Chapter 2

Normal Genetics, Genetic Disorders, Developmental Anomalies and Breeding Programs

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NORMAL GENETICS

Basic Principles of Genetics

It is convenient in zoologic research to have a standard against which deviating forms can be compared. In genetics, it is the phenotype of the normal animal; the "wild type," as it is formally termed. For the domestic cat, this is the smooth-coated mackerel-striped tabby African wild cat, *Felis libyca*. *Felis libyca* is one of a group of small cats inhabiting much of Asia and North Africa. The European wild cat, *Felis silvestris*, is akin to the African wild cat and the 2 species are regarded by some authorities to be geographic forms of a species complex.[31] The domestic cat (*Felis catus*) is almost certainly a domesticate of *F libyca*.

The early association between cats and people was probably a checkered affair because cats have a weak bonding instinct in comparison to dogs. The true domestication of cats was credited to the Ancient Egyptians about 4000 years ago. Domestication may have begun slowly, with cats living close to granaries and their inherent rodent population. The Egyptians revered many animals, and cats featured prominently in both life and death.[1,18] The cat slowly became a religious symbol, to be cherished and protected.

Subjugation of the Egyptians by the Romans secularized the cat, and the animal began to travel beyond the borders as a fascinating household companion. The Romans were primarily responsible for the spread of cats across Europe. There may have been other centers of origin of domestication of cats in the Middle East and India, but these are poorly documented. Other sources contain more detailed discussion on the origin of domesticated cats.[4,19,33]

Feline Karyotype

Karyotype refers to the number and structure of chromosomes within the cell nucleus (karyon = nucleus). Domestic cats have a karyotype consisting of 19 pairs of chromosomes (Fig 1).[2,22] These 19 pairs of chromosomes consist of 5 metacentrics (2 large, 3 small), 11 submetacentrics (7 large, 4 small), and 2 acrocentrics (both small). The remaining pair of chromosomes comprise the sex chromosomes. The X is a medium-sized metacentric, while Y is a small metacentric. Females have 2 X sex chromosomes (Fig 1), while males have an X and Y. Individual chromosomes have characteristic internal banding patterns as prepared with the classic trypsin-Giemsa technique (G-banding) (Fig 1) or the Ronne method (R-banding).[22] The wild species *Felis silvestris* and *F libyca* have karyotypes that are identical to that of domestic cats.

Basic Laws of Heredity

Chromosomes are made of building blocks called genes. Genes are the basic de-

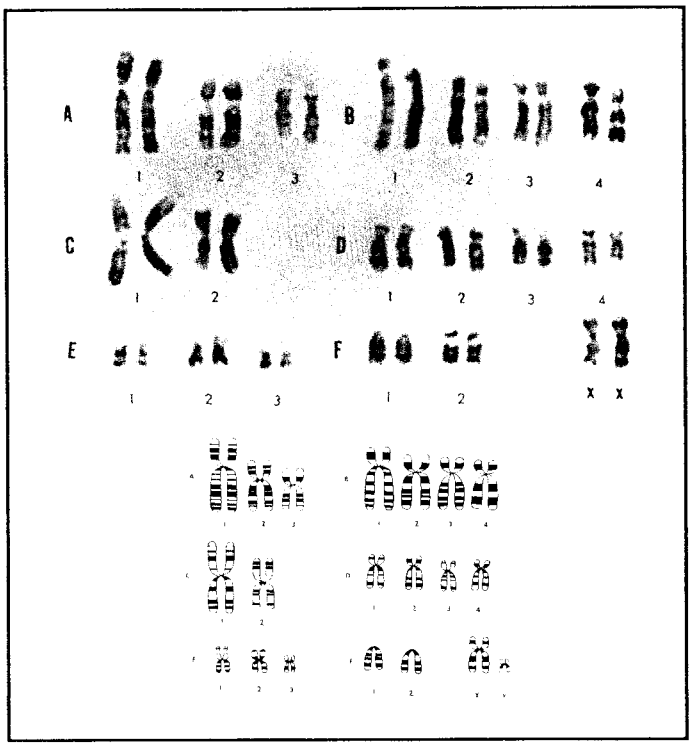


Figure 1. Top: The normal karyotype (19 pairs) of a normal female domestic cat by the G-banding (trypsin-Giemsa) technique.[2] Feline chromosomes are divided into 6 different groups (A-F) according to size and position of the centromeres. Bottom: A drawing of the normal karyotype of a male cat provides a better illustration of the position of the centromeres and the characteristic banding patterns on each pair of chromosomes. The bands correspond to regions within the chromosome that have distinctly different DNA structure, and hence staining affinity. Differences in DNA structure are due to differences in the structure of various genes found in each region. Because analogous genes are always found in the same locations (loci) and have the same basic DNA structure, the banding pattern is virtually identical from one cat to another. (Courtesy of Dr. K. Benirschke and *American Journal of Veterinary Research*)

terminants of heritable structure and function. Each gene provides the genetic code necessary for the cell to produce a single protein. Each protein product has a direct influence on the structure, function, metabolism and embryonic differentiation of cells.

Chromosomes exist as pairs in all body (somatic) cells (Fig 1). Each chromosome reproduces itself during somatic cell division, forming 2, rather than 1, pair of chromosomes. Two of the chromosomes go to 1 daughter cell and 2 to the other, thus restoring the original chromosome number. Body cells containing 1 pair of each of the 19 types of chromosomes are called diploid (di = 2).

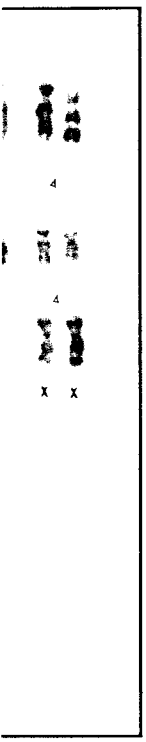
Figure 2. Checkerboard or Punnett square for deriving the expectations in matings of Aa x Aa. The gametes A and a from each parent are written across the top and down the left side of the diagram. The expectations are found by writing within each square the genotype of the sperm at the head of the column and the genotype of the ovum at the side of each row, continuing until each square is filled. The result is the genotypes to be expected for the mating.

	Genotype of Sperm	
	A	**a**
A	**AA**	**Aa**
a	**Aa**	**aa**

Genotype of Ovum

During sexual division in the ovaries or testes, however, the numbers of chromosomes are reduced. As the germ cell divides to produce either sperm or ovum, each pair of chromosomes is not duplicated. Rather, 1 chromosome of the pair goes into 1 of the daughter cells and 1 goes into the other. Sperm and ovum contain 19 single, or unpaired, chromosomes. Cells containing only 1 chromosome of each pair are called haploid (haplo = 1). The normal complement of 19 pairs of chromosomes is restored when sperm and ovum fuse.

Reduction of the number of chromosomes in sex cells, and its restoration by fertilization, is a key factor in genetic diversity. Genes on corresponding chromosome pairs are hardly ever identical to each other. Segregation of chromosome pairs during formation of sperm or ova allows for genes on 1 chromosome to dissociate themselves from genes on the corresponding chromosome. Fertilization not only restores the normal complement of chromosomes, but



allows a chromosome to pair with a new chromosome that will likely carry many different mutant genes.

Each chromosome is made up of several thousand individual genes. These genes are always found at specific sites along the chromosome. Sites where specific genes are found are called loci (Fig 1). Though genes have a high degree of constancy, they are subject to change or mutation. These changes cannot be so great, however, that the gene no longer codes for a functional protein. If the gene mutates too much, its product will be defective and may have a lethal or deleterious effect on the organism (see section on Genetic Defects).

Changes in the structure (genetic code) of a gene will give rise to mutant genes. A mutant gene at the same locus as the original or wild-type gene is called an allele. Allelic genes are somewhat different from the parent wild-type genes; thus the proteins they induce in the cell may be slightly altered as well. If these alterations are not deleterious, they are reflected in slight alterations in the gene protein product, and the structure and function of the cell. These alterations lead to the phenotypic differences among all individuals. Heredity involves transmission of mutant or allelic genes in relation to original or wild-type genes.

Monogenic Inheritance

The fact that chromosomes exist as pairs in body cells, and singlets in reproductive cells, greatly affects the way genes are distributed from parent to offspring. For convenience, genes are symbolized by letters of the alphabet. An underlined capital letter (A) is used for the normal gene, and an underlined lower-case letter (a) for the corresponding mutant allelic gene. If gene A has only 1 mutation, that is, a, these individuals will be genetically characterized as AA, aa or Aa in regard to this gene. AA, aa or Aa is the genetic constitution or genotype of the individual from the time of fertilization until death. Individuals with the same gene on each pair of chromosomes (AA or aa) are called homozygotes (homo = same). Individuals with different genes at the same locus on each pair of chromosomes (Aa) are called heterozygotes (hetero = different). Gametes (sperm or ova) produced by AA individuals are 100% A, while aa individuals produce gametes that are 100% a. The heterozygote (Aa), in contrast, has 50% of its gametes A and 50% a.

Transmission of the hypothetical A and a genes is shown in Table 1. Six different matings are possible and the genetic distribution of offspring is dictated by the random union of germ cells. For instance, the mating AA x Aa gives AA, Aa and aa progeny in the proportion of 25%, 50% and 25%, respectively. These proportions are more often expressed as ratios, such as 1:2:1, than percentages. The random nature of the union of A and a is shown by the checkerboard diagram of Figure 2. The checkerboard derives the expectation for the mating of Aa x Aa. A mating of homozygotes, such as AA x aa, is referred to as the parental (P_1 x P_2) or first-cross, and the offspring as the first filial generation (abbreviated F_1). Such a mating would produce 100% heterozygotes of the genotype Aa. The mating of Aa x Aa could be expressed as F_1 x F_1. This cross would yield the second filial (F_2) generation. These 2 fundamental crosses are employed in experimental genetics to determine the mode of inheritance (dominant, recessive) of a new mutant or allelic gene.

Table 1 shows the progeny of a mating based on the known genotype of the parents. The genotype, in turn, determines the outward appearance of the progeny. The outward or physical expression of the genotype is referred to as the phenotype. The phenotype results from the anatomic and biochemical effects that gene A or a has on development of the organism, beginning at the time the ovum is fertilized by the sperm. The genetic expression of the A gene can follow 1 of 3 patterns: dominant, co-dominant or recessive. Given allelic genes, such as wild-type A and mutant a, it is common for the wild-type gene to be dominant over the mutant gene. The dominant gene is usually written as a capital letter and the recessive gene as a lower-case letter. In the example of the A gene, A is dominant over a and gene a is recessive to A. In a simple dominance/recessive relationship, the dominant gene A "switches off" or represses the recessive gene a when both are present in the same cell. The repressed a gene cannot

produce its protein product. As such, it cannot have any influence on the anatomic or biochemical makeup (phenotype) of the individual. If the a gene were codominant, both the A and a gene products would be produced and both would affect the phenotype.

The effects of dominance are such that the genotypes AA and Aa are outwardly indistinguishable from each other, thus modifying the expectations of Table 1. The mating of 2 parents having genotypes AA and Aa produces offspring with 100% wild-type phenotype of genotype A-. The dash after A indicates that the identity of the second gene is unknown (it could be A or a, and the animal would have the same phenotype). With an Aa x Aa breeding, the offspring are phenotypically 75% A- and 25% aa. This last mating illustrates the well-known phenotypic ratio of 3:1 that results from the matings of 2 heterozygotes.

Multiple Alleles

If a gene can mutate once, it can do so again. An allelic series at the same gene locus could come into being by repeated mutations. Regardless of how many alleles occur, only 2 can be present in the individual, and each of these is transmitted to a different gamete. This rule is shown by the tabulation of matings listed in Table 2. The example presented is 3 alleles for tabby pattern (see later discussion for description of the alleles and phenotypes). With 3 alleles there are 21 possible matings. This results in the progeny expectations shown in Table 2.

Table 1. The descent of a pair of allelic genes for 6 possible matings. The expected frequencies for progeny are shown as percentages. When there is more than 1 type, these are frequently expressed as ratios of 1:1 or 1:2:1, as the case may be. These are known as Mendelian ratios for the assortment of a mutant gene.

	PROGENY (%)		
Mating	**AA**	**Aa**	**aa**
AA x AA	100	–	–
AA x Aa	50	50	–
AA x aa	–	100	–
Aa x Aa	25	50	25
Aa x aa	–	50	50
aa x aa	–	–	100

To demonstrate the descent of the alleles from parent to progeny, the genotypes are tabulated as if no dominance exists between alleles. If the alleles are dominant to each other, for example, T^a to T and t^b, and T to t^b, this aspect must be taken into account in deriving the phenotype. The genotypes are grouped as appropriate. The 1:1 and 3:1 ratios recur as shown for 2 allelic genes.

Note the symbolism for multiple alleles. It is conventional to denote the wild-type gene by a capital letter (here, T), and a recessive gene by a lower-case letter. If there are more than 1 recessive mutant alleles, the lower-case letter is augmented by superscripts (for example, t^b). If the mutant allele is dominant to the wild type, the allele is denoted by a capital letter with a superscript (for example, T^a). In this manner, gene symbols are not merely a convenient shorthand but also convey information.

Sex Linkage

Most gene loci are borne by the ordinary chromosomes or autosomes; hence, heredity is said to be autosomal. In addition to autosomal chromosomes, there is a pair of sex chromosomes denoted as X and Y. Chromosomally, the female is XX and the male is XY (Fig 1). Consequently, the X is sometimes referred to as the "female" and the Y as the "male" chromosome. The X is a large chromosome and probably contains as many gene loci as an autosome of comparable size. Genes carried by the X are known as sex-linked. The mode of inheritance of sex-linked traits is more complex than that for ordinary or autosomal genes.

A well-known example is sex linkage of hemophilia A, which occurs in people, dogs, horses and cats. The responsible gene is carried on the X chromosome and is recessive. It is lethal in males because males do not have a second X chromosome and, therefore, lack a normal compensating dominant allele. Hemophilia A is perpetuated by female heterozygotes. Representing the normal gene as X^H and the hemophiliac gene as X^h, the typical mating that produces a hemophiliac is X^HY x X^HX^h. The genotypic expectations are X^HX^H, X^HX^h, X^HY and X^hY in the ratio of 1:1:1:1. The phenotypic expectation is 2 normal females, 1 normal male and 1 hemophiliac male. One of the fe-

males is a carrier of the hemophiliac gene (X^HX^h).

In contrast to the X chromosome, the Y chromosome is small and carries few genes. Denoting the Y as the "male" chromosome is probably appropriate, because its primary function appears to be converting undifferentiated embryonic gonad tissue into testes. In anomalous XO individuals, where the Y has been lost, the gonads develop into ovaries. Phenotypically, XO individuals are female, even though their ovaries function less efficiently than those of normal XX females. Such individuals are usually sterile.

Bigenic Inheritance

Each chromosome of a pair is transmitted independently of other members of the pair. Genes on one of the chromosomes are inherited independently of genes on the other. It is necessary, therefore, to understand not only how single pairs of genes (A versus a) are inherited, but how many pairs of genes interact in the same mating.

The interaction of pairs of genes can be illustrated by 2 of the basic color mutants of cats. One is a gene for chocolate-brown pigment (b), a mutant allele of the black pigment (B) gene. The second is a mutant gene for slate-blue or dilute color (d), a mutant allele of dark or dense color (D). Allele b and d are inherited as recessive to B and D, respectively. When a brown (bbDD) is mated to a blue (BBdd), the progeny (BbDd) are black because of the dominance relationships of the 2 pairs of genes. When black F_1 offspring are mated together, the F_2 progeny assort into 9 black, 3 brown, 3 blue and 1 lilac.

The derivation of the above 9:3:3:1 ratio is shown by Figure 3. The checkerboard is merely an extension of that shown in Figure 2. This is the case for all checkerboards once the principle of their construction is understood. The above ratio is found by

Table 2. The descent of 3 allelic genes for 21 possible matings. The expectations may be shown alternatively as ratios. For example, the 25:50:25 percentages may be expressed as 1:2:1.

	PROGENY (%)					
Mating Type	T^aT^a	T^aT	T^aT^b	TT	Tt^b	t^bt^b
$T^aT^a \times T^aT^a$	100	–	–	–	–	–
$T^aT^a \times T^aT$	50	50	–	–	–	–
$T^aT^a \times T^at^b$	50	–	50	–	–	–
$T^aT^a \times TT$	–	100	–	–	–	–
$T^aT^a \times Tt^b$	–	50	50	–	–	–
$T^aT^a \times t^bt^b$	–	–	100	–	–	–
$T^aT \times T^aT$	25	50	–	25	–	–
$T^aT \times T^at^b$	25	25	25	–	25	–
$T^aT \times TT$	–	50	–	50	–	–
$T^aT \times Tt^b$	–	25	25	25	25	–
$T^aT \times t^bt^b$	–	–	50	–	50	–
$T^at^b \times T^at^b$	25	–	50	–	–	25
$T^at^b \times TT$	–	50	50	–	–	–
$T^at^b \times Tt^b$	–	25	25	–	25	25
$T^at^b \times t^bt^b$	–	–	50	–	–	50
$TT \times TT$	–	–	–	100	–	–
$TT \times Tt^b$	–	–	–	50	50	–
$TT \times t^bt^b$	–	–	–	–	100	–
$Tt^b \times Tt^b$	–	–	–	25	50	25
$Tt^b \times t^bt^b$	–	–	–	–	50	50
$t^bt^b \times t^bt^b$	–	–	–	–	–	100

counting the numbers of each color as determined by the genotypes and remembering that B and D are dominant to b and d, respectively. The 2 pairs of genes have combined at random in the F_2 to reproduce the original brown and blue and a new color, the lilac. This is a recombinant color, produced by the 2 genes b and d in individuals, with the genotype bbdd.

