 'crinkled' (No. 33). The adult fur lacks the guard hairs and zigzag hairs; a conspicuous area of bare skin behind each ear is due to the fact that zigzags only are found there in the normal mouse. The tail generally lacks hair and tail rings, and it usually has some sharp flexures near the tip. Most agouti 'Tabbies' show a dark streak along the back due to a local absence of agouti banding. Some of the sensory (sinus) hairs of the face are absent. The aperture of the eyelid is smaller than normal. In females heterozygous for 'Tabby' (*Ta*/+) there is some characteristic black transverse banding of the fur which has suggested the name of the mutant; it is due to local absence of agouti banding and is more conspicuous in the baby fur than it is later on.

15. *Mottled* (*Mo*; XX)

This sex-linked semi-dominant gene (Fraser, Sobey and Spicer, 1953; Falconer, 1953) in heterozygous (*Mo*/+) females, shows irregular areas of light-coloured (off-white) hair scattered without pattern over the body; occasionally the light

areas form an irregular transverse pattern as in 'Tabby' heterozygotes. The whiskers (vibrissae) are curled instead of being straight. Many 'Mottled' females and all hemizygous (*Mo*/—) males die as 11-days-old embryos.

16. *Brindled* (*Br*; XX)

'Brindled' females (*Br*/+) are very similar to 'Mottled' females (No. 15). The hemizygous 'Brindled' males (*Br*/—) survive to full term; they are almost white except for ears and eyes, with strongly curled vibrissae and some similar involvement of the body fur. They die at the age of about a fortnight, the cause of death being so far unknown (Fraser *et al.*, 1953). 'Brindled' and 'Mottled' show about the same crossover percentage with 'Tabby', and may be alleles (Falconer, 1953).

17. *Tortoiseshell* (*To*; XX)

This sex-linked semi-dominant gene (Dickie, 1954) in heterozygous (*To*/+) females, resembles 'Mottled', the coat consisting of mottled black, brown, yellow, grey and almost white hairs. The hair is silky with slightly waved vibrissae. Some of the *To*/+ females show slight skeletal defects on fore and hind limbs. No similar males have been observed; they presumably die as embryos as in the case of 'Mottled'. The relationship of 'Tortoiseshell' to 'Mottled' and 'Brindled' has not yet been investigated; perhaps all three genes are alleles.

18. *Piebald** (*s*; III)

The gene for recessive or 'piebald' spotting produces sharply distinct areas of white and pigmented fur which are often asymmetrical in individual mice but show a characteristic pattern when the distribution of pigmented and white areas in a group of such mice is considered. Centres of depigmentation are the forehead, feet and distal part of the tail, the umbilical region of the belly, a belt round the waist and a collar round the neck. These can run together in various ways, the total amount of white varying within wide limits depending on the company of (minor) spotting genes in which *s* finds itself. All spotting genes tend to interact with each other.

19. *Dominant spotting** (*W*, W^v; III)

Two alleles of this gene are known, *W* with an inviable and W^v with a viable homozygote. The spotting produced by these genes in the heterozygous condition (*W*/+; W^v/+) is a variegation with diffuse patches of white and often an intermixture of white and pigmented hairs. The degree of spotting depends greatly on the genetic background. W^v/+ heterozygotes also show a general dilution of the pigmented areas which is not present in *W*/+ heterozygotes. The *W*/*W* homozygote is very anaemic at birth and dies within a few days; it can be kept alive by intraperitoneal blood injections (transfusions) and then grows up to be a black-eyed white mouse. The viable W^v/W^v homozygote shows a similar (normochromic macrocytic) anaemia of lesser intensity; it is a black-eyed white mouse and nearly always sterile (Coulombre and Russell, 1954). The *W*/+ heterozygote has a normal blood picture, but the W^v/+ heterozygote is mildly macrocytic, though not clinically anaemic. The anaemia of W^v/W^v mice persists throughout life and is refractory to liver and folic acid treatment; an effect of liver treatment has, however, been reported in the W^v/+ heterozygote. There is a voluminous recent literature on the subject, much of it in Italian (Bianchi and Manera, 1953; Russell and Fondal, 1951; Russell, Snow, Murray and Cormier, 1953).

20. *Splotch** (*Sp*; XIII)

The heterozygote of this semi-dominant gene shows some spotting, mainly on the belly. The *Sp*/*Sp* homozygotes are completely inviable and die as

13-days-old embryos; they show spina bifida with overgrowth of neural tissue, often cranioschisis, reduction or absence of spinal ganglia, and a curly tail. Transplantation experiments show that the skin of *Sp/Sp* homozygotes is incapable of forming melanin pigment (Auerbach, 1954).

21. *Belted** (*bt*; VI)

'Belted' is a recessive gene causing spotting mainly in the belt region round the waist.

22. *Ruby-spotted*

This recessive gene combines spotting of the piebald type with a dilution of eye colour to a ruby tint; there is no dilution of black or chocolate coat-colour. Homozygotes die round about weaning time from causes not yet ascertained (Weir, 1951).

23–27. *The 'rexoid' coat characters**

The following five coat-waving genes have very similar effects:

23. waved-1* (*wa*-1; XI)
24. waved-2* (*wa*-2; VII)
25. Caracul* (*Ca*; VI)
26. Rex* (*Re*: VII)
27. wellhaarig* (*we*; V)

'Caracul' and 'Rex' are dominant with viable homozygotes; the others are recessive. All of them show curled whiskers and a kind of Persian-lamb-like waviness of the fur which is very obvious in the baby fur, but disappears in later hair generations; however, the coat remains short throughout life. 'Waved-1' and 'waved-2' sometimes have the eyelids open at birth, thus exposing the eyes to injury at a time before regular lid movements and protective reflexes are established (Butler and Robertson, 1953).

28. *Fuzzy** (*fz*; XIII)

In this recessive condition the hair is very thin and faintly wavy; the same applies to the vibrissae, which are not curled as in the 'rexoid' mutants. Of the four hair types distinguished in the normal fur (guard hairs, awls, auchenes and zigzag hairs) the first three categories seem to be missing altogether, while the zigzags are atypical.