The variation produced by recombination of genes between disparate individuals is fundamental to both pure and applied genetics. The principle may be extended to 3, 4 or many pairs of genes. Such recombination has created the many breeds and varieties of cats existing today. The prime source of variation is gene mutation, but this can be greatly extended by recombination and selective breeding. The section on normal feline genetics describes the known mutant alleles of cats and how these have been used to diversify modern breeds.

Epistasis and Hypostasis

The above pairs of genes had phenotypic effects that were independently expressed, resulting in 4 distinct phenotypes by recombination. Pairs of genes frequently interact at a phenotypic level to interfere or prevent expression of one or the other, however. Black cats are a common example of this phenomenon. Tabby cats may be striped or blotched, due to the genes T and t^b, respectively. The tabby pattern occurs in conjunction with the agouti gene A, responsible for the grayish background coloration. The A gene has a mutant allele a, which produces a solid-black cat. The tabby pattern is not manifested upon a totally black background; hence, the a gene obscures or masks expression of the T and t^b genes. This phenomenon is termed epistasis. Gene a is said to be epistatic to T and t^b. Conversely, genes T and t^b are said to be hypostatic to a. Other cases of epistasis/hypostasis are described in later sections.

Figure 3. Checkerboard for deriving the expectations for the simultaneous inheritance of 2 pairs of genes (B versus b, and D versus d). The procedure is the same as that for the simpler checkerboard of Figure 2. The genotypes of the gametes (sperm or ovum) are formed by combining the 2 pairs of genes at random. These are entered within each of the 16 squares to give the genotypes to be expected for the mating. Phenotypes produced by the various genotypes depend upon the degree of dominance of members of gene pairs and interaction of expression between the 2 genes.

		Genotype of Sperm			
		BD	**bD**	**Bd**	**bd**
Genotype of Ovum	**BD**	**BBDD** Black	**BbDD** Black	**BBDd** Black	**BbDd** Black
	bD	**BbDD** Black	**bbDD** Brown	**BbDd** Black	**bbDd** Brown
	Bd	**BBDd** Black	**BbDd** Black	**BBdd** Blue	**Bbdd** Blue
	bd	**BbDd** Black	**bbDd** Brown	**Bbdd** Blue	**bbdd** Lilac

Linkage

Genes are not inherited independently if the 2 gene loci are on the same chromosome. Genes on the same chromosome tend to stay together during the splitting, randomization and recombining of chromosomes during gamete formation and fertilization. This phenomenon is known as linkage. Though one might assume that genes on the same chromosome maintain their relative positions indefinitely, this is not the case. Homologous chromosomes can exchange segments with each other at the time of cell division. The extent to which genes recombine in this manner depends upon their relative positions on the chromosomes. If 2 genes are situated close together, the likelihood that the chromosome will split between them is very small. If the 2 genes are situated some distance apart, the likelihood of such a split is much greater.

Polygenic Inheritance

Genetic variation is either qualitative or quantitative. Qualitative variation is produced by genes that have major effects upon the phenotype. Coat colors produced by the B, b, D and d genes are fitting examples. Allowing for dominance, each gene introduces a major qualitative change to the phenotype. Further, the change is consistent and the genes can be followed from generation to generation by phenotype. Such genes are

termed major genes, with reference to their major effects upon the phenotype.

Quantitative variation, on the other hand, varies from one extreme to the other, and no discontinuity is introduced by a single major gene. The classic example is body size, a characteristic that is easily determined by measurement or weight. The genetic component of body size is due to many different genes that have small effects singly, but large effects cumulatively. The combined effects of these genes produce increasing differences of size, depending upon their numbers and the direction in which they are acting. Such genes are termed minor genes, with reference to their minor individual effects upon phenotype. They are also called polygenes, referring to the number of genes required for the phenotypic expression of a single characteristic.

It is possible to conceive of groups of polygenes: positive polygenes when the effect of each polygene is to enhance the expression of a characteristic, and negative polygenes when the effect is to decrease the expression. Polygenes do not differ biochemically from major genes. The difference is only in the magnitude of their phenotypic effects. Though polygenes are not individually identifiable or easily manipulated, they are the basis of most selective breeding.

Polygenes are ubiquitous and there is no phenotypic characteristic they do not affect to some extent. The extent that polygenes affect the phenotype can be estimated by a factor known as heritability (symbol h^2). Information on the extent to which phenotypic variation may be genetically determined is useful, though interpretation can be tricky. In general, the higher the heritability of a polygenic characteristic, the greater the potential for selective breeding. Conversely, the lower the heritability, the greater the influence of the environment as compared to heredity. If the environment is standardized, and the heritability remains low and the variation large, either an unknown environmental factor has been overlooked or the specific heritability of the characteristic is not understood.

Polygenic inheritance can be manifested in 3 forms. First, it may appear as a "pure" polygenic character that varies continuously from one extreme to the other. Body size is an obvious example. Second, the polygenic variation may interact with a major gene. Such an example is hair length. Long hair is produced by a recessive gene (l); however, the hair length of long-haired (ll) cats is variable, and this is due to polygenes. The same polygenes induce variation in hair length in normal short-coated cats, but their effects are magnified in the presence of the l gene. Polygenes can affect the expression of a mutant gene. Such polygenes are frequently referred to as modifiers and are usually specific for the character they are affecting. Third, the mode of inheritance of a character may be polygenic, yet the expression differs sharply from what is expected. Examples are umbilical or inguinal hernias and cryptorchidism. Animals with one of these defects lack the requisite number of polygenes for normal development.

The distinction between normal and defective is abrupt but the underlying heredity is polygenic, not monogenic as might be anticipated. Such anomalies are known as threshold characters, the allusion being that the defect develops as a result of failure to attain a critical threshold of normal development. Characteristics that develop in this manner can be detected because their prevalence differs from the Mendelian expectation. The frequency of hernias or retained testicles may differ among strains or families of cats, reflecting differences in basic polygenic inheritance.

Color Variation

Free-living domestic cat populations are heterogeneous for coat color and hair quality; this situation has persisted for hundreds of years.[27] The numbers of mutant genes responsible for this variation are few, and their mode of inheritance and phenotype interactions have been largely elucidated.[10] Phenotypic variation was seized upon by cat fanciers (notably in Britain) in the latter half of the 19th century as the basis of breeds.[18,19] Names and exhibition standards of excellence were drafted for breeds with one or more different phenotypes.

Since these early days, additional mutant genes have been discovered that gave rise to further color varieties and styles of coat ac-

ceptable to cat fanciers. Today there is an impressive range of breeds of exhibition cats. A general discussion of the effects of mutant genes upon the phenotype and of the genotypes of breeds may be found in other sources.[16,20]

Table 3 lists the mutant genes found in various cat breeds.

Tabby Alleles

The wild-type tabby is the mackerel pattern of narrow vertical, slightly curving black stripes upon a yellowish-gray background (Fig 4). The stripes may be unbroken or broken into short bars or spots, particularly low on the sides and stomach. The tabby coat color is composed of 2 components: the agouti background and the tabby pattern.

The grayish background is known as agouti. Agouti is the universal camouflaging color of most mammals. It is especially common in rodents such as mice or rats. The coat is composed of black hairs subterminally banded with yellow; the tip is black, followed by a band of yellow and then black, which pales quickly to slate blue as the pigment granules become sparse toward the root. The "brightness" or yellowness of the coat usually depends upon the width of the yellow or agouti band. The tabby pattern is superimposed upon the agouti as a disruptive pattern. It tends to "break up" the outline of the animal, and is a supplementary form of camouflage. The pattern is created by the displacement of agouti-banded hairs with all-black hairs.

Figure 4. The mackerel or striped tabby pattern is found on many wild cat species. The mackerel pattern consists of black stripes with an intervening agouti ticking.

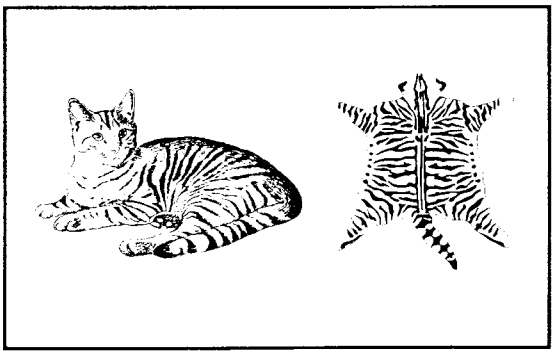


Table 3. Symbols and designations of mutant genes in cat breeds.

Symbol	Designation	Characteristic
a	Nonagouti	Self-color
b	Brown	Chocolate brown
b^1	Light brown	Cinnamon brown
c^b	Burmese	Dark sepia (sable)
c^s	Siamese	Light sepia (sealpoint)
c^a	Blue-eyed albino	White coat
c	Pink-eyed albino	White coat
Cu	Curl	Ear carriage
d	Blue dilution	Slate blue
Dm	Dilute modifier	Lighter blue
Fd	Folded ears	Ear shape
g	Gloving	White nose/paws
hr	Hairless	Absence of hair
I	Inhibitor	Pigment suppression
l	Long hair	Coat length
M	Manx	Taillessness
O	Orange	Red/cream color
p	Pink-eyed dilution	Tan color
Pd	Polydactyly	Extra toes
r	Cornish rex	Short coat
Rd	Dutch rex	Short coat
re	Devon rex	Short coat
ro	Oregon rex	Short coat
S	Piebald	White spotting
T^a	Abyssinian	Tabby pattern
t^b	Blotched tabby	Tabby pattern
W	Dominant white	White coat
Wh	Wire hair	Rough coat

The classic or "blotched" tabby pattern is distinctly different from the striped or mackerel tabby (Fig 5). The name is derived from the irregular spiral and whorls of tabby pattern on the sides of the animal. These may coalesce to form bars and blotches of color. The head markings are unchanged but the bars on the legs and rings of dark pigments on the tail are more pronounced. The overall effect is of a darker tabby. The blotched tabby is inherited as an autosomal recessive to the striped wild type and is symbolized by t^b.

The Abyssinian has a very different form of tabby markings. The amount of tabby markings is sharply reduced, with vestigial markings evident only on the face, lower parts of the legs, tail and flanks (Fig 6). This tabby is the basis of the Abyssinian breed and is inherited as an incomplete dominant to the striped tabby. It is symbolized by T^a.

The locus for the tabby alleles is symbolized as T and the blotched and Abyssinian

Figure 5. The blotched or classic tabby pattern is recessive to the striped tabby pattern. The colored stripes are arranged as irregular whorls and spirals. The ideal shoulder pattern resembles a "butterfly," while the flank should have a solid blotch of color encircled by one or more rings.

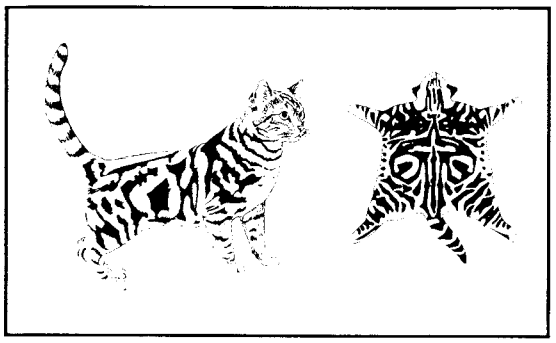


Figure 6. The Abyssinian tabby pattern is dominant to the mackerel or striped tabby patterns. Faint tabby markings remain on the face, and sometimes on the tail and lower legs.

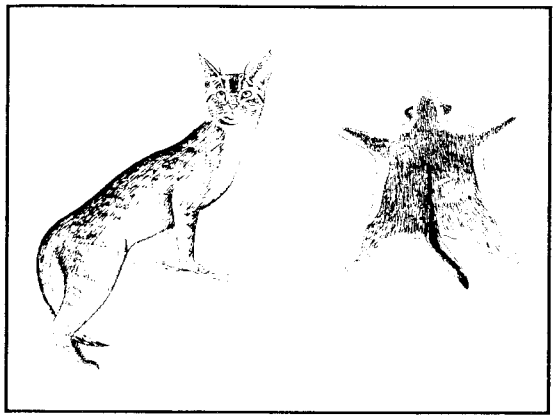
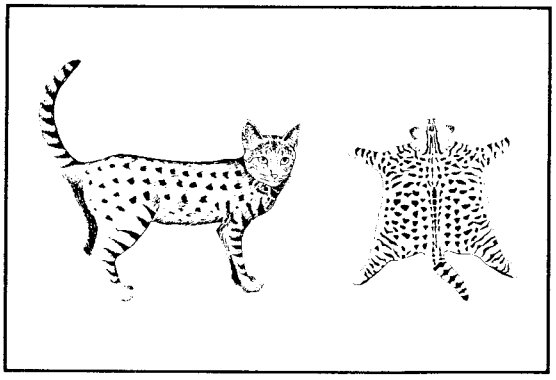


Figure 7. The genetics of the spotted tabby are uncertain. Some people say it is a distinct type of tabby, while others claim it is a "broken-lined" striped or blotched tabby. The broken-line effect would be due to the action of a modifying gene or genes.



patterns are mutant alleles of the locus, as indicated by their respective symbols t^b and T^a. The dominance relationships between the wild-type gene T and the 2 mutant alleles is of interest. The T^a is not fully dominant to T, so that the homozygote T^aT^a shows little or no tabby stripes on the legs, while the heterozygote T^aT shows greater amount of leg striping. The 2 Abyssinians are known as ticked and lined, respectively. The 3 tabby alleles show a steady progression from light to dark tabby pattern.

A fourth type of tabby recognized by cat fanciers is the spotted tabby. In these cats, the striped pattern is not uniform but appears as short bars or spots (Fig 7). There is a tendency for the vertical or classic stripes of ordinary tabbies to be interrupted, and this tendency is enhanced in some cat breeds. One theory is that a gene (or genes) is present that interrupts formation of the solid stripes at intervals along their course. The suggestion has been also made that the spotted tabby is due to a third mutant allele of the T locus. This is speculation, however, because no breeding data have been published to support this.

Nonagouti

The agouti gene A induces the characteristic band of yellow upon the hairs. The locus has produced a mutant a, which produces a phenotype lacking the characteristic. The hairs are consequently unbanded or black tipped, fading to blue toward the roots. This results in the well-known black cat. The allele, designated as nonagouti, is inherited as an autosomal recessive to normal agouti. Note that it is the agouti background coloration that has changed and not the tabby pattern. The tabby markings cannot be observed because of the uniformly black coat, but their presence can often be discerned as a darker "ghost" pattern in the coats of kittens. Tilting the animal from side to side usually reveals the nature of the pattern by reflective light.

Brown Pigmentation

The coat is normally colored by black pigment granules, produced by a gene symbolized as B. The B locus has given rise to 2 mutant alleles, designated as brown (b) and light brown (b^l). The order of dominance is

B over b over b^1. The b allele produces a dark-brown or chocolate color, while the brown of b^1 is distinctly lighter. The difference in intensity is most apparent when b or b^1 is combined with nonagouti a. The genotype aabb produces the Havana brown, and the aab^1b^1 produces the cinnamon brown.

Albino Alleles

The C locus for full production of pigment in the coat has 4 mutant alleles. The C locus determines the quantity of pigment in the pigment granules. Only the wild-type gene C (full color) permits the maximum amount. All of the mutant alleles decrease the amount of pigment in successive steps. The cat is devoid of pigment in the final step. The resultant phenotype is the pink-eyed white cat, or albino. For this reason, the alleles of C are known as the albino series.

Each of the C-alleles progressively reduces the amount of pigment in the coat. The fully colored CC cat is an intense black in combination with nonagouti (aaCC). The Burmese allele c^b produces a dark sepia-brown phenotype that is slightly but perceptively darker on the extremities (head, feet, tail) when substituted for C in the aaCC genotype (aac^bc^b). The iris may be pale yellow or greenish. The Siamese allele c^s produces a light sepia-shaded body with dark extremities (aac^sc^s). The irides are clear blue. The blue-eyed albino (allele c^a) has a white coat, dull-red pupils and light-blue irides.[30] Finally, the pink-eyed albino allele c has a white coat, red pupils and translucent irides.

The order of dominance for the alleles is conventionally taken to be $C > c^b > c^s > c^a > c$. The C gene is fully dominant to all of the mutant alleles, but the alleles are incompletely dominant to each other. For example, the phenotype of c^bc^s is intermediate to c^bc^b and c^sc^s. The extremities of c^bc^s individuals remain dark sepia but the body fur is appreciably lighter than that shown by c^bc^b, The result is the so-called Tonkinese cat. However, there is variation of expression, and some c^bc^s individuals may be so dark as to be difficult to distinguish from c^bc^b. Incomplete dominance between alleles of the albino series is common, for the cat as well as for other species.

The c^b and c^s alleles are thermosensitive, that is, the biosynthesis of melanin pigment is responsive to skin temperature. The lower the temperature, the more pigment is produced. This is the reason for the darker extremities of phenotypes induced by these alleles; the temperature of the extremities is slightly lower than that of the trunk. If a Siamese (aac^sc^s) is kept in a cool environment during the molting period, the new coat will be appreciably darker than the old. Conversely, if a bandage is applied to a small area of shaven skin, the new growth of hair under the bandage is white.[5]

There is a quantitative reduction in the eye pigmentation in Siamese cats.[25] The layers of pigmented cells are fewer than normal and the pigment granules are less densely packed. All parts of the eye are affected, especially the iris and choroid tissues. The different albino alleles have similar but graded effects upon eye pigmentation. There is an increasing interference with pigmentation until full albinism is reached.

Blue Dilution

The intensely colored hairs of black or chocolate cats are due to the regular and dense packing of myriad pigment granules in the cells of the hair shaft. The number of granules decreases toward the base of the hair, causing the hairs to be black or chocolate at the tip and bluish at the base. The slate-blue color of blue cats is due to interspersing of hairs with more-pigmented hairs containing less pigment.[8,9,21] The color clumping results from the faulty disposition of pigment granules during hair growth. The pigment granules of the eye tissues are not affected.[9] The locus responsible for the regular disposition of granules is designated as D (dense) and the mutated allele that induces irregular disposition as d (dilute). The d allele is inherited as an autosomal recessive to D.

Dilute Modifier

The dilute modifier (Dm) gene is only expressed in conjunction with the dilution gene d. The effect of Dm is to lighten the color of dd, and to produce a brownish cast to the coat.[28]

Inhibitor

The inhibitor gene I partially suppresses pigment production in the coat. The gene is inherited as an autosomal dominant to wild type.[29] The hairs are colored at the tips and become colorless toward their base. The I gene disrupts normal biosynthesis of pigment granules by melanocytes in the hair follicles.[8] Suppression is greater for the lighter agouti areas of the coat than for the darker tabby markings. Hence, the phenotype is a whitish cat with a dark tabby pattern (silver). Eye color is unaffected.

Pink-Eyed Dilution

As the designation of this mutant allele implies, the coat is diluted to a light tan and the eyes are pinkish (depigmented). The mutant allele was discovered but could not be perpetuated.[26] The allele may recur in the future. It would be a desirable addition to the known mutant alleles of the cat. Pigment granules in hairs of pink-eyed dilute cats were very small and yellowish brown, in contrast to the normal dark-brown or black coloration.[8]

Sex-Linked Orange

The ginger, marmalade, red or yellow coat color is due to a mutant gene O (orange). The O gene gives rise to some unusual phenotypes. These are derived from the fact that the gene is sex-linked, the O locus being on the X chromosome. While the female may have 1 of 3 genotypes on the X chromosomes, OO, Oo or oo, the male can have only 2, OY or oY, where Y is the male chromosome. The mode of inheritance of O is shown in Table 4.

The phenotype produced by the O gene is a Tabby pattern with a yellow ground color and Tabby markings accentuated by orange or red. The action of the gene is to convert biosynthesis of eumelanin (a black-brown pigment) to phaeomelanin (a yellow-orange pigment). The Tabby pattern remains because of a greater concentration of pigment granules in the markings than in the background. The nature of the Tabby is determined by the Tabby alleles, exactly as for the ordinary gray Tabby. Therefore, the genotypes of the striped, classic and Abyssinian Tabby are OOTT, OO$t^{b}t^{b}$ and OO$T^{a}T^{a}$, respectively.

Only the female can be heterozygous for O and the wild-type gene o. The phenotype of Oo cats is not orange, but a mosaic of orange and wild type (usually, orange and Tabby or orange and black) known as Tortoiseshell. Tortoiseshelling occurs because of variable inactivation of one or the other of the 2 X chromosomes in cells of the developing female egg. Areas of skin resulting from inactivation of the X chromosome carrying an O gene are normally colored; areas of skin arising from cells where the X chromosome carries the O gene is active are orange. The heterozygous Oo female cat is

Table 4. Inheritance of the sex-linked gene orange (O). The chromosome constitution is shown for each individual, where X^{o} represents the O-bearing X chromosome.

Mating			Offspring	
Dam		Sire	Males	Females
Orange $X^{o}X^{o}$	x	Orange $X^{o}Y$	Orange $X^{o}Y$	Orange $X^{o}X^{o}$
Black XX	x	Orange $X^{o}Y$	Black XY	Tortoiseshell $X^{o}X$
Tortoiseshell $X^{o}X$	x	Orange $X^{o}Y$	Orange $X^{o}Y$	Orange $X^{o}X^{o}$
			Black XY	Tortoiseshell $X^{o}X$
Tortoiseshell $X^{o}X$	x	Black XY	Orange $X^{o}Y$	Tortoiseshell $X^{o}X$
			Black XY	Black XX
Orange $X^{o}X^{o}$	x	Black XY	Orange $X^{o}X^{o}$	Tortoiseshell $X^{o}X$
Black XX	x	Black XY	Black XX	Black XX

Black = nonorange (black, tabby, blue, chocolate, etc)

in effect composed of 2 types of cells in respect to functioning genes on the X chromosome.

When a mutant gene on the X chromosome has obvious phenotype expression, the heterozygote would be expected to show the simultaneous effects of each. Therefore, the heterozygote Oo would be expected to have a coat displaying both orange (O chromosome functional) and wild-type (o chromosome functional). The coat displays a mosaic of orange/tabby or orange/black due to the competitive spread of melanoblasts as these populate the skin to ultimately become melanocytes responsible for coloring the hairs. Those melanocytes with the functioning O gene produce orange hairs, while those with a functioning o gene produce Tabby or black hairs. The expression may vary from mosaics with little expression of orange to others with extensive areas, reflecting the irregular migration of embryonic melanoblasts.

The conversion of eumelanin to phaeomelanin makes the O gene epistatic to alleles at the agouti (A and a) and black gene loci (B and b). Cats of genotypes AABBOO, aaBBOO, AAbbOO and aabbOO are of indistinguishable orange phenotype. This may be seen by examining the corresponding tortoiseshells of genotype AABBOo, aaBBOo, AAbbOo and aabbOo. In each case, the orange areas of the mosaic are indistinguishable orange, while the nonorange areas are Tabby, black, chocolate Tabby and chocolate, respectively. The last 2 tortoiseshells are uncommon and the first 2 types common. The black Tortoiseshell is the conventional "tortie," while the Tabby Tortoiseshell has been called a "torbie" or "patched tabby."

Piebald Spotting

Cats with splotchy white markings are known as piebald. Piebald spotting is due to the autosomal dominant gene S. Expression of the S gene varies widely. Some cats have small spots or streaks of white on the chest and ventral midline of the abdomen. Others are extensively white, with remnants of pigmentation confined to the head and base of the tail. In spite of this variation, there is regularity in the progressive increase of white coloring. As the amount increases, the ventrum (abdomen, chest, throat) becomes white. With more white, a white "blaze" extends from the nose to between the eyes, and white creeps up the sides of the animal. A "collar" of white often forms around the shoulders. With the greatest amount, most of the trunk becomes white and the colored areas occur as patches or spots of decreasing size.

A depiction of the progression of white spotting is shown by Figure 8. The depiction should be regarded as merely a guide since there is considerable variation. When cats are graded by the amount of white in the coat, the frequency distribution strongly suggests that the S gene is incompletely dominant. The heterozygous expression ranges over grades 3 to 6, and the homozygous expression over grades 5 to 9. There is overlapping of phenotype for the 2 genotypes.

The wide variation of white spotting may be due to 2 alleles: restricted spotting and piebald spotting.[32] These data can also be explained in terms of single incomplete dominant gene. Other investigators explained their observations as the inheritance of spotting by a single incomplete dominant gene with genotypes of SS and Ss.[7]

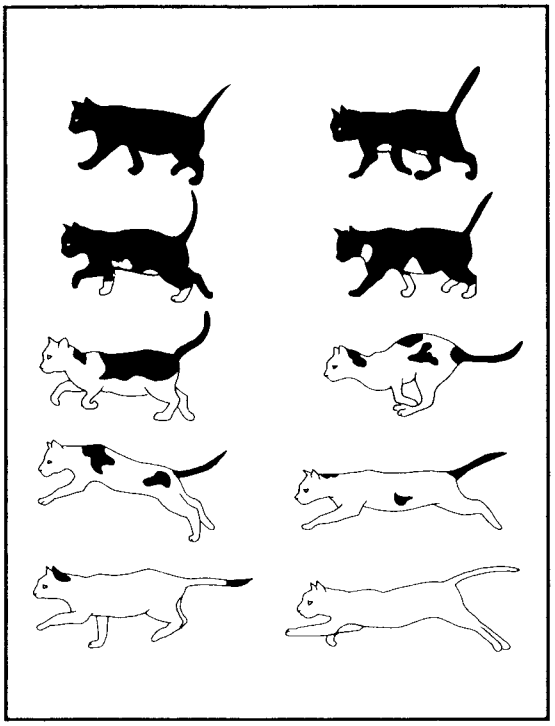
Gloving

Gloving is a form of restricted spotting, with the white confined to the paws and occasionally on the nose, chest and abdomen. Gloving has been ascribed to an autosomal recessive gene g, though the supporting evidence is not extensive. In a minority of heterozygotes Gg, the dominance of G is incomplete. It is unknown if g is independent of S or is an allele of the locus.

Dominant White

The dominant white gene W produces a completely white coat in most cats. Some kittens with this gene have small spots of colored fur on their heads that disappear with age. The iris may be yellow, blue or heterochromatic. It is common for one iris to be yellow and the other blue; such animals are called "odd-eyed." Deafness, unilateral or bilateral, is common in dominant-white cats. It has been suggested that W is an allele of S.[32] Though there is evidence to support this, it is not wholly convincing. For

Figure 8. Piebald spotting is due to an autosomal dominant gene that varies greatly in the degree to which it is expressed. Coat colors under the genetic influence of the piebald spotting gene can range from all white to all black, with any gradation in between.



practical purposes, W assorts independently of S.

The W gene interferes with migration of cells from the neural crest of the early embryo, probably by reducing their numbers. Neural crest cells are responsible for development of several tissues and organs. Included among these cells are the melanoblasts that populate the skin to form melanocytes for hair pigmentation. The absence of melanocytes produces the white coat that is a consistent feature of the W gene. Studies revealed that the eyes of yellow-eyed white cats were normally pigmented, while those of blue-eyed white cats were markedly pigment deficient.[25] In particular, the tapetum was completely absent. Depigmentation of the eye was due to an absence of stromal pigment cells.

A deficiency of eye pigmentation (blue irides) coupled with defective hearing, is a less consistent manifestation of W. Among a sample of 185 white cats, 68% had blue eyes and 44% displayed signs of deafness. Among the 60 cats with yellow eyes, 22% were deaf, while among the 125 cats with blue eyes, 55% were deaf.[3] The cause of deafness in W cats has been the subject of intensive investigation.

Whiteness is not inevitably associated with deafness. White cats with the underlying c^s Siamese gene have deep blue eye color and are not deaf.

Variations in Coat Hair

In addition to providing camouflage for stalking prey, the coat of cats protects the skin from abrasion and insulates against sunburn and heat loss. These properties result from the composition of coat hairs. There are 2 primary types of coats: the top coat and undercoat. The top coat affords a protective covering for the softer undercoat and has tactile properties. The vibrissae and stout facial hairs have a sensory function. The undercoat provides the main insulation from fluctuating temperature.

The coat is composed of 3 types of hair: guard hair, awn hair and down hair. Guard hairs are the least numerous. They are stout and straight, tapering to a fine point. Awn hairs are more numerous and thinner than guard hairs, and have a characteristic subapical thickening before tapering to a fine point. These 2 hair types constitute the top coat. Down hairs are the thinnest and by far the most numerous. They have a similar diameter throughout their length. Their main function seems to be as insulation. All awn hairs have a subapical swelling, but some are straight like guard hairs and others are undulated. The 2 forms are distinguishable, but there tends to be a gradual rather than distinct transition from one to the other.

Long Hair

The extra-long coat of the long-haired or Persian breeds is due to an autosomal recessive gene l. The coat is composed of the same types of hairs as present in the short-haired coat but they are greatly elongated. Two possibilities exist to explain the longer hair: the hairs grow more rapidly before the growth phase terminates, or the period of growth is extended. Long-haired cats have not been examined in respect to these 2 possibilities. If studies on long-haired Angora

rabbits (a comparable genetic hair type) can be extrapolated, an extension of the growth period is the more likely explanation.

Rex Mutants

The rex coat is shorter than normal, while the vibrissae are excessively curved, bent, broken or less numerous, depending on the particular rex mutant. There is a tendency for the coat to have marcel waving, but this is not a universal feature. Rex cats have received considerable publicity, and as a consequence, a number of rex mutants have been reported. Only a few of these have been genetically investigated. Rex mutants from different areas have similar phenotypes but there may be subtle differences. Most are inherited as autosomal recessives, but a recent rex mutant appears to be an incomplete dominant.

The Cornish rex mutant (r) displays recessive inheritance. The coat is short and plush, with a tendency toward marcel waving. The whiskers are shorter and more curved than normal. The density of the coat is reduced, varying from a sparse covering to a thick pelage. Guard hairs appear to be lacking or closely resemble the thinner awn hairs. The subapical swelling of the awn hairs is less obvious than normal or may be absent.[13,21]

The German rex mutant resembles the Cornish rex phenotypically.[11] The mutant gene is recessive to the normal coat gene. Though there is good evidence that the German rex is also a spontaneous mutant, breeding experiments prove that the Cornish and German mutants are identical.[13]

The Devon rex (re) superficially resembles the Cornish rex. The coat is shorter than normal and inclined to be sparse. There is a frequent loss of hair from the abdomen, chest and shoulders. In extreme cases, the whole trunk is naked. Transient growth of hair is often apparent. All 3 types of hair are present, but they are of irregular diameter. The hairs are frequently broken, which is unusual for such a resilient substance as keratin. The vibrissae are reduced in number and easily bent or broken, and may appear as stubble. Cornish and Devon rexes are caused by different mutant genes at independent loci.[12]

The Oregon rex (ro) gene is inherited as a recessive.[14] Superficially, the Oregon rex resembles the Cornish rex. The guard hairs are absent, and the awn and down hairs appear to be thinner than normal. On the other hand, the subapical swelling of the awn hairs is more pronounced and straighter than awn hairs of the Cornish rex. The awn hairs project above the down hairs, as normally expected. Though the data are not conclusive, the Cornish and Oregon rex genes appear to be different.[14]

Unlike the above rex mutants, the Dutch rex gene (Rd) is inherited as an autosomal dominant.[17] The coat is short and has a bristly feel. Guard hairs are absent or reduced in size and appear like awn hairs. They are tortuously wavy and protrude in random directions above the down hairs, giving the cat a bristly texture. The down hairs are excessively wavy. The vibrissae are of normal number but they are crinkled and bent. The coat thins with age and may be lost from some regions of the body. Preliminary breeding data suggest that the coat of the homozygote RdRd is more abnormal than the heterozygote Rdrd. The coat of the former is sparser and more prone to loss.

There are additional reports of rex-type mutants from the US (2 additional cases), England (1 additional case), Australia, Italy and Sweden.[16] Breeding data on these rexes are meager, but the mutants appear to be recessive in nature. It is impossible to tell at this time whether these represent mutants at loci different from those listed above. Repeat mutations at the same gene loci are known to recur at a low rate, as indicated by the same rex mutants occurring in England and Germany.

Wire Hair

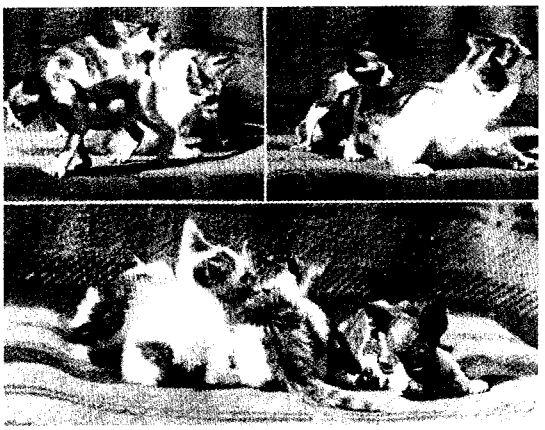
The wire-haired coat appears unkempt, wavy and coarsely textured when stroked. All 3 hair types are present but they are thinner than normal and show exaggerated curvature. Some may be coiled like springs, while others display a "shepherd's crook" configuration at the distal end. A dominant mode of inheritance is indicated by fanciers' breeding records. The mutant allele is symbolized by Wh.[16]

Sphynx

The Sphynx or hairless cat is not totally hairless. Most have a fuzzy growth on parts of the body such as the shoulders. Others may show a seasonal transitory weak growth of hair. The hairlessness is inherited as an autosomal recessive (symbol hr).[15]

Hairless cats have appeared spontaneously for eons, and some have been called "dog-cats."[23,24] Such cats have evoked a great deal of notoriety for the discoverers (Fig 9).

Figure 9. Hairlessness is inherited as an autosomal recessive defect.[23] The appearance of such mutants has created a great deal of notoriety in the past. Such hairless mutants have often been referred to as "cat-dogs," probably due to their resemblance to several thinly haired breeds of toy dogs. Lately, such a defect has been used as the basis of a new breed of cats typified by the Sphynx. (Courtesy of Dr. H. Sternberger and *Journal of Heredity*)



Physical Variation

In addition to mutant genes that affect color and coat, a number of genes modifying physical attributes have been recognized. Because none of these genes is linked to color and coat genes, they are found in many breeds. Unfortunately, some of these mutant genes are associated with undesirable anomalies.