29. *Rough* (*ro*; V)

In this recessive condition the vibrissae are waved as in the 'rexoid' characters, but the hairs of the coat are not wavy. The coat looks untidy and, in albinos, somewhat off-white. The hairs have thickened internal septa and reduced air-spaces, many of which contain fluid rather than air. The hairs are also greasier than in a normal mouse (Falconer and Snell, 1952).

30. *Frizzy* (*fr*; I)

In this recessive condition the whiskers are curly or wavy and remain so throughout life. The baby coat is somewhat short and rough, and for a short time slightly wavy. Later on, the coat is short and thin. It contains all four hair types, but the coarser types (guard hairs, awls and auchenes) are scanty, most of the fur consisting of the fine zigzag hairs (Falconer and Snell, 1952).

31. *Ragged* (*Ra*; V)

Heterozygotes for this semi-dominant gene (*Ra*/+) show a sparse, non-waved fur which includes many guard hairs, awls and auchenes, but only a small proportion of zigzag hairs. In agouti mice the middle of the back is much darker than usual. 'Ragged' homozygotes (*Ra*/*Ra*) are often born with a massive generalized oedema, and few of them survive the first few days. Those which do

are almost completely naked, except for a few hairs posteriorly and on the belly and a few sinus hairs, though these are usually short (Carter and Phillips, 1954).

32. *Furless* (*fs*)

In this recessive condition, the baby coat is lost from about the 19th day onwards. Depilation starts by thinning of the hair between the eyes and then spreads over the whole body. About the sixth week a new coat is produced, but this also is soon lost, and adult mice show at any one time a varying amount of hair, being rarely as completely naked as 'hairless' mice (No. 37). The second coat grown after the first depilation contains all four types of hairs, but all of them are shorter than normal (Green, 1954).

33. *Crinkled** (*cr*; XIV)

This autosomal recessive condition is indistinguishable in appearance from the homozygote and hemizygote of the sex-linked 'Tabby' (No. 14). There is absence of guard and zigzag hairs, with a bare patch behind the ears, and a dark coloration along the back in agoutis. The tail is bare and without rings, but with some kinks near the tip. Some sensory hairs of the face are absent.

34. *Ichthyosis** (*ic*)

The primary anomaly of this recessive condition seems to reside in the skin, the fur being only secondarily involved. The skin is dry, hard, and becomes scaly; the scales are sometimes small, but occasionally hard and plate-like, and then are shed only with difficulty. The dry skin of the tail usually forms some rings which interfere with the circulation and lead to necrosis of the tail tip. In adult life, ichthyotics may grow a thin curly coat or they may remain almost completely bare except for a few short curly whiskers. Most males fail to develop a scrotum, while in females the vaginal opening is usually displaced forward over the pubic symphysis and effectively closed.

35. *Matted* (*ma*)

In this recessive condition the hairs are inflexible and brittle and stand up (Searle and Spearman, 1956); clumping of hairs occurs when the coat is licked with normal saliva (moistened paint-brush effect). The skin histology is normal and the hair follicles have well-formed end bulbs. The hairs are imperfectly keratinized in patches along the fibres as shown by fluorochrome fluorescence. Breakage may occur in all hairs except the sinus hairs, but the resulting baldness is less severe than in 'Naked' (No. 38) or in 'Alopecia' (No. 36). Black melanin changes to a brown colour in old broken hairs.

36. *Alopecia* (*Al*)

In this semi-dominant condition abnormal animals can first be identified at the age of 25–32 days. *Al*/+ heterozygotes lose all their hairs except the guard hairs on the ventral surface, and the rest of the coat, which is not shed, is not quite so smooth as that of a normal mouse. At the same time, *Al*/*Al* homozygotes lose all but the guard hairs over the whole of their body surface. Following this moult, the other hairs are replaced and the coat for a time appears almost normal; but at each successive moult, replacement becomes less and less complete and the animals look very patchy (Dickie, 1955).

37. *Hypotrichosis cystica* (*hr**, hr^{rh}*, hr^{ba}; III)

The following three alleles of this gene have been described:

a. hairless (*hr*)
b. rhino (hr^{rh}) and
c. bald (hr^{ba}).

In all three mutants, a normal baby fur is formed; this is shed during the third and fourth week so that the animals are then almost completely naked. The shedding starts on the head and, in 'hairless', proceeds in a sharply defined wave in a posterior direction; in 'rhino', the hair loss is usually more diffuse, and 'bald' (Garber, 1952a) is intermediate in this respect. Later hair generations are shed almost as soon as they are formed; they become increasingly feeble so that the animals are practically naked throughout their lives. In older animals the skin becomes progressively thickened by the formation of cysts from hair roots and sebaceous glands; this process is comparatively slight in 'hairless', more marked in 'bald', and very extreme in 'rhino' where it leads to the formation of enormous skin folds. In all three mutants the claws become long and spiralized; whether this is due to overgrowth or to reduced wear and tear is not certain.

38. *Hypotrichosis hypokeratotica** (*Naked*, *N*; VI)

Heterozygotes for this semi-dominant gene ($N/+$) grow a baby fur which is, however, not so sleek as that of normal mice. During the second and third week the hairs break off above the skin level, except at the nose, feet, tail, and genital region, the process starting on the head and spreading in a posterior direction. Later hair generations, which become increasingly irregular, share the same fate, but $N/+$ mice usually show more or less irregular patches of hair belonging to different hair generations simultaneously, and thus usually do not look as bare as 'hairless' mice (No. 37). The claws are not affected. N/N homozygotes never grow a complete coat and lack the sensory hairs. The claws are underdeveloped and abnormal in structure. The anomalies of $N/+$ and N/N are due to a dyskeratosis or hypokeratosis.

39. *Hypotrichosis juvenilis** (*hj*)

A recessive condition in which anomalies are confined to the baby fur while the adult coat is completely normal. This gene is now extinct.

40. *Pituitary dwarfism** (*dw*)

This much-studied recessive condition is basically due to reduction or absence of eosinophil cells in the anterior lobe of the pituitary. Virtually all the other endocrine organs are secondarily involved to a greater or less extent. 'Pituitary dwarfs' react to parabiosis with a normal mouse, to implantation of normal pituitaries and to the administration of various endocrine preparations.

41. *Obese* (*ob*)

This recessive condition (Ingalls, Dickie and Snell, 1950) has given rise to an extensive American literature, some of which has been summarized (Mayer, 1953; Mayer, Russell, Bates and Dickie, 1953). 'Obese' animals become inordinately fat, with weights of two or three times the normal. Both sexes are sterile. Obesity is associated with hyperglycaemia, glycosuria, increased resistance to insulin, and hyperplasia of the islands of Langerhans. The blood cholesterol is high. The basal metabolic rate is very low. The basic biochemical lesion of the obese animals seems to be a slowing down of the rate of oxidation of acetate to carbon dioxide and water. Whether this metabolic block is primarily enzymatic or hormonal is not yet clear.

42. *Absence of the corpus callosum** (*ac*)

Mice with this recessive anomaly lack the corpus callosum completely or in part, but have a tract of fibres (longitudinal callosal bundle) in the brain which does not occur in normal mice. Clinically, the animals are completely normal. The condition is now extinct.

43. *Loop-tail** (*Lp*; XIII)

In this semi-dominant condition the manifestation of abnormalities in the *Lp*/+ heterozygotes is incomplete. Many animals have a characteristic tail twist, and a somewhat greater proportion show a behavioural abnormality of the head, called 'wobbly'. Among *Lp*/+ females, the vagina often remains imperforate. *Lp*/*Lp* homozygotes are inviable; they can be recognized from the ninth embryonic day onwards by non-closure of the mesencephalon and hind brain (cranioschisis) which is often, but not always, accompanied by an extreme degree of spina bifida (craniorachischisis). Embryological work (Stein and Rudin, 1953) indicates that in the neighbourhood of the optic stalk there is an increased mitotic activity in the nervous system, while in the spinal cord this does not seem to be the case.

44. *Curly-tail* (*ct*)

This recessive condition (Grüneberg, 1954a) has an extremely irregular manifestation, and on most genetic backgrounds the majority of homozygotes are phenotypically quite normal. Affected animals may have a tail twist like 'Loop-tail' (No. 43); if the twist is at the root of the tail, it is generally associated with spina bifida occulta. Spina bifida aperta of the lumbosacral region and, more rarely, cranioschisis, is found in some animals which die at birth. Embryological work shows that where a tail twist only is found, it is caused by a spina bifida confined to the tail region; later this is no longer recognizable because the spinal cord of the tail does not persist.

45–47. *Hydrocephalus*-1*, -2* and -3* (*hy*-1; V; *hy*-2; *hy*-3)

Three recessive genes for hydrocephalus have been described; the first two of these, *hy*-1 and *hy*-2, were genetically distinct from each other; both are now extinct. The third gene, *hy*-3, has not been tested against the two older ones; it is thus not known whether it is a distinct entity or an allele of one of the older genes. All three genes produce an internal hydrocephalus which increases during the first few weeks and usually leads to a dome-shaped, much enlarged calvarium. In the case of *hy*-3, at any rate, many affected animals, though their development is retarded and they ultimately die soon after weaning, show no overall enlargement of the cerebral hemispheres. There are detailed studies concerning the embryonic developments of *hy*-1, and particularly of the cerebellum, whose vermis is reduced or absent; see, however, Grüneberg (1952).

48. *Trembler** (*Tr*; VII)

The dominant gene for 'Trembler' in young mice produces a spastic paralysis, particularly of the hind limbs, an action tremor, and epileptiform convulsions which occur either spontaneously or on stimulation. Later in life, the convulsions tend to disappear and the spasticity becomes less marked, but the action tremor remains unchanged. No anatomical lesions have been discovered in the cerebrum, the cerebellum or the spinal cord; electrocorticograms were normal, and the acetylcholine system at the motor endplates has shown no abnormalities (Braverman, 1953).

49. *Reeler** (*rl*; III)

Mice homozygous for this recessive gene can be recognized from the age of about a fortnight. Affected animals have difficulty in keeping their hindquarters upright; when running, they tend to fall over on their sides as if intoxicated, but they right themselves easily. There may be a slight tremor when the animals are excited and active. With increasing age, the tendency to fall over diminishes, but the gait remains abnormal.

50. *Jimpy* (*jp*; XX)

Mice carrying this sex-linked recessive gene (Phillips, 1954) show a marked intention tremor which is detectable from the age of about 11 days onwards. From the age of about three weeks there is a tendency to convulsions; when handled or otherwise disturbed, such mice may "become tensed, with head thrown back, fore limbs scrabbling and hind limbs stretched sideways." After such a seizure, which lasts for about five seconds, the mouse may return to normal, or "go into a rigid extensor tetanus with fore and hind limbs extended posteriorly and fingers and toes extended and abducted, with some flexing of the wrist." This lasts for about 20 seconds and is followed by a period of about 15 seconds during which the mouse lies on its side. 'Jimpy' mice die some time during the 4th to 6th week.

51. *Ducky* (*du*; II)

The behaviour of mice homozygous for the recessive gene for 'ducky' has been described as follows (Snell, 1955): "The first expression is usually a slightly hunched appearance and a toeing out of the hind feet. In more advanced stages there is a waddling or reeling gait and a tendency to fall to one side. In older animals the toeing out usually disappears, but the reeling and falling become more pronounced, the gait suggesting intoxication. In some partly grown mice the first manifestation noted may be jumpiness and an absence of co-ordinated running. In such cases, however, the reeling and falling appear after the excitement of a few minutes of handling." 'Ducky' mice can usually be recognized clinically during the third or fourth week, but sometimes not until they are 40 days old. They may reach sexual maturity and breed.

52. *Jittery** (*ji*; X)

Mice homozygous for this recessive gene can be recognized at the age of about a fortnight or earlier. Muscular incoordination is shown by the zigzag course which the animals follow in attempting to maintain an upright position while running. Soon they are no longer able to run for any distance without falling, and they tend to move about by creeping. Epileptiform convulsions make their appearance early on. Death takes place when the animals are about a month old.