Manx

The most well-known gene is for tailessness in the Manx or tailless cat. The tailless condition is due to a dominant gene M, which is a prenatal lethal when homozygous (MM). Though heterozygotes (Mm) are viable, they are subject to a number of life-threatening anomalies of the lower vertebral column and intestinal tract. A sufficient number of heterozygotes survive, however, thus allowing the Manx to persist.

Four grades of Manx are recognized: the true Manx or "rumpy", which lack tail vertebrae; "rumpy-riser", in which a small number of vertebrae can either be seen or felt; "stumpy," in which where sufficient vertebrae are present to form a short tail, often movable but usually knobby or kinked; and "longie," in which the tail is almost as long as normal (Fig 12). Normal cats (mm) bred from heterozygotes are known as "tailed Manx." Normal females, while not strictly "Manx," are useful in perpetuating the Manx breed through matings with Manx males.

Japanese Bobtail

These cats have a short tail about 2-3 inches long and characterized by curves and angles. Little is known of the inheritance of the truncated tail, though the condition is thought to be inherited as a recessive. The Bobtail has extensive white areas with patches of black (aaSS), orange (aaOOSS) or black and orange mosaic (aaOsSS).

Scottish Fold

The pinnae of the adult Scottish Fold are folded forward, giving the cat a somewhat dejected look. The ear fold is not present at birth but becomes evident at about 4 weeks of age. The ears become more rigid with age. The condition is due to an autosomal dominant gene Fd. The heterozygote Fdfd is normal except for the folded ears. The homozygote FdFd is subject to a crippling thickening of joints of the limbs and tail, however (Fig 10).[6] Some heterozygotes Fdfd also develop similar joint anomalies, though much milder than those of homozygotes. Affected animals eventually are unable to walk. Fold-to-Fold matings should be avoided. Folds should only be mated to normal-eared animals (bred from similar matings).

American Curl

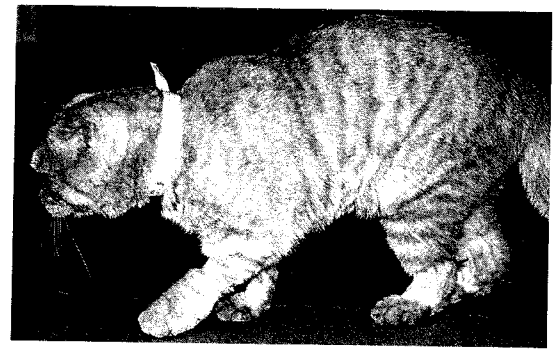
The American Curl has the distal portion of the ear pinnae slightly curled backward.

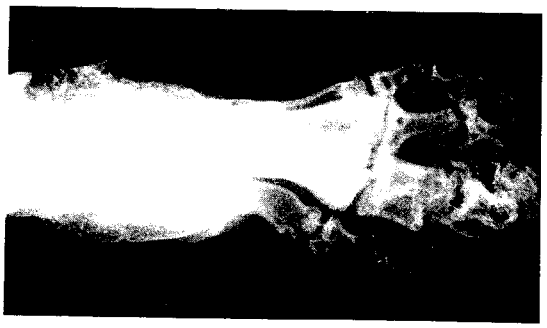
This gives an alert appearance to the animal. The Curl condition is due to an autosomal dominant gene Cu. Preliminary observations indicate that the homozygote CuCu is devoid of other anomalies, but this requires confirmation. The heterozygote Cucu suffers from no apparent problems in other organs.

Polydactyly

These cats have extra toes on the feet. Both front and back paws are affected, but the back feet are never affected unless the front feet also have extra digits. There is variation in both the numbers of supernumerary toes and the degree of development of the extra toes. The maximum for the front legs is 7 toes. The condition is due to an autosomal dominant gene Pd.

Figure 10. Top: A cat that is homozygous for the Scottish Fold gene. The cat has severe skeletal disease resulting from overexpression of the basic cartilage anomaly caused by the gene. Heterozygotes have abnormalities mainly of the ear cartilage, but some may also have skeletal anomalies that are generally minor compared to those manifested by homozygotes. Bottom: A radiograph of the distal hind limb of this cat shows severe bone and joint changes characterized by compression and thickening of the long bones, collapse of joint spaces, destruction of joint surfaces and underlying subchondral bone, and extensive periarticular new bone formation.





Genetics of Breeds

The primary determinants of cat breeds are color, coat quality and conformity (body shape and stance). It is difficult to say which is the most important. Coat color and quality are determined by major genes and combinations thereof. These features are monogenic, therefore. In contrast, conformation is determined mainly by polygenes.

Two broad categories of conformation have been recognized: a stocky, powerfully built animal; and a more gracile, sinuous animal. The first category usually embraces "homegrown" breeds, that is, breeds that are "native" to the western hemisphere and classified as American, British or European. The second category embraces "foreign" or "oriental" breeds. The last category must not be taken too literally. It came into being due to the importance of the uniquely colored Siamese during the latter part of the 19th century. These cats had a graceful body conformation as compared with British breeds. Henceforth, any cat originating from the Far East or of slender build was regarded as having foreign conformation. A number of breeds that have been created in countries far removed from southeast Asia are regarded as "foreign," however. Differences of head shape and body build exist between breeds of both "western" or "foreign" categories, but these are minor and usually subtle except to the astute cat fancier.

In discussing the genotypes of breeds, varieties or colors of cats, it is conventional to list only mutant genes. This focuses attention on the relevant genes and avoids unnecessary repetition. Exceptions occur when the full genotype is not known. A general exposition of genotypes of breeds has been published.[16]

Short-Haired Breeds

Tabbies: The common gray-brown domestic Tabby is usually striped or blotched. Both forms are due to a single gene difference. The spotted Tabby may differ by a major gene, but this is debatable (as explained earlier). Many spotted forms are

striped cats in which the stripes are interrupted to produce short bars or spots. These can be bred by selection, which implies that at least part of the breakup of the striping is inherited. Conversely, those who desire well-defined, unbroken, stripes must select for the feature.

The exhibition brown Tabby differs from the domestic Tabby; it has a definite body conformation, brighter agouti color, and a prominent tabby pattern. The tabby pattern can be bred in many colors by combining the alleles with other mutants (Table 5). Some of these mutants are common and may be observed in domestic cat populations. The less common mutants are becoming increasingly popular among the more modern oriental category of breeds. Note that the brown Tabby is the fancy name for the black Tabby; the genetic brown Tabby is the chocolate Tabby (chestnut tabby in the US).

Abyssinian: The Abyssinian is a distinctive form of tabby. The tabby pattern is virtually absent from the body, but a limited amount of striping may sometimes occur on the flanks and lower part of the forelegs. This has been eliminated by selective breeding in exhibition strains. Obvious striping occurs in first-cross Abyssinians because the allele $\underline{T}^a$ is incompletely dominant to other Tabby alleles. Some typical tabby markings remain on the head and distal portion of the tail. The Abyssinian allele has been systematically combined with other genes to engender an impressive range of varieties (Table 6). The basis for the Abyssinian breed is the unique phenotype produced by the $\underline{T}^a$ allele. Some varieties have been selected for a richly colored rufescent phenotype.

Table 5. Genotypes of striped and blotched (classic) Tabbies.

Name	Striped	Blotched (classic)
Brown	TT	t^bt^b
Chocolate	bbTT	bbt^bt^b
Blue	ddTT	ddt^bt^b
Lilac	bbddTT	$bbddt^{bb}$
Cinnamon	b^1b^1TT	$b^1b^1t^bt^b$
Fawn	b^1b^1ddTT	$b^1b^1ddt^bt^b$
Silver	IITT	IIt^bt^b
Red	OOTT	OOt^bt^b
Cream	OOddTT	$OOddt^bt^b$
Torbie	OoTT	Oot^bt^b

Singapura: This breed has the Abyssinian allele $\underline{T}^a$ combined with the Burmese allele $\underline{c}^b$. It differs from the Abyssinian breed in not having the rufescent polygenes and in displaying dark brown ticking on a pale ivory background color. The breed also differs in conformation.

Self-Colors: The nonagouti allele $\underline{a}$ is responsible for the self-colors. Alone, the allele produces the solid black. In combination with the $\underline{b}$ and $\underline{d}$ mutants it produces 3 additional colors: chocolate ($\underline{aabb}$), blue ($\underline{aadd}$) and lilac ($\underline{aabbdd}$). These 4 phenotypes may be viewed as the basic colors of cats, since they recur regularly within breeds. No matter how breeds may differ for coat texture and body conformation, color is inherited independently. This permits development of distinctive breeds with identical color genotypes (Table 7). The outstanding example of this process is the self-blue. Several well-established breeds are of this color. These breeds differ not only in conformation, but also in the intensity of the shades of blue.

Red Tabby and Tortoiseshell: The ginger or marmalade exhibition version of the domestic cat is known as the red Tabby. The intensity of color is greatly enhanced, especially the darker tabby markings. In this respect, the blotched (classic) is preferred because the patterned area is greater than that normally shown by the striped Tabby. The richness of color is due to rufescent polygenes that determine the intensity of red/yellow pigmentation.

The red Tabby is produced by the sex-linked gene $\underline{O}$. Since the $\underline{O}$ gene is borne on the $\underline{X}$ chromosome, the male genotype is $\underline{O}Y$, where $\underline{Y}$ represents the male chromosome. The female genotype is $\underline{OO}$, homozygous for the $\underline{O}$ gene. The heterozygote $\underline{Oo}$ is the Tortoiseshell, a mosaic phenotype of orange and nonorange colors, where $\underline{o}$ is the nonorange wild-type gene. Only the female genotype of $\underline{OO}$ will be discussed in this section, the male genotype $\underline{O}Y$ being taken for granted. This is to distinguish between the orange ($\underline{OO}$) and tortoiseshell ($\underline{Oo}$) for expository purposes. When the Tortoiseshell is

Table 6. Genotypes of British Abyssinian varieties.

Name	Genotype
Black* (Ruddy)	T^aT^a
Chocolate	bbT^aT^a
Blue*	ddT^aT^a
Lilac	$bbddT^aT^a$
Sorrel* (Red)	$b^1b^1T^aT^a$
Fawn*	$b^1b^1ddT^aT^a$
Red	OOT^aT^a
Cream	$ddOOT^aT^a$
Black Tortoiseshell	OoT^aT^a
Chocolate Tortoiseshell	$bbOoT^aT^a$
Blue Tortoiseshell	$ddOoT^aT^a$
Lilac Tortoiseshell	$bbddOoT^aT^a$
Sorrel Tortoiseshell	$b^1b^1OoT^aT^a$
Fawn Tortoiseshell	$b^1b^1ddOoT^aT^a$
Black Silver	IIT^aT^a
Chocolate Silver	$bbIIT^aT^a$
Blue Silver	$ddIIT^aT^a$
Lilac Silver	$bbddIIT^aT^a$
Sorrel Silver	$b^1b^1IIT^aT^a$
Fawn Silver	$b^1b^1ddIIT^aT^a$
Red Silver	$IIOOT^aT^a$
Cream Silver	$ddIIOOT^aT^a$
Black Silver Tortoiseshell	$IIOoT^aT^a$
Chocolate Silver Tortoiseshell	$bbIIOoT^aT^a$
Blue Silver Tortoiseshell	$ddIIOoT^aT^a$
Lilac Silver Tortoiseshell	$bbddIIOoT^aT^a$
Sorrel Silver Tortoiseshell	$b^1b^1IIOoT^aT^a$
Fawn Silver Tortoiseshell	$b^1b^1ddIIOoT^aT^a$

* Four colors recognized by CFA in the US.

combined with piebald spotting (QoSS), the color is known as tortoiseshell and white or calico.

The O gene is epistatic to alleles A, a, B and b. All OO cats that are homozygous or heterozygous for any of the alleles are indistinguishably red Tabby. The situation is different for the Tortoiseshell. Though the orange areas of the mosaicism are red Tabby, nonorange areas show the effects of the above alleles. The "standard" Tortoiseshell is the black of genotype aaOo. The Tabby Tortoiseshell ("torbie" or "patched tabby") of genotype AAOo is common among domestics. The other tortoiseshell colors, such as chocolate (aabbOo), chocolate Tabby (bbOo), cinnamon (aab^1b^1Oo) and cinnamon Tabby (b^1b^1Oo), are appearing in some foreign and oriental breeds.

Cream and Blue-Cream: The Cream is a red Tabby degraded in intensity of pigmentation by the dilution gene d; the genotype is ddOO. Cream is an apt description of the color. The markings of the blotched Tabby appear as dark cream against a pale-cream background. The pattern of the striped tabby is not so obvious, however, with some individuals appearing almost as a self-color.

The exhibition blue Tortoiseshell, known as the blue-cream, has the genotype aaddOo. Phenotypically, the cat is a mosaic of cream and blue pigmentation. The blue Tabby Tortoiseshell ("blue torbie" or "blue patched tabby") (ddOo) is not easily distinguishable from the blue Tabby (dd), especially if the cream areas are small or diffuse. Other light-colored Tortoiseshells are being bred in some foreign and oriental breeds, such as the lilac Tortoiseshell (aabbddOo) and Fawn (aab^1b^1ddOo).

Silver, Tipped and Smoke: In the Silver, the yellow-gray agouti component of the Tabby is absent, creating the superficial illusion of an off-white cat with black Tabby markings. These cats may have any of the 3 tabby patterns, of which the blotch or classic is probably the most outstanding. Breeders have selected for a clear white background color and solid Tabby markings to realize maximum contrast. The Silver phenotype is produced by the I allele, and the genotypes are IITT (striped or "mackerel"), IIt^bt^b (blotched "classic") and IITaTa (Abyssinian).

Table 7. The names and genotypes of self-colors in the US and UK.

UK	US	Genotype
	American SH black	aa
British Black	British SH black	aa
Foreign Black	Oriental SH black	aa
Bombay	Bombay	aa
British Blue	British SH blue	aadd
Foreign Blue	Oriental SH blue	aadd
Russian Blue	Russian Blue	aadd
Chartreux	Chartreux	aadd
Korat	Korat	aadd
	Havana Brown	aabb
Havana	Oriental SH chestnut	aabb
Foreign Lilac	Oriental SH lilac	aabbdd
Cinnamon	Oriental SH cinnamon	aab^1b^1
Caramel		aaddDm-

The I gene inhibits pigment in the hair to a variable degree. The silver may be regarded as the minimum degree of inhibition. The inhibition may be more pronounced, giving rise to the shaded silver. Such cats have obvious white undercoats and rarely discernible tabby markings. The most extreme expression is the tipped or "chinchilla". In these animals, only the tip of the hair is pigmented and the tabby markings are not discernible.

The effectiveness of the I gene in eliminating pigment is due in part to the fact that the silver and tipped breeds are agouti. When the I gene is combined with nonagouti, the reduction is significantly less. In fact, all of the hairs are now distally pigmented and not merely the tabby pattern hairs, as in the silver tabby. These aaII individuals are known as Smoke. The expression of light undercolor varies from indistinguishable, or barely distinguishable, from the slate blue of the normal nonagouti (aa), to light blue and finally white. There are several cases on record of black cats breeding as Smokes. These are almost certainly instances of very dark Smokes.

The Silver tabby, shaded Silver, Tipped (chinchilla) and Smoke phenotypes may be combined with b, d and O alleles to produce the usual range of colors (Table 8). These have been exploited in the oriental group of breeds to establish phenotypes not recognized by the traditional breeds. The Silver tabby, shaded Silver and Tipped varieties have identical genotypes, differing only in the expression of I. The expression of the I gene is probably governed in part by modifying polygenes.

Siamese: The Siamese is probably the best known of the exotic breeds. Siamese have a light-colored body, dark extremities and blue eyes. The amount of pigment in the extremities is sufficient to be modified by other mutant genes. It is possible, therefore, to have many varieties of Siamese, while retaining the characteristic coloration and pattern.

The original Siamese is the Seal Point, with the simple genotypes of aac^sc^s. Other varieties have been developed by combining various color genes (Table 9). The Lilac Point variety is also known as Frost Point. The Tabby varieties are sometimes designated as Lynx Points.

The 2 phenotypically identical red and red Tabby Point Siamese are worth noting. They owe their existence to the objection of breeders that the agouti allele could be inadvertently introduced into their stock by indiscriminate mating of the 2 genetically different Red-Point Siamese. This problem was overcome, or at least contained, by ensuring that each type of Red Point is mated only within its respective series.

Tonkinese: The Tonkinese is a name given to the heterozygote aac^bc^s. Typically the coloration is midway between Burmese (aac^bc^b) and Siamese (aac^sc^s). The coat is a dark to medium sepia brown, being closer in appearance to the Burmese than to the Siamese. However, the body fur is lighter, contrasting with the dark sepia-colored extremities. The usual color is the seal (aac^bc^s), but any of the nonagouti Burmese or Siamese varieties may occur as Tonkinese.

Burmese: The Burmese is a nonagouti that, when combined with the c^b allele, produces a blend of sepia browns. They are shaded dark dorsally and light ventrally, with rich dark extremities. The basic genotype of aac^bc^b has been combined with other color genes to create the varieties listed in Table 10. The action of the c^b allele is to lighten the color. As a consequence, the genotypes listed in Table 10 have the usual

Table 8. Genotypes of Silver and Smoke varieties of Orientals and other breeds.