53. *Agitans* (*ag*)

Mice homozygous for the recessive gene for 'agitans' (Hoecker, Martinez, Markovic and Pizzaro, 1954) can be recognized at the age of about 10 days. A generalized tremor, which may be present at rest but increases in intensity during purposeful movements, is combined with ataxia and restlessness. The gait is stiff-legged and hurried; the mice often fall over sideways, or their hind legs give way so that they come to rest on their haunches, from which position they can get up only with difficulty. Later the gait changes to a duck-like waddle, with legs held wider apart than in normal mice. A few 'agitans' mice live to the age of 2–3 months, but are sterile. Anatomically there is some atrophy and degeneration of Purkinje cells in the cerebellum which is not yet detectable in 9–13 days old 'agitans' mice (Martinez and Sirlin, 1955).

54. *Ataxia* (*ax*)

Mice homozygous for this recessive gene (Lyon, 1955b) can be recognized when about a week old by hyperactivity and walking with unduly straight legs. Later, the hyperactivity is lost, and a paresis of all four limbs develops, along with tremor, loss of co-ordination of the limbs, and muscular weakness. In the end, the mouse can no longer maintain itself in the prone position, but

lies on its side and tries to drag itself along very slowly with the forelegs. Death occurs as a result of intercurrent diseases when this stage of complete helplessness has been reached.

55. *Wabbler-lethal* (*Wl*)

This gene is semi-dominant, as heterozygotes can be recognized by experienced observers by certain minor features of behaviour. Homozygotes can be identified some time during the third week by their difficulty in walking. "The animals pulled their hind feet along rather than actually shoving with them and in their effort to walk their whole bodies shook and shimmied." (Dickie, Schneider and Harman, 1952). Affected animals die round about weaning time. Myelin degeneration, as studied by the Marchi technique, affects various components of the vestibular, spinal and cerebellar systems in the order of their myelination, and has been regarded as probably the primary lesion. The telencephalon is not affected.

56. *Vacillans* (*vc*; VIII)

Mice homozygous for this recessive gene (Sirlin, 1956) can be identified at the age of a fortnight or a little earlier by a tremor when they attempt to walk and by a swaying movement of the hindquarters. Later the gait becomes duck-like. There are certain atypical reflexes, e.g. locking of hands and feet on being picked up by the tail, and the muscular vigour is reduced. Both sexes may be fertile.

57. '*Myelencephalic*' *blebs** (*my*)

The manifestation of this recessive condition is very irregular; most homozygotes show part of the syndrome only, and some are completely normal. Anomalies produced by this gene include various eye defects, club feet, syndactylism, hypodactylism, polydactylism, pseudencephaly (anencephaly), aplasia of one or both kidneys, hydronephrosis, and other rarer effects (Carter, 1956). Most of the foot and eye anomalies are mechanically caused by sub-epidermal blebs of a clear liquid which are present in 12- to 13-day-old embryos, or by thrombi which form in some of the peripheral vessels. It has been claimed that the sub-epidermal blebs contain cerebrospinal fluid which has oozed through the area membranacea of the fourth ventricle and travelled under the skin towards the eyes and limbs. It has recently become clear (Grüneberg, 1955b) that the blebs cannot contain CSF; in any case, some of the effects of this gene, e.g. pseudencephaly, kidney anomalies, must be due to different mechanisms.

58–63. *Waltzer-shaker mutants; degenerative group*

There are altogether twelve mutants with similar behaviour anomalies (Nos. 58–69). These fall into two sharply distinct groups of six genes each: the first of these includes conditions with a labyrinth which is normal as far as its main features are concerned, but in which degenerations occur in post-natal life; the second includes gross disturbances in morphogenesis of the labyrinth which arise early in embryonic life. The degenerative group includes the following six genes:

58. waltzer* (*v*; X)
59. shaker-1* (*sh*-1; I)
60. shaker-2* (*sh*-2; VII)
61. jerker* (*je*; XII)
62. pirouette* (*pi*; III)
63. Varitint-waddler* (*Va*)

Nos. 58–62 are recessive and cannot be recognized in the living mouse except by its abnormal behaviour; No. 63 is semi-dominant; heterozygous 'Varitint-waddlers' (*Va*/+) have a curious combination of colour dilution and spotting of the fur; some of the pigmented areas of the fur are dilute and become lighter with age; *Va*/*Va* homozygotes are lighter in colour and, in addition to the classical symptoms of the group, have a tendency to epileptiform seizures. The typical symptoms of the group consist of circular movements, head-shaking or tossing in a dorsal direction, and deafness. The behaviour anomalies can be recognized at the age of 12–14 days or earlier. Deafness is present from the beginning in all these mutants except 'shaker-1' which can hear for a short time before becoming deaf. All six mutants have a similar pathology of the labyrinth (Deol, 1954, 1956a). The main features of the labyrinth are normal, and histological maturation of the neuro-epithelia etc. proceeds normally; this is, however, followed by a de-differentiation of Corti's organ, degeneration of the spiral ganglion, and abnormalities in the stria vascularis. The vestibular apparatus (maculae, cristae ampullares, ganglion vestibulare) is involved in all six mutants, though to a varying extent. The mutants differ from each other quantitatively and in the time of onset of the various defects. 'Shaker-1' also has some internal hydrocephalus, apparently as the result of a reduction in the corpus striatum.

64–69. *Mutants with morphogenetic defects of the labyrinth*

Of the following six mutants, the first four are recessive, the others dominant or semi-dominant; No. 64 is now extinct.

64. shaker-short* (*st*)
65. kreisler* (*kr*; V)
66. fidget* (*fi*; V)
67. dreher (*dr*)
68. Twirler (*Tw*)
69. Zigzag (*Zg*)

'Shaker-short' combines cerebral hernias and shortening of the tail with a very rudimentary labyrinth without division into separate chambers, without an endolymphatic duct and without semicircular canals. In the case of 'kreisler', there is no endolymphatic duct and no sacculus, and the semicircular canals are often imperfect; the ductus cochlearis does not form a spiralized cochlea. Presumably as a result of the absence of normal drainage by way of the endolymphatic duct, the pressure of the endolymph is greatly increased, and cysts, often quite large, evaginate through the internal acoustic meatus. In the case of 'fidget' (Truslove, 1956), the cochlea is normal and the animals can hear, but the semicircular canals are rudimentary; in addition, there are eye abnormalities (corneal ulcers, absence of lacrimal glands, etc.) and there is often an involvement of the skeleton, particularly of the fossa acetabuli, with occasional dislocation of the hip; there is also polydactylism of the hind feet in many 'fidgets'. In 'dreher' (Falconer and Snell, 1952; Hertwig, 1955) the ductus endolymphaticus is absent or reduced, the sacculus and utriculus are not separate from each other, and there are considerable defects of the semicircular canals. The cochlea is normal in its main features. In post-embryonic life, the walls of the membranous labyrinth are distended at the expense of the perilymphatic spaces, as in 'kreisler'. 'Twirler' (Grüneberg, 1956b), which can hear, shows absence of otoliths and reduction and malformation of the semicircular canals. 'Zigzag' mice

(Grüneberg, 1956b) walk with a zigzag motion of the head and make frequent changes of direction. One or both horizontal semicircular canals are missing. The sense of hearing is not affected.

The gross defects of the labyrinth in all these mutants arise early in embryonic life. The behaviour of the animals is similar to that of the mutants of the degenerative group (Nos. 58–63) and includes circling and head shaking, but only 'shaker-short', 'kreisler', and 'dreher' are deaf; the others can hear.

70. *Shaker with syndactylism** (*sy*)

This recessive mutant combines skeletal with labyrinthine anomalies. The membranous labyrinth is normal at birth, but from about the third day onwards there is a progressive atrophy which leads to a narrowing of the semicircular canals and of the sacculus and utriculus, and to a collapse of the scala media cochleae (Hertwig, 1951). Syndactylism is present on most hind feet, but is often absent in the forefeet; it involves either digits 2 and 3, or 3 and 4, or all three of them; there are also extensive fusions between carpals and tarsals. Additional anomalies are present in certain other elements of the skeleton (Grüneberg, 1956a).

71. *Deaf* (*df*)

'Deaf' is a recessive gene for deafness without locomotor disturbances (Deol, 1956b). The anomalies of the cochlea are like those of the degenerative mutants (Nos. 64–69), i.e., de-differentiation of the organ of Corti, degeneration of the spiral ganglion, and anomalies of the stria vascularis cochleae. The vestibular apparatus is not involved.

72. *Anophthalmia** (*ey*-1 and *ey*-2)

There is virtually complete absence of the eyes in about 90 per cent of the animals, and reduced eyes up to nearly normal eyes in the remainder. This condition is probably due to the combined action of two pairs of genes, 'eyeless-1' and 'eyeless-2' which, singly, do not usually have this effect. One of them is carried in the inbred strain, C57BL, in which reduced eyes are found in a small percentage of animals. See also Garber and Hauth (1950).

73. *Rodless retina** (*r*; IV)

In this recessive condition, now extinct, the outer nuclear layer together with the rods of the retina is either completely absent or greatly reduced. In rodless mice, the separation into inner and outer nuclear layers, which normally begins towards the end of the first week after birth, either does not take place at all, or produces only a rudimentary outer layer with rudimentary rods.

74. *Retinal degeneration*

In this recessive condition (Brückner, 1951; Tansley, 1954; Sorsby, Koller, Attfield, Davey and Lucas, 1954) the retina undergoes a rapid and complete degeneration of the outer nuclear layer and the rods during the third week of life. The authorities disagree as to whether the degeneration occurs in a retina which was completely normal (Tansley, 1951; Karli, 1951) or whether the last stages of histological maturation were already defective (Sorsby *et al.*, 1954). It is also contested whether initial stages of degeneration can already be made out from the tenth day onwards, i.e., before full maturity of the retina (Karli, 1951). Secondary changes in the retina and choroid, including pigment migration into the retina, resemble retinitis pigmentosa in man.

75. *Lens rupture** (*lr*)

'Lens rupture' is a recessive type of cataract in which much of the lens substance, including the lens nucleus, is extruded into the vitreous through a

lesion in the posterior lens capsule. The remainder of the lens is often torn from its suspensory ligaments and may be displaced into the anterior chamber of the eye; it may get stuck in the pupil and is then constricted into a dumb-bell shape.

76. *Cataracta subcapsularis*

The age of onset of this dominant condition varies between 10 days and 14 weeks (Paget, 1953). Liquefaction of a subcapsular zone between the cortex and the nucleus of the lens leads to cataract of the cortex and the lens nucleus. The lens capsule always remains intact. With the exception of the nucleus, the whole lens material may become liquefied, and much of it may pass through the intact lens capsule into the vitreous.

77. *Eyelids open at birth**

The normal mouse is born with its eyelids closed; they open at about 14 days after birth. Mice born with open eyelids have their eyes exposed in the nest to injuries, such as corneal erosions, which may lead to ulcers with later corneal opacities, or to deeper infections with cataract or panophthalmitis ending in phthisis bulbi. 'Eyelids open at birth' has been described as an independent entity which is probably determined by several genes (Hauschka and Brown, 1954). It also occurs as an effect of certain hair-waving genes, such as 'waved-1' and 'waved-2' (Butler and Robertson, 1953).

78. *Dystrophia muscularis* (*dy*)

In this recessive condition (Michelson, Russell and Harman, 1955) there is a general and progressive atrophy of the muscles of trunk and limbs, convulsive nodding of the head, kyphosis, and a paresis of the hind limbs which is accompanied by spasmodic flexion and flaccid extension and ultimately leads to complete paralysis of the hind limbs and premature death. Pathologically, the condition seems to be a primary myopathy, both the central and the peripheral nervous system being apparently normal.