Name	Silver	Smoke
Black	II	aaII
Chocolate	bbII	aabbII
Blue	ddII	aaddII
Lilac	bbddII	aabbddII
Cinnamon	b^1b^1II	aab^1b^1II
Red	OOII	OOII
Cream	ddOOII	ddOOII
Black Tortie	IIOo	aaIIOo
Chocolate Tortie	bbIIOo	aabbIIOo
Blue Tortie	ddIIOo	aaddIIOo
Lilac Tortie	bbddIIOo	aabbddIIOo

Table 9. Genotypes of British Siamese varieties.

Name	Genotype
Seal*	aac^sc^s
Chocolate*	$aabbc^sc^s$
Blue*	aac^sc^sdd
Lilac*	$aabbc^sc^sdd$
Red	aac^sc^sOO
Cream	$aaddc^sc^sddOO$
Seal Tortie	aac^sc^sOo
Chocolate Tortie	$aabbc^sc^sOo$
Blue Tortie (Blue Cream)	aac^sc^sddOo
Lilac Tortie (Lilac Cream)	$aabbc^sc^sddOo$
Seal Tabby (Lynx)	c^sc^s
Chocolate Tabby (Lynx)	bbc^sc^s
Blue Tabby (Lynx)	c^sc^sdd
Lilac Tabby (Lynx)	bbc^sc^sdd
Red Tabby (Lynx)	c^sc^sOO
Cream Tabby (Lynx)	c^sc^sddOO
Seal Tortie Tabby (Lynx)	c^sc^sOo
Chocolate Tortie Tabby (Lynx)	bbc^sc^sOo
Blue Tortie Tabby (Blue Cream, Lynx)	c^sc^sddOo
Lilac Tortie Tabby (Lilac Cream, Lynx)	bbc^sc^sddOo

* Recognized by CFA in the US. Other colors recognized as colorpoint shorthaired breed.

phenotypes but are perceptibly paler in tone.

Burmilla: The Burmilla was developed by crossing the Burmese and Chinchilla, engendering a unique phenotype that has been exploited by breeders. The undercolor is white, overlaid with colored ticking and Tabby barring on the legs and rings in the distal tail. The basic genotype is $\underline{I}it^b\underline{t}^b$. The color of the ticking depends upon the presence of other genes, such as the chocolate $bb\underline{I}it^b\underline{t}^b$ or blue $dd\underline{I}it^b\underline{t}^b$. Other Tabby alleles may replace $\underline{t}^b$.

White Coat with Orange, Blue or Odd-Colored Eyes: The coat is completely white due to the presence of the W gene. The iris may be orange or blue, depending on whether or not the W gene can change the normal orange color to blue. In a small proportion of cats, the iris may be partially orange and blue, commonly affecting one eye more than the other. Such cats are known as odd-eyed. The variation of iris color results from the erratic influence of W upon eye pigmentation. A deficiency of pigment produces a wholly or partially blue eye.

Foreign White: This cat is a true-breeding blue-eyed white of genotype $c^sc^s\underline{W}W$. The W gene produces the completely white coat but the iris is not invariably blue. However, the irides can be made consistently blue by combining W with the c^s gene.

Bicolors: These cats have large white areas due to the piebald gene S. The amount of white should not be too extensive because this would upset the "balance" of colored and white markings. The colored areas may be any one of the usual known colors, tabby or black being the most common.

Snowshoe: The Snowshoe is a cat of Siamese coloration, with the addition of restricted white spotting. The lower portion of the front and rear legs is white, often accompanied by an inverted V wedge of white extending between the eyes to the nose, and small areas of white on the stomach. The g or a similar gene is probably involved. Varieties of Snowshoes include the Seal, Chocolate, Blue and Lilac, with identical genotypes for the comparable nonagouti series of Siamese.

Long-Haired Breeds

The major difference between the short- and long-haired or Persian breeds is the coat length. There are additional differences in head and body conformation, but less emphasis is placed upon these. The difference in coat length is due to the gene l

Table 10. Genotypes of Burmese varieties.

Name	Genotype
Brown* (sable)	aac^bc^b
Chocolate* (champagne)	$aabbc^bc^b$
Blue*	aac^bc^bdd
Lilac* (platinum)	$aabbc^bc^bdd$
Red	aac^bc^bOO
Cream	aac^bc^bddOo
Brown Tortie	aac^bc^bOo
Chocolate Tortie	$aabbc^bc^bOo$
Blue Tortie	aac^bc^bOo
Lilac Tortie	$aabbc^bc^bOo$

* Recognized by CFA in the US.

for long hair. However, the luxurious coat of the exhibition long hairs differs appreciably from the Domestic Long Hair. The coat is longer, softer and more dense. These differences are due to modifying polygenes that enhance the effect of the primary l gene.

The color genes are inherited independently of the long-hair gene, and almost all of the phenotypes of short-haired cats are also found with long hair. These breeds often have comparable names, which aids identification. Exceptions will be discussed in this section.

Cameo: The Cameo is an orange cat with a light or white undercolor, due to the joint effects of the O and I alleles. The amount of undercolor, or conversely the amount of distal pigmentation varies. Consequently, 3 varieties of Cameo are recognized: Shell, the lightest, in which only the tips of the hairs are orange; Shaded, in which the amount of orange is greater; and Smoke, the darkest, in which the hairs are most heavily pigmented. The cream Cameo, produced by addition of d to the genotype, also occurs in 3 varieties that parallel those for the red (Table 11). The Tortoiseshell and blue-cream Cameo are mosaics of red Cameo and nonagouti Smoke, and cream Cameo and blue nonagouti Smoke, respectively.

Himalayan and Kashmir: The Himalayan varieties are long-haired Siamese differing in both hair length and conformation. They have the sturdy build of the traditional long-haired breeds. The 10 varieties of the nonagouti Siamese series are recognized for exhibition purposes. The genotypes are identical to the first 4 of column 2 of Table 9, with the addition of the ll gene. In Great Britain, the Himalayan is known as the Colorpoint. Varieties that have colored points other than self-color are known as Kashmir. Because of extensive cross-breeding to Persians, the Himalayan is now a variety of the Persian in the United States.

Birman: The Birman is similar to the Himalayan, but with the addition of low-grade white spotting. The spotting is ideally confined to the feet. They are "gloves" for the forefeet and short "stockings" for the hind legs. The spotting is probably due to the g gene. Accordingly, the genotypes of the various colors are identical to those of the Himalayan, with the addition of gg.

Table 11. Genotypes of British longhair Cameo varieties.

Name	Genotype
Red Shell* (chinchilla)	aaIIIIOO
Red Shaded*	aaIIIIOO
Red Smoke*	aaIIIIOO
Tortoiseshell* (shell, shaded, smoke)	aaIIIIOo
Cream Shell	aaddIIIIOO
Cream-Shaded	aaddIIIIOO
Cream Smoke	aaddIIIIOO
Blue Cream* (smoke)	aaddIIIIOo

*Recognized by CFA in the US.

Balinese and Javanese: The Balinese and Javanese are basically long-haired Siamese. Both the coloration and conformation are typically Siamese, the latter differentiating the Balinese from the more sturdily built Colorpoint. Balinese is the name given to the 4 nonagouti varieties (Seal, Chocolate, Blue and Lilac Points), while Javanese is the name given to all of the other varieties. Their genotypes are identical to those of the Siamese varieties, with the addition of ll.

Tiffanies: Tiffanies are long-haired Burmese that occur in the usual Burmese colors. The genotypes of Tiffanies are identical to those of the Burmese, with the addition of ll.

Silver, Chinchilla and Smoke: The long-haired Silver is identical in structure to the short-haired Silver. The genotype is identical, with the addition of ll. The Chinchilla represents the extreme expression of the inhibitor gene I. The coat is white except for pigment at the extreme tip of the hair. The long hair effectively obscures the pigmented hair tips, but their presence is apparent on the coat of young kittens. When the hair is very short, a tabby pattern similar to that of the Silver Tabby may be observed. As the hair continues to lengthen, however, the pattern gradually diffuses. The Smoke is a combination of nonagouti and inhibitor (aaIIII), being blackish with a light or white undercolor.

Golden Chinchilla: The Golden is a segregant of Chinchilla parents that are heterozygous for I. The Golden has a Tabby pattern more dispersed than that found in the ordinary brown Tabby. The effect is to produce a brighter-yellow cat; hence the name Golden. The dispersion of the Tabby pattern is probably a means of creating the light color of the Chinchilla. The action of the I gene is strongest when the amount of pigment is already reduced by other genes. Dispersion of the Tabby would facilitate creation of the Chinchilla phenotype. Exactly how the Golden differs from a brown Tabby is unclear.

Turkish Van: This breed displays the extreme expression of piebald spotting combined with orange. The coat is completely white except for small patches of orange on the head or shoulders and an orange tail. The genotype is llOOSS. The cream Turkish is phenotypically identical except that the patches and tail are cream; the genotype is ddllOOSS.

Ragdoll: This breed displays combinations of genes not found in older breeds. Ragdolls may be likened to colorpoints, with the addition of the spotting gene S. Indeed, when the S gene is absent, the variety is called "Colorpoint." When a small amount of white is present (probably the heterozygote Ss), the variety is called "Mitted." When the white areas are extensive (probably Ss or SS), the variety is called "Bicolor." Four colors are recognized: Seal, Chocolate, Blue and Lilac. The genotypes are identical to those for the comparable Colorpoint, with the addition of Ss or SS as described above.

Angora: The Turkish Angora is a long-haired breed with a sinuous body conformation, as opposed to the more stocky conformation of most other long-haired breeds. In this respect, the Angora resembles foreign-type breeds with long hair. It differs by having no short-haired counterpart. The cat may be bred in all of the usual colors.

Somali: The Somali is a long-haired Abyssinian, having the same range of varieties and identical genotype, with the addition of ll.

Maine Coon: This breed originally was bred in the northern United States as a domestic for catching vermin. Recently, it has been adopted as a breed for exhibition purposes. The coat is long, due to the l gene, but more heavy and shaggy than the other long-haired breeds. The Maine Coon is bred in the usual range of colors.

Norwegian Forest Cat: This is another breed developed from long-haired domestics originally bred to reduce rodent populations. Now recognized for exhibition purposes, these cats have a coat that is dense and shaggy, differing from the fuller and softer coat of the traditional Long Hair. Most of the usual colors occur in the breed.

Cymric: The Cymric is a long-haired Manx of genotype llMm. Most colors are recognized.

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GENETIC DISORDERS

Surveys of genetic disorders in cats are few. One extensive compendium covers primarily congenital (developmental) diseases, but includes many traits that are probably not genetic.[143] Other authors are careful to distinguish between "probable" and "possible" genetic disorders.[48] Some are written mainly for laymen.[135] Some reviews deal only with metabolic diseases of genetic origin.[38,107,119] Included as disorders are genetic deviations from the norm that may not necesarily be harmful to the cat.

Genetic Disorders of the Skin

The haircoat of cats is composed of 3 distinct types of hairs, each having different functions. The stouter primary guard hairs are the longest and taper to a fine point. The secondary guard or awn hairs are slightly thinner than the primary guard hairs and are more numerous. They have a subapical swelling and taper to a fine point. Some awn hairs are straight but most show some degree of undulation. The wool or down hairs are the most numerous. They are very fine, flexible and of even diameter. The primary and secondary guard hairs make up the topcoat, and the wool hairs the undercoat. One of the functions of the haircoat, particularly the wool hairs, is to insulate the skin against excessive heat loss. The guard hairs act as a protective covering for the softer wool hairs. The primary guard hairs also have a sensory function. The vibrissae and other facial whiskers are extra stout hairs and presumably serve a tactile purpose.

Long Hair

Long hair (l) is not usually viewed as an anomaly.[135] However, the long coat is due to exceptional growth of the hair fibers. No studies have been made of the growth of individual hairs in cats. Measurements of growth of hairs in long-haired Angora rabbits (due to a recessive mutant gene comparable to that of cats) revealed that the rate of growth per day is normal but the growth or anlagen phase was of longer duration.[49] Exhibition long-haired cats have a longer and fuller coat than ordinary domestic cats because modifying polygenes increase the length of the hairs, especially the wool hairs.

Rex Coat

Four distinct rex-type coat mutant genes are known and others may also occur. The 4 genetically independent mutants are: Cornish rex (r), Devon rex (re), Oregon rex (ro), and Dutch rex (Rd).[129,132,137,145] A fifth rex (German rex) is inherited as a recessive to normal coat.[130] This gene mutated independently of the others, but it is either a repeat of the Cornish rex or is a similar allele at the same locus.[131] The coat type is easily recognizable and rex cats have originated from many parts of the world. Additional cases have been described in the United States, Italy, Australia and Sweden.[136] In each case, monogenic recessive inheritance is indicated. It is not known if these are distinct from the 4 known rex genes.

The coat of the rex breeds is abnormally short, waved or curled. All of the hair types are reduced in length, especially the guard

hairs, which are usually grossly abnormal or even absent. The vibrissae are short, typically bent, twisted or wriggly, depending upon the severity of affliction. No studies have been published on the growth of the rex coat in cats. An analysis of growth of the rex coat in rabbits, which is due to a recessive gene comparable to that of cats, showed that the growth phase was of normal length but the rate of incremental growth per day was less.[49]

The coat of the Cornish rex feels thinner than normal due to an absence of primary but not secondary guard hairs. Some coat may be lost, leaving bare areas. This is relatively uncommon. On the other hand, the Devon rex is very prone to coat loss, especially over the shoulders, chest and abdomen. All 3 hair types are present but grossly abnormal in comparison with those of the Cornish rex. The hairs show marked constriction of diameter along their length and break easily. It is characteristic of Devon rex for the vibrissae to appear stubby due to breakage.[129] The dominant gene for Dutch rex produces a rex type of coat in the heterozygote Rdrd and a very thin coat in the homozygote RdRd.[137,139]

Wire Hair

The wire-hair (Wh) coat appears unruly in contrast to the smooth coat of normal cats.[135] All 3 hair types are thinner in diameter than normal, and the primary guard hairs are curved instead of straight. The awn hairs are very undulated and may even be coiled. A "shepherd's crook" type of configuration may be present in the region of the subapical swelling. The wool hairs display exaggerated undulations. The coat may be slightly springy to the touch.

Sparse Fur

Sparse fur (sf) individuals exhibit partial alopecia, resulting in a thin coat that is rough to the touch. All of the hairs are short and deformed, while the vibrissae are bent or curled. A reddish or reddish-brown encrustation forms about the eyes, nose and mouth, and frequently affect the fur of the chest and abdomen. The eyelids become thickened and the globe shows signs of septic deterioration if left untreated.[139]

Hairless

Hypotrichosis has a long history of recurrence among cats. Cases have been described in Europe, North Africa and North America over the last 50 years (Fig 9). At least 3 distinct mutant genes (h, hd, hr) have been implicated. Cats with the 3 mutant genes have not been interbred; hence, it is unknown if 2 or more are alleles at the same locus or if all 3 represent independent loci.

Hairless cats are not completely devoid of hair, at least not until they are fully adult. Sparse down may be evident in kittens, but it is subsequently lost. Some hair growth occurs with each successive molt cycle as the individual matures. This is transitory, however, and the adult may be virtually hairless. The French hairless (h) may be temporarily covered by hair and the vibrissae are normal.[89] On the other hand, the Canadian hairless (hr) never has much hair and the vibrissae are short and curly.[133] Microscopic studies revealed that 2 types of hair fibers are present. One is distinctly thicker than the other, possibly representing vestigial guard and wool hairs, respectively. All of the fibers lack well-formed hair bulbs. The skin is thicker than usual and a number of hairless kittens display retarded growth.

The Redcar hairless (hd) manifests the most extreme expression of hypotrichosis.[65,136] Affected kittens never have more than a fine coating of down. The skin is soft at birth but steadily became thickened and wrinkled. The vibrissae are short, thin and crinkled. A brownish secretion can be seen about the nostrils and eyes, and under the chin. Few Redcar hairless kittens live beyond 2 weeks of age. One male that survived to about 3 months had defective, easily split claws. This tendency toward early death differentiates the Redcar hairless from the other 2 hairless mutants, both of which are viable and relatively hardy.

Cutaneous Asthenia

Scattered reports of cutaneous asthenia (cut) are found in the literature. It was not until 1977 that the genetic basis of the disorder in cats was elucidated, in spite of the fact that a similar malady was known to be a heritable trait in dogs, mink, cattle and

sheep. The condition arises from a severe deficiency of connective tissue, involving packing defects of the collagen fibrils and fibers in the reticular layer of the dermis. The skin is extremely hyperextensible and fragile (Fig 11). It is easily lacerated, even by normal scratching or play, and healing leaves white paper-chain scars. The skin often feels velvety to the touch. The anomaly is due to a dominant gene.[120]

A similar anomaly has been designated as dermatosparaxis.[23,29,70] No genetic studies were made with the affected cat, but reports described defective structure of the collagen fibrils, fibers and bundles. Conversion of precursor proteins to mature collagen is due to amino acid deficiencies in the NH_2-terminal procollagen peptidase.

Genetic Disorders of Sensory Organs

Progressive Retinal Atrophy

Progressive retinal atrophy (PRA) is an insidious malady. Retinal degeneration can be well-advanced before outward signs are obvious. In the late-developing type, this may even be after the cat has reproduced. This increases the difficulties of elimination by selective breeding. At least 3 different forms of PRA are known (rt, Rdy, rdy). They are differentiated from each other by age of onset and mode of inheritance. The PRA syndrome of cats is similar to retinitis pigmentosa in people and could serve as a useful animal model for the human disease.[112]

Figure 11. A cat with cutaneous asthenia. The skin is hyperelastic and easily stretched. (Courtesy of Dr. D. Patterson and *Journal of Laboratory Investigation*)

The clinical signs of PRA are bilateral dilation of the pupils (mydriasis), some nystagmus, hyperreflectivity of the tapetum lucidum, and progressive diminution of the retinal blood vessels. The photoreceptor layer of the retina, containing the rods and cones, undergoes progressive degeneration, with consequent steady deterioration of electroretinogram readings. Defective vision is manifested by cautious behavior and stumbling into objects that are normally avoided. The uniform descriptions of PRA in cats do not indicate that they are necessarily identical, either genetically or in their pathogenesis. When the onset of the rod-cone degeneration occurs at an early age, the process could be described as dysplasia rather than atrophy.

Scarcely any of the early reports on PRA showed that the condition was inherited. One exception hinted that some Siamese cats displayed a familial tendency for the malady.[15] Other data suggest a dominant mode of inheritance.[164] Signs of PRA were seen in kittens as early as 3 weeks of age, followed by rapid and progressive degeneration of the photoreceptor cells within a few months. Since retinal development is not completed until about 6 weeks of age, degeneration was thought to be rod-cone dysplasia.[42]

Another type of PRA described in Persian cats was clearly inherited.[141] The quantity of breeding data was limited but sufficient to indicate monogenic recessive inheritance (proposed gene symbol rt). The condition was apparent by 12-15 weeks of age, as evidenced by mydriasis. Histologic examination revealed only remnants of rods and cones and thinning of the outer layers of the retina.

The retinopathy in Abyssinians that occurs at an early age, is midway between the types of PRA described above.[4] The first signs were observed in 4- to 5-week-old kittens, and degeneration was well advanced by about 12 weeks. The anomaly was due to a dominant gene designated Rdy. A search for a homozygous individual among 4 affected kittens from heterozygous parents failed, however. Another group described a

stock of affected Abyssinian cats descended from a single male.[160] The investigators noted the resemblance of the disorder to taurine deficiency but were unable to document a defect in taurine homeostasis.

A third type of retinal degeneration, in Abyssinians, was found to be due to a recessive gene rdg.[110,111] This form differs from the preceding ones by a later age of onset and slower progression. The condition is diagnosed in most affected individuals between 18-24 months of age; the advanced stages of the disease are not reached until about 3 1/2-4 years. The initial signs of degeneration are in the peripheral and central regions of the photoreceptor layer of the retina. The central area is not involved until the final stages, and then less severely than that of the periphery. The inner retinal layers and the pigment epithelium appear to be unaffected.[112,113] Analysis of DC-recorded electroretinograms indicated that the rods are affected earlier than the cones.[114] The late onset of retinal degeneration indicates atrophy of the rod-cone layer, rather than dysplasia.

Central Progressive Retinal Atrophy

A form of PRA commencing in the area centralis of the retina was thought to be heritable.[6,63] The pathologic condition can be induced, however, by a dietary deficiency of the amino acid taurine.[3,64]

Cataract

Extensive bilateral cataracts by 12 weeks of age have been reported in Himalayan cats.[140] The cataracts were sufficiently dense to interfere with normal tapetal reflection in one case. In another case, the cataracts were extensive but insufficiently dense to be visible without ophthalmic examination. The amount of breeding data was limited but adequate to establish a monogenetic recessive heritability of the malady.

Epibulbar Dermoids

A unilateral epibulbar dermoid, attached by a broad pedicle to the conjunctiva inside the lateral canthus of either eye is familial in cats.[66] The pigmented dermoids have hairs that cause irritation of the cornea and keratitis if not removed. Dermoids may be due to an autosomal gene with incomplete penetrance or they may have a polygenic threshold inheritance.

Corneal Mummification

The occurrence of corneal mummification in semi-inbred strains of the colorpoint breed in Britain prompted the suggestion that the condition is caused by a recessive gene.[158] Mummification occurred in cats from 10 months to 8 years of age.

Corneal Edema

Corneal dystrophy is probably inherited, but the mode of inheritance has not been determined.[9] The anomaly was manifested at about 4 months of age as progressive edema of the anterior corneal stroma. The edema increases as the condition worsens, the corneal stroma thickens, and bulbous lesions appear in the corneal epithelium. This is followed by breakdown of the corneal stroma and epithelium and secondary bacterial infection.

"Cherry Eye"

Prolapse of the gland of the third eyelid (nicitating membrane) has been seen most often in Burmese cats, in which it is thought to be a heritable condition. The problem is thought to be due to weakness in the cartilage or fibrous tissue that supports the gland. The prolapsed gland becomes very edematous, enlarged and hyperemic, resembling a small cherry attached to the third eyelid.

The treatment has been excision of the prolapsed gland, though this can lead to complications of inadequate tear production. Newer reconstructive surgeries are therefore recommended.

Abnormal Visual Pathways

Albino mammals completely lack melanin pigment; hence, their eyes are pink or red and the coat white. They also have a misrouting of the visual pathway from the retina to the brain. The anomaly has been detected in albinos of all species so far examined, including Syrian hamsters, guinea pigs, rabbits, mice, rats, ferrets, mink and

one species of monkey. The visual pathway is affected in cats carrying either the albino (c) or Siamese (c^s) allele, but not the Burmese (c^b) allele.

The ganglion axons from the retinal cells of the eye normally travel to the lateral geniculate nucleus of the thalamus. This nucleus is sited in each side of the brain. Each eye contributes fibers to defined layers of the lateral geniculate nuclei. A disproportionate number of fibers in Siamese cat (c^sc^s) crosses to the lateral geniculate nucleus on the side opposite to the eye. The lateral geniculate nuclei are incorrectly innervated in reverse order. The cat's brain probably does not receive a distorted picture, however.

Elegant experiments suggest that the visual field is compensated by either of 2 methods.[57,72,82] The most direct is apparent suppression of the abnormal information when it reaches the visual cortex (the "midwestern pattern"). The other compensation method involves rearrangement of information inputs to recreate a normal visual field (the "Boston pattern"). The 2 methods of compensation may not be absolute, but rather part of a continuum.[24,25] The method of compensation may depend upon the extent of the erroneous crossover of ganglions. Misrouting is present from the earliest prenatal stages of development of the ganglion pathway and arises at the optic chiasm.[147] Misrouting may interfere with normal binocular depth perception and is responsible for the convergent squint to which Siamese are particularly prone.[83]

The Siamese allele (c^s) falls short of complete albinism, but the complete albino allele (c) has recently been recognized. Examination of the visual pathway in albinos reveals misrouting to be much greater than in Siamese. A much higher proportion of the ganglion axons crosses over to the opposite lateral geniculate nucleus. As a consequence, organization of the visual field in the cortex differs from that observed for Siamese.[31,90] The albino allele is completely recessive to full color (C) as regards eye and coat color, but not for misrouting of ganglion axons. Heterozygous Cc albinos or Siamese have similar misrouting, but less extreme.[91]

Deafness in Mixed-Breed White Cats

White coat color is due to a dominant gene W.[156] These cats may have yellow or blue irides (or heterochromatic for yellow/blue), unilaterally or bilaterally. They may also be unilaterally or bilaterally deaf. Blue irides, though indicative of partial depigmentation, are not considered to be anomalous. Deafness, on the other hand, is considered to be detrimental. The W gene has a slight but significant effect on postnatal viability.[8]

Blue color of the iris and deafness are correlated, as may be seen from the following observations extracted from the literature.[8,99] Among a group of 240 mixed-breed white cats, 68% had blue eyes and 45% were deaf. However, when the 2 traits are considered together, 39% were blue-eyed and deaf, 29% were blue-eyed but were not deaf, 7% had yellow eyes and were deaf, and 25% had yellow eyes but were not deaf. The correlation coefficient between the 2 traits is 0.34 (1.0 being total correlation). The association is increased when considering the relationship between color of the eye and deafness on the same side of the head. Among a sample of 748 eye and ear combinations, 49% were blue and deaf, 18% were blue and were not deaf, 8% were yellow and deaf, and 25% were yellow and were not deaf. The correlation between ipsilateral blue eyes and deafness is $r = 0.46$.

The simplest explanation of these observations is that the W gene has a syndrome of effects.[135] The gene is completely penetrant regarding coat depigmentation but is only partially penetrant for blue iris color and deafness. Arguments supporting independent genes for blue irides and deafness are not convincing. The penetrance of these 2 traits probably depends upon the genetic background against which the W gene is assorting; thus, the incidence of either trait varies among strains of cats. In this connection, long-haired animals displayed a higher incidence of blue irides and deafness than short-haired cats.[99] The chromosome carrying the long-haired gene may also carry genes enhancing penetrance of blue eye color and deafness.

The incidence of blue irides and deafness is higher among mixed-breed white kittens

when both parents are white than when one parent is white, suggesting that penetrance of both traits is greater in homozygous WW individuals. This implies that W is incompletely dominant in its primary effect. This would not be apparent if coat color alone is considered, because the presence of a single W gene would suffice to remove all pigment from the hair. In support of this hypothesis, the small spots of colored fur seen in a minority of white kittens, but not apparent at adulthood, are more frequent in heterozygotes than in homozygotes.[8]

Pigmentation of the eye in yellow-eyed white cats is essentially normal. On the other hand, the eyes of blue-eyed white cats are partially depigmented. The iris and retina epithelia are normally pigmented but pigment is absent, wholly or in part, from the iris, choroid stromata and tapetum. The partial depletion of pigment is comparable to the macroscopically observable heterochromia of the iris.[151] The absence of tapetum usually results in marginal or obvious dilation of the pupil.[8] Tissues affected by the W gene originate from the neural crest, while those derived from the embryonic optic cup (iris and retinal epithelium) are not affected.[151]

Loss of hearing is due to degenerative processes in the inner ear, unilaterally or bilaterally. Histologically, these degenerative changes have been traced back as far as the fourth and sixth days postpartum.[11,12] The extent of the cochlear anomaly is variable and may affect each ear differently. The changes appear to begin with collapse of Reissner's or tectorial membranes and atrophy of the stria vascularis. Eventually, all or part of the organ of Corti and spiral ganglion neurons are involved. Variability is such that some organs may appear superficially normal (tunnel of Corti and hair cells), while others are wholly abnormal.[100,126] Hearing loss may progress rapidly over several weeks, or slowly, extending for months. Degenerative changes may slow down or halt with time.[127] Degenerative changes of the cochlear structures are associated with progressive deterioration of the primary ganglion neurons. The deterioration was initially considered to be a secondary change. However, it seems that the neural elements may be subtly affected from the onset. An unusually high proportion of unmyelinated fibers can be seen in the lamina spiralis, as well as in neurons with clear and empty cytoplasm and minute nuclei. The nonmyelination could be noted in 2- and 4-day-old kittens, earlier than the first appearance of histologic lesions.[100] The age of onset of spiral ganglion degeneration may be variable. In some strains of W individuals it may be delayed for several months. Whatever the time course, the malady appears to be progressive.[44,163]

Investigation of the retinogeniculate ganglion pathways in W cats revealed no signs of abnormality.[56,92] A few blue-eyed white animals were clearly abnormal, but breeding experiments showed that their genotypes were $c^s c^s Ww$. The W gene is epistatic to c^s in regard to coat color. On the other hand, eye color is invariably blue due to the degrading action of the c^s gene on production of melanin pigment. It is evident, therefore, that the c^s gene can disrupt normal decussation of the visual pathways independently.

Preliminary analysis of the distribution of 16 amino acids and sugar content among perilymph, cerebrospinal fluid and serum revealed both qualitative and quantitative differences. Notable differences were not observed, however, among fluids from white cats with normal hearing or deafness.[45]

The W syndrome of white coat, blue or heterochromatic iris, and deafness has been compared with Waadenburg's syndrome in people. Defects in the embryonic neural crest are common to both syndromes, but they have a different genetic basis. The effect on hair pigmentation in people is confined to a white forelock, a far less drastic suppression of pigment than found in cats. The facial abnormalities observed in people are absent in the feline syndrome.

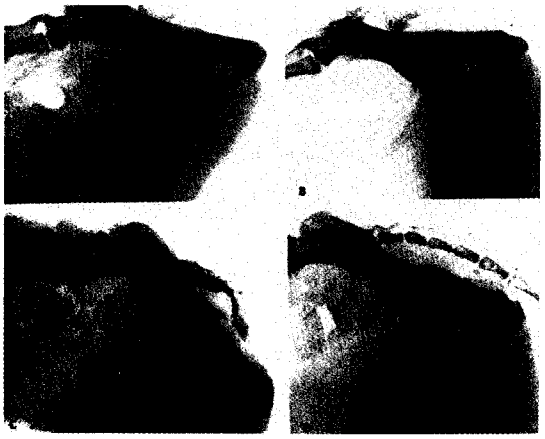
Deafness may be avoided in white cats by using underlying c^s genes. This is why purebred white cats are usually not deaf.

Malformations

Manx Taillessness

Manx taillessness is due to a dominant gene M, which is a prenatal lethal when homozygous MM.[150,154] Manx cats with no or abbreviated tails are heterozygotes. Since the Manx gene varies in expression, most

Figure 12. The 4 tail types in Manx cats are: rumpy, the absence of coccygeal vertebrae (top left); rumpy-riser, reduced number of rigid vertical coccygeal vertebrae (top right); stumpy, reduced number of coccygeal vertebrae in a ventral position (bottom left); and normal-tailed Manx (bottom right). (Courtesy of Dr. J. Howell and *Journal of Heredity*)



Manx cats are not totally tailless. Four categories of taillessness are recognized: rumpy, in which no coccygeal vertebrae are apparent; rumpy-riser, in which 1-7 vertebrae can be felt, usually immovable; stumpy, in which 2-14 vertebrae are present, usually movable but often knobby or bent; and longie, in which the tail is shorter but superficially normal (Fig 12). The rumpy is held as the ideal of the breed.

Some heterozygotes, though born alive, have anomalies of sufficient severity to affect them as kittens or later in life. The proportion of such overly anomalous heterozygotes may be linked to additional genetic selection for short body conformation. Manx cats bred for short body conformation produce more diseased heterozygotes than Manx with longer bodies.

Some heterozygous Manx cats may exhibit abnormalities in addition to the obvious tail defects. In the mildest cases, the gait in the hind limbs is often affected. A peculiar stilted walk or hopping movement is due to maldevelopment of the caudal vertebral column. The whole spine is probably affected to some degree, but the major changes occur in the caudal part. The thoracic, lumbar, sacral and coccygeal vertebrae are small, deformed, occasionally fused and reduced in number.[71] In Manx with more severe caudal spinal deformities, both fecal and urinary incontinence are frequent occurrences, apparently due to denervation insensitivity of the anal and perineal area.[36,74,88,101] The perineal fur of such kittens is often stained and matted. Both the colon and bladder may be greatly enlarged. Some heterozygotes may develop megacolon, constipation and obstipation later in life. Such cats probably have partial denervation of the colon at birth. The colon tends to become larger, more sacculated and more atonic over time. Spina bifida and related gross anomalies are seen in a smaller proportion of heterozygotes.

The Manx syndrome is caused by abnormal development of the caudal region of the embryonic neural tube. This leads to defects of the caudal vertebral column, especially spina bifida, and the spinal cord. The spinal cord may terminate abruptly due to an absent sacral cord segment, which normally would innervate the colon, bladder, hind leg muscles and perineum. Vertebral anomalies are derived from the same neural tube disorder.[36,88]

Manx cats have been associated with the Isle of Man, situated off the west coast of England; hence the name Manx. The Manx cat has been said to originate on the island, but this is doubtful. The belief is encouraged for commercial and social reasons. Cats with the Manx gene have appeared in small numbers in many parts of the world. The gene even occurs in "pockets" of unusually high frequency, which is unusual considering its highly deleterious nature. Human preference for novelty is probably responsible for such pockets. However, the M gene may have a selective advantage that would enhance its frequency.[1] The hypothesis is based upon breeding data that show that M is assorted from the normal allele at a significantly higher proportion than could be accounted for by random assortment.[150,154] A model was proposed to reflect this selective advantage and applied to the unusually high frequency data for M in the Isle of Man cat population. The model could not explain all the observed high frequency in the population, and the author concluded that both human preference and selective advantages were maintaining the high frequency.[1]

A sample of 314 progeny from Manx x Manx matings drawn from the records of a prominent English breeder consisted of 201 Manx and 113 tailed kittens. This closely fits to the expected 2:1 ratio of Manx:tailed.[139]

Brachyury

An inherited shortening of the tail has been described in the Siamese cat.[109] The tail was consistently shorter than normal, though with some variation. Breeding data were consistent with a monogenic recessive inheritance (br).

Polydactyly

Polydactylous cats have extra or partly formed digits on the feet. This is especially noticeable in the front feet. Polydactyly is induced by the action of a dominant gene Pd, possibly by enhancing the growth potential of the preaxial region of the embryonic limb bud.[17,33,34,144] Expression of polydactyly is variable. One investigation listed as many as 8 recurring types of anomalies, 3 for the fore and 5 for the hind feet. Once the gene has affected a certain developmental path, the outcome is more or less prescribed. Variation in expression extends from enlargement of a single digit to the presence of 3 quasi-normal extra digits. Difference of expression is frequent between right and left feet and front and rear feet. The hind feet are very rarely affected in the absence of front feet anomalies. Breeding data are inadequate to establish whether any of the various types are genetically controlled by modifying polygenes.