79. *Grey-lethal** (*gl*)

This recessive gene combines absence of yellow (phaeomelanin) pigment in the fur with complete absence of secondary bone absorption. As a result, all bones develop characteristic shape-anomalies during growth (Bateman, 1954), there is retention of all the teeth, and the animals die on weaning. Reciprocal transplantation experiments show that 'grey-lethal' bone is absorbable, and that 'grey-lethal' parathyroids produce parathormone. It is probable that 'grey-lethals' in some way inactivate parathormone, to which they are also very resistant, when it is injected.

80. *Microphthalmia* and White** (*mi*, Mi^{wh}; XI)

Two different alleles of this gene are known (Grüneberg, 1953c). 'White' (Mi^{wh}) is semi-dominant. Heterozygotes show a dilution of the eumelanin pigment both in fur and, to a slight extent, in the eyes, together with some white spotting. Homozygotes are completely white with pink eyes like albinos; the eyes are microphthalmic to a varying extent and sometimes have a fine ring of pigment round the pupil. The gene for 'microphthalmia' (*mi*) in heterozygotes dilutes the eye colour but not the fur pigmentation; on certain genetic backgrounds it also produces some spotting. The *mi*/*mi* homozygote is snow-white with pink eyes; the eyes are microphthalmic (Müller, 1950, 1951/2); there is a virtually complete absence of secondary bone absorption as in the 'grey-lethal' (Bateman, 1954), but it is not uncommon for some molars to erupt, and occasionally some incisors also, and this, where it occurs, permits survival.

81. *Congenital hydrocephalus** (*ch*; XIV)

This recessive gene is lethal at birth. Homozygotes have a congenital hydrocephalus with shortening of the basis cranii, absence of the calvarium, eyelids open at birth, and anomalies of certain sensory (sinus) hairs on the face. The anomalies of the base of the skull which give rise to the hydrocephalus are part of a general disturbance of the skeleton, including larynx and trachea, which takes place in the mesenchyme stage (Grüneberg, 1953b).

82. *Short-ear** (*se*; II)

'Short-ear' is a recessive gene with widespread skeletal effects, including ear and larynx, all of which are comparatively minor in character, or at any rate not grossly pathological. 'Short-ear' animals tend to have a defect of the diaphragm, and hydronephrosis is fairly common (Green, 1951; McNutt, 1954).

83. *Pygmy** (*pg*)

This recessive gene reduces body-weight to about one half of the normal at the age of six weeks; a slight effect on body-weight is present in heterozygotes. No gross defects of the skeleton or endocrine organs have been discovered (King, 1955).

84. *Undulated** (*un*; V)

'Undulated' is a recessive gene which affects the axial skeleton from one end to the other (atlas-axis fusions; reduction of transverse and spinous processes; split lumbar vertebrae; reduction of tail length to about 80 per cent, etc.). In addition, the acromion scapulae is absent as an osseous element, but is represented by a ligament, with muscular anomalies in that neighbourhood. The development of 'undulated' indicates that material normally incorporated into the vertebrae is included in the intervertebral discs (Grüneberg, 1954b).

85. *Tail-kinks* (*tk*)

'Tail-kinks' is a recessive gene with effects on the axial skeleton (Grüneberg, 1955b). The cervical and upper thoracic regions are grossly abnormal, with involvement also of ribs and sternum. The lower thoracic and lumbar region is only slightly affected, but the tail, in particular its distal parts, is again highly abnormal. The anomaly can be traced to early defects in the differentiation of the sclerotomes. The distribution of abnormalities over the vertebral column is such that the vertebrae derived from small somites at the two ends of the vertebral column are severely affected, while vertebrae derived from the large somites in the middle are almost immune. 'Tail-kinks' increases the number of presacral vertebrae (Grüneberg, 1955a).

86. *Bent-tail* (*Bn*; XX)

This sex-linked semi-dominant gene (Garber, 1952b) manifests itself regularly in hemizygous (*Bn*/—) males, but overlaps normal in some heterozygous (*Bn*/+) females. The main effects on the tail are a reduction in size of the vertebrae which becomes more marked distally, and, in males, a reduction of the number of tail vertebrae by about four or five. The smallest of the tail vertebrae tend to ossify from bilateral twin centres (Grüneberg, 1955c).

87. *Vestigial-tail* (*vt*; VII)

In this recessive condition, the tail is absent except for a stump or a small filament (Heston, 1951). The number of presacral vertebrae is reduced (Grüneberg, 1955a).

88. *Crooked-tail* (*Cd*)

Heterozygotes for this semi-dominant gene (*Cd*/+) may have tail kinks, but are sometimes quite normal externally. Many homozygous (*Cd*/*Cd*) embryos

die in early stages of development, some live to develop pseudencephaly (anencephaly), and a minority are born alive. The latter always remain small and have a multitude of abnormalities: the lower incisors are rudimentary and do not erupt, while the upper incisors are normal; third molars are often absent; characteristic fusions of vertebrae occur in the lumbo-sacral region and the proximal tail; the tail is usually kinky, almost devoid of hair, and there are few or no tail rings; the eyes are reduced in size and sometimes absent; nervous head movements are common (Morgan, 1954).

89. *Tail-short* (*Ts*)

In heterozygotes (*Ts*/+), the head is wider and shorter, the body is shortened, and the tail is short and kinky or altogether absent. Additional effects sometimes encountered are foot anomalies, which may occur on the forefeet or hind feet; these are of various kinds, and include syndactylism, oligodactylism, polydactylism and others. Spotting and spina bifida have also been observed. These effects vary with the genetic background, and in some cases the *Ts*/+ heterozygote seems to be virtually incompatible with life. The *Ts*/*Ts* homozygote is probably always lethal (Morgan, 1950).

90. *Pintail* (*Pt*; VIII)

In this semi-dominant gene, the tail is shortened to a varying degree; the proximal caudal vertebrae are always normal; structural anomalies start abruptly some way along the tail. Homozygotes tend to be more strongly affected than heterozygotes; they also sometimes show atresia ani and similar malformations. Surviving homozygotes may be quite vigorous and may breed (Hollander and Strong, 1951).