Split-Hand

An extrosyndactyly designated as split-hand is due to a dominant gene Sh. It is usually expressed by a central cleft of the forefeet with some syndactyly (fusion of digits). The anomaly varies from reduction in the number of phalanges to disorganization of the metacarpal and carpal bones. Syndactyly is evident as double claws and fused paw-pads. Even the most severely affected cats can run and jump normally, though climbing is somewhat impeded.

Folded Ears

The pinnae of normal cats are carried in an upright, "pricked-eared" position. The pinnae of fold-eared cats, however, are bent forward at the apex. The ears appear normal for the first 4 weeks of life, but then begin to bend forward. The fold is permanent by about 3 months of age. The condition is inherited as an autosomal dominant (Fd).[135]

Fold-eared cats are usually heterozygotes Fdfd without other abnormalities. The homozygote FdFd not only has folded pinnae but sometimes gross anomalies of the coccygeal vertebrae and distal bones of the limbs. Clinically, the tail is inflexible, stubby and thick, and the feet are swollen and arthritic (Fig 10). The activity of such animals is curtailed. The toenails grow in a curve to penetrate the pads. The coccygeal vertebrae and smaller bones of the distal limbs are shorter than normal and the deformed vertebrae have wide epiphyseal plates. The primary cartilage anomaly results in disturbed epiphyseal growth. Ossification is deficient and irregular.[73]

Early observations of fold-eared cats indicated that the skeletal anomalies were confined to homozygotes. It has been subsequently found that some heterozygotes could also be grossly affected, with thick short tails, swollen feet, and impaired activity.[139]

American Curl

The American curl (Cu) is a recently discovered mutant gene. It is outwardly expressed by backward curving of the pinnae. The degree to which the ears curve backward is variable, though the abnormal gene appears to be fully penetrant. Most affected cats examined have been heterozygotes resulting from numerous outcrosses to unrelated stock. About 50% of the resultant kittens had curled ears, indicating a dominant mode of inheritance. A homozygous curl-eared male has not revealed any other anomalies by 2 years of age, thus differentiating the condition from the folded ear trait.[139] Early breeding reports have indicated a potential problem in some cats with hard cartilage. There is a tendency toward narrowness at the base of the ear, making it difficult to clean the ears. Breeders are beginning to select for a broad ear base to avoid this problem.

Meningoencephalocele

This malformation is due to herniation of meninges and brain tissue through a fissure in the skull. It is perinatally lethal. A pedunculated mass of skin filled with brain tissue and fluid may be seen arising from the top of the head. The mandible is normal but the tongue is large and often split. The maxilla is shorter than normal, with a cleft replacing the nostrils and sometimes extending into the palate. Dentition is abnormal, and the eyes and sometimes eye sockets are missing. The top of the skull may be depressed. The dorsal cerebrum is herniated and the parts of the brain remaining in the skull are compressed. There is extensive hemorrhaging. Primitive eye tissue may be present in the skull, consisting of groups of retinal cells, pigmented epithelium and portions of optic nerves and lens.[168]

The frequency of affected kittens corresponds with the assortment of an autosomal recessive gene mc. The gene may have variable heterozygous expression, but the evidence is ambiguous.[149]

An inherited midfacial malformation has also been described in Burmese cats.[149] The genetic basis of this disorder was the same as meningoencephalocele but the description of the anomaly was somewhat different.

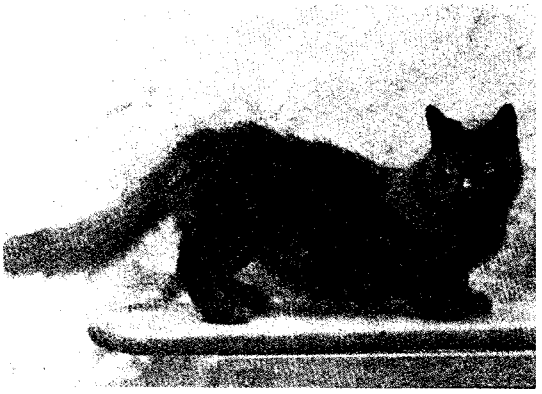
Four Ears

The name is prompted by a small extra pinna on each side of the head. This is probably only one superficial expression of a more fundamental affliction. Affected cats are microphthalmic, with slightly undershot jaws. Body size seems to be unaltered and the animals are often lethargic.[93] The anomaly has also been called "duplicated pinnae" (gene symbol dp).

Osteogenesis Imperfecta

Osteogenesis is an inheritable disorder of bone that leads to excessive bone fragility and pathologic fractures. It is a heterogeneous syndrome in people, with each type having its own peculiar pattern of inheritance, clinical symptomatology and biochemical defects. A 12-week-old domestic kitten with severe bone fragility and multiple pathologic fractures has been described.[171] The kitten may have resulted from a mother-to-son mating. This condition is not to be confused with secondary nutritional hyperparathyroidism, an acquired bone disorder of kittens that is caused by feeding excessive amounts of organ meat.

Figure 13. Cat with foreleg micromelia.[165] Such animals are often called "kangaroo cats" by laypeople. The hind limbs are of normal size but the long bones of the forelimbs are shorter than normal. (Courtesy of Dr. H. Williams-Jones and *Veterinary Record*)



Patellar Luxation

Luxation of the patellae is becoming more common in cats. The Devon rex was one of the first breeds recognized to have this condition. No obvious defects of bone structure appear to be responsible for the luxation. Occasional luxation may not lead to lameness, but recurrent luxation can cause lameness. The breed incidence suggests a genetic influence but the mode of inheritance is unknown.[35,47] The proportion of affected animals is less than 25% on the basis of assortment of a recessive gene. Either a proportion of affected individuals have escaped detection or the anomaly has a polygenic threshold character.

Medial patellar luxation has also been seen in the Chartreux, an old and rare breed of French short-haired cats. The luxation is particularly severe by 1-2 years of age. The trait is definitely genetic in this breed, but the precise mode of inheritance is unknown. The defect is probably polygenic. An increasing incidence of medial patellar

Figure 14. Severe cleft palate in a newborn Siamese kitten.[97] (Courtesy of Dr. H. Loevy and *Cleft Palate Journal*)

luxation has recently been recognized in Abyssinian cats.

Foreleg Micromelia

An apparent case of foreleg micromelia has been described.[165] The affected cat had unusually short long bones in the forelegs (Fig 13). It was healthy but measured merely 6.75 inches from shoulder to ground and 9.25 inches from croup to ground. The animal could move quickly in spite of the abbreviated forelimbs. Similarly affected kittens occurred in at least 4 other litters. The dam, a great dam and some of the animal's progeny also had the deformity. These details suggest that micromelia is inherited but do not establish the mode of inheritance.

Protruding Sternum

Protrusion of the cranial sternum is commonly seen in Siamese cats, and in breeds derived from Siamese. The defect is less common in Abyssinian cats and mixed-breeds. The defect does not appear to be associated with any health problems. The qualification status of purebreds with this defect is unresolved. The defect is heritable, but the mode of inheritance is unknown.

Cleft Palate

The condition is often genetic. The first sign is usually inability of affected kittens to suckle properly. The extent of the cleft is variable. In mild cases only the soft palate is involved, while in severe cases there may be clefting of the hard palate and a harelip (Fig 14). In studies of the defect in families of Siamese, the anomaly was clearly familial yet the precise mode of inheritance was unclear.[96,97] The frequency of anomalous kittens among 10 litters of 43 kittens was 30.2%, a close approximation to the expected 34.9% of an autosomal recessive gene. An alternative possibility is that cleft palate is a polygenic threshold character. Cleft palate can also have nongenetic causes, often from medicating pregnant queens with such drugs as griseofulvin during pregnancy.

Craniofacial Anomaly of Burmese

The condition is caused by an autosomal dominant gene with variable expression depending on modifying genes.[115,168] It is manifested by exencephaly, lack of eyes or a nose, mild to severe hydrocephalus, and a severely protruding jaw. Some affected individuals may also exhibit a double set of whisker pads, cleft palate and rotated ear flaps. The defect has been linked to a change of the head shape in the breed. In fact, it is thought that Burmese cats with exceptionally rounded heads and short faces are heterozygous for the gene. A few cats with normal heads have produced abnormal kittens, and some Burmese cats with extreme head structure consistently produce normal kittens.

Neuromuscular Disorders Due to Heritable Errors of Metabolism

An increasing number of inherited neuromuscular defects has been recognized in cats. They share features of abnormal behavior, such as tremor or ataxia, and generalized weakness. The degenerative changes in the neuronal pathways may be similar for several of the maladies even though they are caused by deficiencies of different enzymes. Some of the anomalies may serve as models for comparable human diseases.

GM1 Gangliosidosis

Kittens with this neuronal degenerative syndrome are normal until 2-3 months of

age, when a fine tremor of the head and hind legs becomes apparent. The tremor becomes more pronounced in the ensuing months, lead to generalized dysmetria. Affected cats show spastic quadriplegia by 7-8 months, and grand mal seizures by one year of age. There is steady deterioration of vision in the final stages.

Histologic examination of the spinal cord and brain reveal extensive neuron ganglia degeneration, as indicated by swelling and cytoplasmic vacuolation.[2] Total ganglioside N-acetyl-neuraminic acid content in the cerebral cortex is about 2 1/2 times normal. A pronounced deficiency in beta-galactosidase activity is present in affected homozygotes. The deleterious gene (ga-1) behaves as a codominant at the biochemical level. Phenotypically, GM1 gangliosidosis is expressed as a recessive trait. The disease is remarkably similar to juvenile GM1 gangliosidosis in people.[3,46]

GM2 Gangliosidosis

The signs of this disease are similar to those of GM1 gangliosidosis but are caused by a different enzyme deficiency. Affected kittens are normal until 6-10 weeks of age when a fine head tremor appears. The tremor increases in severity and is followed by ataxia that progresses to paresis and paraplegia. The head has an unusual rounded appearance and the corneas are diffusely opaque. Affected kittens have difficulty eating because of the head tremor and occasional dysphagia.

Neuron cell bodies throughout the nervous system, including the autonomic ganglia and retina, are distended and almost devoid of Nisi substance, and have foamy cytoplasm. The total ganglioside content is 2-3 times greater than normal, especially for the GM2 ganglioside component. Beta-galactosidase activity is at normal levels, but levels of beta-hexosaminidase are only a fraction of normal. The activity of the latter enzyme in heterozygotes is intermediate to those of homozygous affected and normal cats. Though phenotypically the anomaly may be regarded as a complete recessive, the ga-2 gene behaves as a codominant at the biochemical level. The associated histopathologic lesions are remarkably similar to those of GM2 gangliosidosis type II (Sandhoff disease) in people.[26,27]

Mannosidosis

Glycoproteins containing branched alpha-mannosyl residues are constituents of cell membranes and are found in many body fluids. A deficiency of alpha-mannosidase causes abnormal metabolism of alpha-mannosides and excessive accumulation of mannose-rich oligosaccharides in body fluids and within cell lysosomes. A genetic deficiency of alpha-mannosidase has been reported in domestic and Persian cats.[14,75,157] It appears to be an autosomal recessive trait by pedigree analysis (Fig 15).

Figure 15. Top: Pedigree analysis of a group of Persian cats with mannosidosis. Bottom: Typical affected kitten. Kittens with mannosidosis are apathetic in appearance, demented and generally weak. They rapidly develop tremors, ataxia and impaired righting reflexes. (Courtesy of Dr. M. Haskins, University of Pennsylvania)

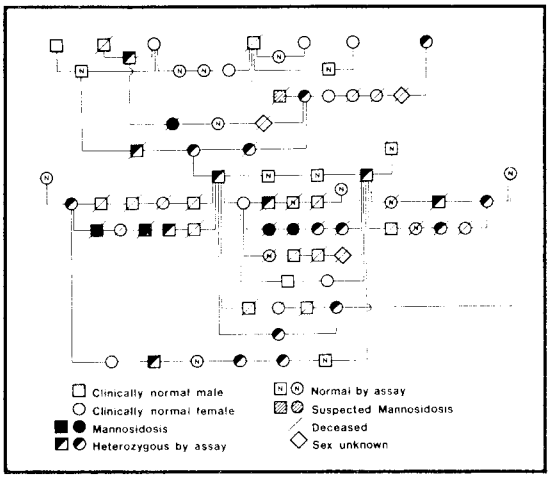
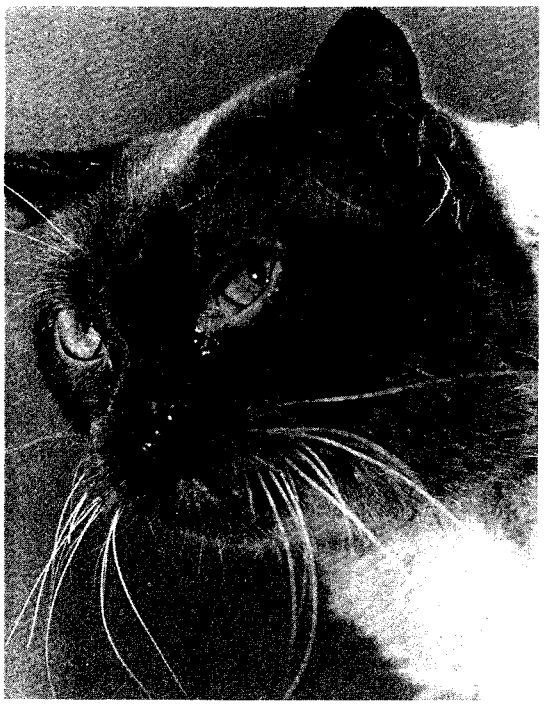


Figure 16. Siamese cat with mucopolysaccharidosis I. Affected cats have broad faces with shortened noses, frontal bossing, depressed nasal bridge, small ears, thickened skin over the neck and corneal opacities. (Courtesy of Dr. M. Haskins, University of Pennsylvania)



Clinical signs of mannosidosis appear during the first days or weeks of life and include generalized weakness, apathy and diarrhea, followed by progressive tremor, ataxia and impaired ability to recover a normal posture (Fig 15). The voice steadily weakens and the abdomen becomes swollen due to hepatomegaly. The most obvious histologic findings are vacuolation of neurons and glial cells of the central nervous system and hepatocytes. Vacuolation is minimal in kittens at 7 days of age but extensive from 12 days of age on. Vacuoles in cells appear "empty," but they are filled with mannosides. Analyses of lysosomal enzyme activity reveals a dramatic reduction in levels of alpha-mannosidase and increased levels of 7 other associated enzymes.[157]

Most affected kittens show none of the above clinical signs but are born dead or die in the neonatal period. It is uncertain if this early death is related to mannosidosis or to acute infections possibly associated with immunologic incompetence. Several affected kittens lacked thymic tissue; thymic atrophy may be due to disease in general and not specifically to mannosidosis, however. The inheritance pattern of the feline disease is consistent with an autosomal recessive gene (man).[75]

Mucopolysaccharidosis I

The primary features of mucopolysaccharidosis I in adult cats are a broad, short nose, frontal bossing, depressed nasal bridge, small ears, corneal opacity and thickened skin over the dorsal aspect of the neck (Fig 16). Affected animals adopt a crouched position, with forelegs spread. Pain can be elicited by manipulation of the head, neck and hips. The skeleton is defective; cervical vertebrae are wide, asymmetric and frequently fused, and the sternum is unusually concave. Bilateral coxofemoral subluxation, associated with shallow acetabula and abnormally shaped femoral heads, is also common.

Postmortem examination reveals hepatosplenomegaly; both the liver and spleen are difficult to section. The left atrioventricular heart valves are thick and white. Cerebral

Figure 17. Cat with mucopolysaccharidosis VI. The head is smaller than normal, the face flattened and the muzzle short and broad, with a depressed nasal bridge. The upper eyelids are swollen and drooping. (Courtesy of Dr. M. Haskins, University of Pennsylvania)

ventricles appear abnormally large. Neurons in the cranial nerve nuclei, reticular formation, hypothalamus, hippocampus and middle layers of the cerebral cortex, and of the dorsal horn of the spinal cord, are grossly swollen with vacuolated cytoplasm. Electron microscopic studies demonstrate mucopolysaccharide-filled lysosomes in neurons of the spinal cord, left atrioventricular valve, neutrophils, hepatocytes and fibroblasts of the eye and spleen.[60,61]

Assay of enzymatic activity in peripheral leukocytes and cultured fibroblasts reveals a marked deficiency in alpha-L-iduronidase, but not of other lysosomal enzymes. Cells from the mother of one affected cat, and 1/3 half-siblings, revealed alpha-L-iduronidase activity of about half normal. This observation is consistent with the assortment of an autosomal semidominant or codominant gene (Mps-1). Histopathologic lesions closely resemble those of Hurler's syndrome in people.[61,62]

Mucopolysaccharidosis VI

Signs of this disease appear at 3-6 weeks of age. Body size and tail length are reduced, the head is smaller than normal, and the face is flattened, with a short, broad muzzle and depressed nasal bridge (Fig 17). The upper eyelids also appear to be swollen and drooping, with the palpebral opening narrower than normal. The corneas have a ground-glass opacity with prominent Descemet's membranes. Retinal atrophy is observed in some animals, while the pupils of other animals respond only to very bright light. Affected animals adopt a crouched posture, with abducted stifles, cervical inflexibility, and a gait that becomes increasingly clumsy. Posterior paresis occurs at about 7 months of age in some individuals. Spot tests of urine are positive for glycosaminoglycans, in contrast to normal animals in which none are found. The primary glycosaminoglycan is dermatan sulfate.[59,63,76,104]

Many parts of the skeleton are severely anomalous, particularly in older cats. The spinal column is severely affected, with fusion and proliferative lesions of the cervical, thoracic and lumbar vertebrae. Fusion is evidenced by bony ridges and disruption of the intervertebral disks. The pelvis has shallow acetabula, and the femoral heads are flattened and sometimes subluxated. All of the long and many of the short bones exhibit epiphyseal dysplasia. Some osseous changes are progressive.