91. *Hook* (*Hk*)

In this dominant gene, the end of the tail is curved ventrally like a fish-hook; the anus is displaced posteriorly, often on to the ventral surface of the tail; it is slit-like rather than circular, and a depression sometimes extends from the 'high vent' along the ventral surface of the tail for some distance. While the manifestation of the anomaly of the anus seems to be regular, the tail hook is sometimes absent. Some homozygotes at least seem to be viable (Holman, 1951).

92. *Brachyury** (*T*, t^o, t^1, etc.; IX)

For details about this genetically very complicated series of multiple alleles see Grüneberg (1952). *T*/+ mice lack the distal part of the tail to a greater or less extent, and *T*/*T* mice die as 10-days-old embryos. Defects of the notochord seem to be responsible in each case. There exists a long series of '*t*' alleles which, in T/t^n heterozygotes, lead to complete absence of the tail. Such *t* genes are very common in wild mouse populations (Dunn and Morgan, 1953); they are recessive in combination with the wild-type normal allele ($+/t^n$), but many of them are lethal in t^n/t^n homozygotes. In addition to the anomalies of the axial skeleton, there are also defects of the neural tube and occasional anomalies like intestinal atresia, etc.

93. *Fused** *and Kinky-tail** (*Fu*, Fu^{Ki}; IX)

These two semi-dominant genes are probably alleles (Dunn and Gluecksohn-Waelsch, 1954). Both produce shortening of the tail, usually associated with ankyloses of tail vertebrae, in the heterozygous condition, and both may produce head-shaking, circling, and deafness, like that in the 'shaker-waltzer' group (Nos. 58–63). 'Fused', which may overlap normal both in *Fu*/+ and in *Fu*/*Fu* mice, also produces abnormalities (fusions, etc.) of the ribs and occasionally

bifurcation of the tail; there is anaemia at birth and occasionally also spina bifida; in *Fu*/*Fu* homozygotes, absence or abnormalities of the kidneys have been reported. While *Fu*/*Fu* homozygotes are viable, Fu^{Ki}/Fu^{Ki} homozygotes die in embryonic life; they show all intergrades between complete twinning, double (or even triple) monsters or duplication of parts of the embryo, and a mere hyperplasia of neural ectoderm, etc.

94. *Screw-tail** (*sc*)

This recessive gene causes widespread effects in skeleton and dentition. The tail at birth is spirally twisted due to a shortening of the tendons. Various vertebrae ossify from bilateral twin centres rather than from a single centre. The number of presacral vertebrae is increased. The sternum is shield-like and not segmented as in a normal mouse, except for the xiphoid process; the cause of the sternal abnormalities is a reduction in embryonic rib growth. There are numerous anomalies in the skull and in dentition (Bhaskar, Schour, MacDowell and Weinmann, 1951); the latter include lack of occlusion of the incisors and lack of occlusion, stunting, and impaction of the molars.

95. *Posterior reduplication**

This condition is probably due to a constellation of genes rather than to a single-gene difference. The manifestation is very variable and ranges from complete duplication of the hind parts of the body down to quite rudimentary forms which would hardly be recognized as belonging to this type of anomaly when found by themselves.

96. *Hemimelia tibiae** (*luxate*, *lx*; III)

The gene for 'luxate' is semi-dominant; many heterozygotes show preaxial polydactylism or triphalangy of the hallux or both. In *lx*/*lx* homozygotes, the tibia is more or less reduced; it may be absent altogether, or its proximal end may be osseous while its distal end is represented by a ligament. The hallux is triphalangous and often duplicated; in more extreme cases there may be, on the other hand, oligodactylism with absence of digit 1 and sometimes even digit 2. The forelimbs are never affected. The number of presacral vertebrae is decreased. In the urogenital system, hydronephrosis and horse-shoe kidney are commonly encountered (Carter, 1953, 1954).

97. *Luxoid* (*lu*)

While the effects of this gene are, superficially, very similar to those of 'luxate' (No. 96), in several respects they tend in the opposite direction. The +/*lu* heterozygote on certain genetic backgrounds shows preaxial triphalangy or polydactylism of the hind limbs, or both. The same effects occur in the *lu*/*lu* homozygote, with occasional cases of preaxial reduction. The tibia is reduced to a varying extent. Unlike 'luxate', preaxial triphalangy or polydactylism may occur in the forelimbs. Tail kinks are commonly found in *lu*/*lu* and perhaps in +/*lu*. Again, *lu*/*lu* increases rather than decreases the number of presacral vertebrae, of pairs of ribs and, very slightly, of sternebrae (Green, 1955).

98. *Brachypodism* (*bp*; V)

In this recessive condition (Landauer, 1952) the hands and feet are much reduced. Metacarpals and metatarsals are considerably shortened, and each digit lacks one phalanx; other bones of the hands and feet are also reduced. There are supernumerary metacarpals and metatarsals. The long bones of the limbs are also somewhat shortened, those of the hind limbs more than those of

the forelimbs, and the proximal bones (humerus, femur) more than the distal ones (ulna, tibia). The general body size and the remainder of the skeleton are not affected.

99. *Syndactylism* (*sm*)

In this recessive condition, all four feet are regularly affected (Grüneberg, 1956a). 'Syndactylism' involves primarily digits 3 and 4, and digit 2 is often also affected. Fusions are usually osseous in the hind feet, but are often only of soft tissue in the forefeet. Phalanges only are involved, usually all three of them, while metacarpals and metatarsals are not affected. The naviculare and cuboideum tend to be fused. The fusions between phalanges are primary, those between tarsalia secondary. Many *sm*/*sm* mice have anomalies in the distal half of the tail.

100. *Oligosyndactylism* (*Os*)

The homozygote of this semi-dominant gene is inviable (Grüneberg, 1956a). All four feet of *Os*/+ heterozygotes are regularly affected; syndactylism is usually confined to digits 2 and 3; soft-tissue fusions are more common in the forefeet, hard-tissue fusions in the hind feet. Fusions first involve the phalanges and then also the metacarpals and metatarsals. Complete fusion may lead to a four-toed foot with a composite digit 2+3, or there may be complete absence of digit 2; sometimes the material for digit 2 seems to be shifted towards digit 1 which may then be duplicated. Extensive fusions in the carpus and tarsus are secondary, except that between cuboideum and cuneiforme 3, which is primary. Some fusions between phalanges are primary, but others, as well as fusions between metacarpals and metatarsals, are secondary.

101. *Oligodactylism** (*o*; I)

In this recessive condition there is a reduction of digits which starts on the postaxial (ulnar and fibular) side and, in extreme cases, may lead to reduction or absence of the latter elements as well (Freye, 1954). The forefeet are more severely affected than the hind feet, and the left side more severely than the right. In the carpus and tarsus, there is loss on the postaxial side as well as fusion of some elements. The 13th pair of ribs is absent, and there may be fusions between ribs and between sternebrae. The tail is shortened and often kinky, and in extreme cases there are anomalies, as in the 'uro-recto-caudal syndrome' (No. 107). Reduction in the size of the spleen, cystic and horse-shoe kidneys, and absence of the kidneys are common.

102. *Preaxial polydactylism of the hind feet** (*py*; XIII)

Preaxial polydactylism of the hind feet, i.e., involving the hallux, can occur as a single-gene effect (Fisher, 1953). The same anomaly can also appear as part of more complicated syndromes ('myelencephalic' blebs, 'fidget', 'luxate', 'luxoid') and as a result of a constellation of several genes (Chase, 1951).

103. *Postaxial polydactylism of the forefeet*

A rudimentary extra digit on the ulnar side of the forefeet (Center, 1955) is probably due to the interaction of several genes rather than to a single pair of genes.

104. *Siderocyte anaemia* (*flexed-tail belly-spot*)* (*f*; XIV)

This recessive gene combines ankyloses of the tail vertebrae and some belly spotting, neither of which is regularly present, with an embryonic anaemia which always manifests itself. The anaemia is not present in the primitive (yolk sac) generation of red blood cells, which are fully haemoglobinized. It comes into being with the intermediate (liver) erythrocytes, which are normocytic

hypochromic, and contain free (non-haemoglobin) iron in granular form (siderocytes). The anaemia disappears spontaneously as the intermediate generation of erythrocytes is replaced by the definitive red blood cells during the first two or three weeks after birth. A small percentage of siderocytes is, however, present in the circulation throughout life.

105. *Another anaemia** (*an*; VIII)

This recessive anaemia (Thoms, 1951–2; Kunze, 1954) starts early in embryonic life, but reaches its greatest severity a few days after birth; a small minority only of the affected animals survive into adult life; they are always sterile. The anaemia is normochromic and nearly normocytic (slightly macrocytic) with reduced reticulocyte values on an absolute, and usually also on a relative, basis. The liver of newborn young contains fewer haemopoietic foci than in normal animals, and these also disappear more quickly. The bone marrow is deficient in cells and contains few normoblasts. The anaemia has been interpreted as due to progressive insufficiency of the erythropoietic tissues (Kunze, 1954).

106. *Danforth's short-tail** (*Sd*; V)

This semi-dominant gene affects the skeleton and the urogenital system. In *Sd*/+ heterozygotes, there is early degeneration of the distal part of the tail, almost complete breakdown of the whole notochord with absence of the nucleus pulposus from the intervertebral discs, and absence of the odontoid process of the axis (Grüneberg, 1953a; Theiler, 1952, 1954); the latter situation leads to the formation of an atypical articulation between atlas and axis. Depending on the genetic background, there may be various malformations of ureter and kidney, up to complete absence of both kidneys; the more extreme forms of abnormality in *Sd*/+ mice are, of course, inviable. *Sd*/*Sd* homozygotes are tailless, with imperforate anus, absence of a rectum, and a persistent cloaca; kidneys and ureters are usually completely absent; a bladder may be present, but is usually small; the genital papilla is absent or much reduced.

107. *The uro-recto-caudal syndrome** (*ur*)

By itself this recessive gene, in homozygous condition (*ur*/*ur*), produces shortening and kinkiness of the tail, cleft palate, and disturbances of normal kidney function as shown by reduced alkaline phosphatase activity of the kidneys and an increased relative water content of the newborn animals; the kidneys are not grossly abnormal morphologically (Gluecksohn-Waelsch and Kamell, 1955). Soon after birth, the animals with cleft palate die as a result of difficulties in breathing and sucking; the few survivors develop hydronephrotic or polycystic kidneys in later life. In combination with members of the 'Brachyury' (*T*) series (No. 92), *ur*/*ur* mice have a similar 'imperforate' syndrome as *Sd*/*Sd* homozygotes; i.e., imperforate anus, absence of rectum, persistent cloaca, etc. Kidney abnormalities are also often observed in such animals; they are, however, more like those encountered in the case of 'myelencephalic' blebs (No. 57).

108. *Imperforate vagina**

This condition is probably due to a combination of genes rather than to a single 'main' gene. The same condition is often encountered in *Lp*/+ heterozygotes (No. 43).

109. *Harelip and cleft palate**

This condition is very similar anatomically to the corresponding human malformation; it is probably due to a constellation of genes rather than to a

single 'main' gene. It occurs frequently in a highly inbred strain of mice ('A' strain). The genetics of a type of median harelip (with a cleft separating the incisors) is not completely known; the entity is now extinct.

110. *Hydrops*

The 'hydrops' of mice (Hertwig, 1955) traces back to a male whose sire had been subjected to X-ray treatment. In this strain, various types of anomaly are encountered. These include embryos with pseudencephaly, hydropic animals which die soon after birth, and various other lethal types which die in the first few weeks; the latter include one group of young with a characteristic stilt-like gait and degenerative processes in the flocculus cerebelli. It has been suggested that the anomalies found in this stock are the result of a reciprocal translocation between two chromosomes. On this interpretation, the various anomalies, at least in part, represent different unbalanced genotypes; they are not, as in many of the other conditions described in this catalogue, variable expressions of the same gene mutation.

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