Histologic examination reveals vacuolation of the cytoplasm in fibroblasts of the atrioventricular valves, eyes, skin, aorta and spleen, bone marrow granulocytes, keratoblasts and pigment epithelium. Affected cells are packed with small inclusions when viewed by electron microscopy. These are not readily observable at the light microscopic level. The inclusions have a clear, granular or lamellar appearance.

Fibroblasts from homozygous affected individuals are deficient in arylsulfatase B lysosomal enzyme. Levels of 5 other lysosomal enzymes are significantly elevated.[63] Heterozygotes may have lower arylsulfatase B activity than normal, but the range of variation overlaps that of homozygous normals. Heterozygotes are usually detectable by assaying both arylsulfatase B and arylsulfatase A activities, and calculating the ratio of the former to the latter.[105,106,159]

The first arylsulfatase B-deficient cat was discovered in 1976 and was used to develop an inbred strain of affected animals. Subsequently, a second cat with the defect was discovered and it was also established as a strain. Both cats were Siamese but unrelated. Crosses between heterozygotes of the 2 strains produced affected individuals identical in every clinical respect to those of the 2 strains, suggesting that the 2 deleterious genes are identical alleles. A thorough analysis of partially purified arylsulfatase B from the 2 types of affected cats revealed 2 different variants with different and distinctive physical and chemical properties, however.[104] The gene products of each allele could be separated by gel electrophoresis. It is apparent that the alleles behave as codominants to the normal gene and to each other. The allele carried by the first strain is designated Mps-6^a and the allele carried by the second strain as Mps-6^b.

Successful alleviation of mucopolysaccharidosis has been accomplished by bone marrow transplants. After a male cat with advanced disease received whole-body irradiation to destroy its own bone marrow cells, it then was infused with bone marrow

cells from a histocompatible female sibling.[51] The transplantation was successful and subsequent karyotyping revealed a stable chimeric situation of 73% recipient cells and 27% host bone marrow cells. This corneal opacity completely disappeared and the face became more normal in appearance. There was an improvement in movement of the head and neck, and in ability to walk.

This anomaly is being extensively researched. The information obtained from this work is of considerable interest to researchers in feline medicine but also holds considerable promise for those studying human medicine. Feline mucopolysaccharidosis VI is similar but not exactly identical to the Maroteaux-Lamy syndrome of people. Other than hepatosplenomegaly, which is absent in affected cats but present in affected people, the similarities are striking.

Glycogen-Storage Disease

Various metabolic defects in the enzymatic processing of stored glycogen to glucose have been observed in people and dogs. Three related Norwegian Forest Cats have been found to have an inherited deficiency of alpha-1, 4 glucan:alpha-1, 4 glucan 6-glucotranserase (branching enzyme).[169] Two of the cats developed generalized muscle tremors, weakness and fever beginning at 5 months of age. These signs progressed to tetraplegia with severe muscle atrophy and limb contractures by 8 months of age. Serum creatine phosphokinase activity was greatly increased. One of the 2 severely affected cats died of heart failure at 13 mnths of age. The third cat died before clinical signs developed. Histologic examination of all 3 cats demonstrated intracytoplasmic storage of PAS-positive material in skeletal and cardiac muscles and the nervous tissues. Family studies suggest a simple autosomal recessive inheritance.[169] The condition is analagous to type-IV glycogen-storage disease of people.

Glycogenesis is thought to be a heritable disease of cats.[142] No genetic studies have been made, however. The initial affected individual was described as "a young, apparently healthy cat." The absence of clinical signs was thought to be due to accumulation of glycogen that had not yet reached a critical level. The glycogen-glucose content of the gray matter of the brain and spinal cord of the affected cat was about 6 times greater than normal. The cytoplasm of both nerve and glial cells contained large numbers of spherical glycogen-loaded bodies. The overall clinical appearance closely resembles Pompe's disease, which is a recessive inherited glycogen storage anomaly of people.

Neuroaxonal Dystrophy

Neuroaxonal dystrophy is a progressive axon dystrophy mediated by a recessive gene nd. The disease is likened to infantile neuroaxonal dystrophy in human infants and may be a useful animal model.[166] Affected cats have a light grayish coat color similar to that of the lilac phenotype. Defective kittens behave normally for the first few weeks of life but then develop progressive ataxia. Nodding of the head progresses to shaking by 5-6 weeks of age. The gait becomes uncoordinated several weeks later. Ataxic individuals overreach with their paws and have poor or no placing ability. A slow pupillary reflex indicates impaired vision. The inner ear shows marked depletion and abnormal neurons in the spiral ganglia.

The most prominent lesion in the brain is ballooning of the nerve cell processes in the superior lamina of the inferior olivary and lateral cuneate nuclei. The nucleus ventralis lateralis and ventralis anterioralis of the thalamus and cerebellar vermis are affected to a lesser extent. The swollen axons have a fine granular quality, with an occasional dark center. There is neural loss and increased glialization. Loss of Purkinje cells and depopulation of the granular cell layer occur in the cerebellar vermis.

Spheroid Lysosomal Disease

Kittens with spheroid lysosomal disease are normal until about 8-12 weeks of age, when a tremor develops and progresses to head nodding and body swaying.[86] Locomotion is slow, with ataxia, dysmetria and falling. The sense of direction also is disturbed. Handling precipitates seizures of short duration. The appetite is normal but feeding habits are clumsy. The anomaly is due to an autosomal recessive gene (sl).[10]

Neuronal lesions are present throughout the brain, particularly in the frontal cortex,

medial geniculate body, superior colliculi, caudate, dentate, cuneate and ambiguous nuclei, and cerebellum. The cervical spinal cord is less severely affected. The most striking lesion is numerous spheroid bodies. These are inapparent in the frontal cortex but prominent in the corpus callosum, brainstem and cerebellar white matter. The spheroid bodies are presumed to be swollen myelin sheaths. The lymph nodes and spleen contain large vacuolated macrophages. This may be a lysosomal storage disease, though the accumulated substance has not been identified.[86]

Sphingomyelinosis

Three cases of sphingomyelinosis have been described.[162] Affected cats developed tremor, ataxia, posterior dysmetria, anorexia and loss of interest in surroundings beginning at 4-5 months of age. A higher-than-normal amount of GM2 and GM3 gangliosides were found in the brain, and a 9- to 10-fold increase of cholesterol and sphingomyelin in the liver of affected individuals. Tissue assays failed to detect sphingomyelinase activity. A study of 8 suspected heterozygotes revealed 5 with one-half normal levels of sphingomyelinase activity. Though the deleterious gene (sp) could be regarded as a recessive based upon clinical phenotype, it behaves as a semi-dominant or codominant at the biochemical level. The anomaly is very similar to Niemann-Pick's disease in people.

Tremor

This nervous disorder is manifested as a continuous whole-body tremor in kittens 2-4 weeks of age.[117] The trunk and head roll and bob in an undulating manner, while the tail weaves in circles. Shaking abates when the animal is at rest or when it is held very firmly. Affected kittens continue to tremble even when suspended by the neck. The gait is normal except for some stumbling on rough surfaces. Swimming ability is slightly impaired. Electroencephalograms of one kitten revealed significant seizure-like activity. Affected individuals grow less quickly than normal and may be less viable. No gross histologic changes in the cerebellum can be detected.

Hydrocephalus

Most cases of hydrocephalus arise as isolated events and probably constitute mishaps of embryonic development. Nevertheless, a series of affected animals in a partially inbred strain of Siamese cats indicated a simple monogenic recessive inheritance (hy) of the trait.[148] Affected kittens were stillborn, hydrocephalic and often bloated, with edema of the limbs.

Globoid Leukodystrophy

Early signs of this disease are weakness and incoordination of the hind limbs beginning at 5-6 weeks of age.[77] The condition becomes steadily worse and the dysmetria may spread to the forelimbs. A tremor is present. Affected kittens are usually euthanized at an early age before the disease has run its full course. The cerebellum is apparently normal, but the white matter of the brain has a dull color with extensive loss of axons and myelin. Globoid cells are distributed throughout the more severely affected areas. Evidence favoring a genetic basis for the anomaly is weak. A similar disease is inherited as a recessive trait in dogs and people.[77]

Hyperchylomicronemia

Kittens with hyperchylomicronemia (hce) exhibit normal growth but have persistent lipemia.[5,79-81] At about 8-9 months of age, the animal develops signs of peripheral nerve paralysis. Both the cranial and cervical nerves are affected. There may be absence of the corneal reflex, inability to chew food, absence of the patellar reflex and inability to extend the digits. The major clinical feature of the anomaly is disseminated, often multiple nodular granulomas and hematomas in many tissues. These lesions appear to compress the peripheral nerves, especially at sites where the nerves are subject to injury. There is some evidence of axonal degeneration and loss of myelinated fibers. Individuals fed a high-fat diet had more pronounced lipemia and more severe neuronal signs. A low-fat diet diminishes the level of lipemia and reverses clinical signs. The condition is inherited as a recessive, with the proposed symbol hce for the causative gene.

Thiamin Deficiency

A group of enzyme deficiencies in people causes a relative or absolute deficiency of thiamin (vitamin B_1). The Wernicke-Korsakoff syndrome is a neurologic disorder seen mainly in alcoholics and other people on vitamin-deficient diets. People with the defect (abnormal transketolase enzyme) have a relative deficiency and are clinically normal when eating diets containing recommended levels of thiamin but show clinical signs when eating diets containing inadequate amounts of the vitamin.

A thiamin-responsive neurologic disorder has been recognized as an autosomal recessive defect in Burmese kittens.[102] The kittens were normal until 4-10 months of age, when they developed episodes of hind limb ataxia, forelimb rigidity, hopping gait, hypermetria, protrusion of the claws, pupillary dilation, muscle tremors, head-nodding, weakness and convulsions. Attacks appeared to be precipitated by fish diets or stress. A poor to good response, depending on the individual, was seen after thiamin supplementation (100-500 mg/day). An autosomal recessive disorder of domestic short-haired kittens was clinically and histopathologically similar to Leigh's disease (subacute sclerosing encephalomyelopathy) in people.[68] Affected kittens developed progressively worsening intention tremors and undulating body movements when they began to walk and died at 10-12 weeks of age of convulsions. The kittens had elevated serum pyruvate and lactate levels, indicating a pyruvate carboxylase or thiamin triphosphate catalyzing enzyme deficiency.

Hematologic Disorders of Genetic Origin

Chediak-Higashi Syndrome

There is a remarkable transspecies similarity of Chediak-Higashi syndrome (CHS) for various species in which the anomaly has been described (cattle, mice, mink, people).[22] In all of these species and in cats, the anomaly is caused by a recessive gene ch.

The Chediak-Higashi syndrome is characterized by a varied spectrum of signs. The coat color is lighter than normal due to massive coalescence of the pigment granules in both the medulla and cortex of the hair. The color has been termed "blue-smoke," which is said to be lighter than the normal blue-smoke. The pigmentation of the eye is reduced. The iris is paler than normal, being light yellow, yellow-green or greenish. A reddish fundic reflection is apparent, instead of the usual bright yellowish-green. The tapetum is mostly depigmented or absent. Consequently, affected cats are photophobic. Fine nystagmus is evident. Most affected animals have cataracts of varying severity.[122,123]

Affected cats have large intracytoplasmic abnormal granules of different sizes in the WBC of bone marrow and blood. The bleeding time is prolonged after minor surgery and small hematomas frequently form at the site of venipuncture. This may be due to a defect of platelet function. Affected cats may be more susceptible to infectious disease (as in other species with CHS), but this has yet to be demonstrated.[85]

Cats with CHS have misrouting of the optic fibers similar to that observed in Siamese and albino cats. The anomalous condition is less severe than that observed in albino animals, though this could have been due to the fact that the CHS cats examined were more pigmented specimens.[30]

Pelger-Huët Anomaly

This anomaly is manifested as hyposegmentation of nuclei of circulating granulocytes.[87,161] Erythrocytes, lymphocytes and platelets appear normal. There is a small decrease in lobation of nuclei of megakaryocytes of bone marrow. The Pelger-Huët anomaly probably arises from a defect in nuclear segmentation or lobation of hematopoietic stem cells.[87] Breeding data are consistent with monogenic dominant inheritance (Ph). The condition is often benign, though chemotactic function of neutrophils and *in-vitro* immunologic responsiveness is depressed.

Neutrophil Granulation

The cytoplasm of normal feline neutrophils has a pale, indistinct granular appearance after staining with eosin dye. However, individuals have been observed in which the cytoplasm contained fine eosino-

philic granules. This granulation could have resulted from a qualitative difference in the enzyme content of normal granules or the presence of abnormal granules (probably lysosomal). Cats with these unusual neutrophils are not clinically sick. The condition is inherited as a recessive trait (ng) to normal cytoplasm.[69]

Hageman Factor Deficiency

A deficiency of blood clotting factor XII (Hageman Factor) results in a prolonged thromoboplastin time. Cats homozygous for factor XII deficiency have only 1-2% of normal factor XII activity in their plasma, while heterozygotes had an average of 64%. The disease is caused by an incompletely dominant gene (hag). The trait is usually regarded as recessive, however, because heterozygotes are not clinically normal.[55,84]

Hemophilia A

Hemophilia is characterized by hematoma formation and prolonged bleeding following injury or surgery. Bleeding results from failure of one of the steps in the complex process of blood clotting. A common form of hemophilia is designated as hemophilia A. The condition is monogenically inherited and sex-linked; the locus for the responsible gene is carried by the X chromosome. Typically, only males are affected. If the deficiency is pronounced, males may not survive to breeding age.

Cats with a marked deficiency of clotting factor VIII, indicative of hemophilia A, have been described.[28] No breeding results were given, but all 3 affected cats were males. The manifested signs are typical of the disease in people. Hemorrhaging is less severe following minor trauma in comparison with that shown by affected dogs, however.

Hemophilia B

A family of cats deficient in blood clotting factor IX has been described.[40,41] The deficiency gives rise to hemophilia B, which is characterized by spontaneous and protracted bleeding following injury or surgery. Clinical signs are milder than those of hemophilia A.

von Willebrand's Disease

A bleeding disorder compatible with von Willebrand's disease in people and other animals was identified in a 9-year-old Himalayan.[50] The cat did not manifest bleeding problems earlier in life and related cats had no history of similar problems. The condition in people and other animals is inherited as an autosomal recessive or dominant trait associated with decreases in factor VIII-von Willebrand's protein and problems with platelet aggregates.

Porphyria

Hemoglobin, the principal oxygen-carrying protein in RBC, is synthesized from heme and globin. Defects in heme synthesis or degradation result in accumulation of precursor molecules, mainly uroporphyrin I and coproporphyrin I. These precursor molecules are deposited in large amounts in various tissues and secreted in great amounts in the urine. Uroporphyrin and coproporphyrin are colored compounds that impart a brownish discoloration to the teeth and bones of affected individuals and a brown to red discoloration of urine. Urine, bone and teeth fluoresce red under ultraviolet light (Fig 18).

At least 2 different genetic defects in heme biosynthesis have been recognized in cats.[37,52-54,153] The disease in domestic cats is associated with teeth and urine discoloration, mild anemia and increased numbers of refractile bodies in RBC. Otherwise, the animals are not clinically ill. This type of porphyria is inherited as an autosomal re-

Figure 18. Siamese cat with the dominant form of porphyria. When illuminated with a Wood's lamp, the teeth glow intensely under fluorescent lighting because of porphyrin pigment. (Courtesy of Dr. M. Haskins, University of Pennsylvania)

cessive trait (po). There is a reduction of porphobilinogen deaminase activity to about half of normal in RBC and liver.[37] This type of enzyme deficiency is similar to that described for hepatic porphyria in people.

Porphyria of a different type has been described in Siamese cats.[37] Affected animals had a similar discoloration of teeth, bones and urine but were ill with depression, listlessness and severe hypochromic anemia, with abnormally shaped RBC (anisocytosis, poikilocytosis, target cells, nucleated RBC). Pedigree analysis of this trait was consistent with an autosomal dominant or recessive inheritance. More thorough biochemical and genetic analyses are required to define the differences in these 2 types of porphyria in cats.

Aplastic Anemia

A delayed-onset form of aplastic anemia has been observed in some bloodlines of Japanese Bobtail cats. Affected kittens are normal until 6 months of age or so, and then develop progressive myelofibrosis and pancytopenia over the next few months. The genetic basis for the disorder has not yet been determined.

Genetic Disorders of Miscellaneous Organs

Patent Ductus Arteriosus

A higher incidence of patent ductus arteriosus in the Siamese breed suggests a genetic basis.[146] Patent ductus arteriosus results from failed closure of the fetal vascular bypass between the aorta and pulmonary artery. It can lead to heart failure later in life.

Primary Endocardial Fibroelastosis

Endocardial fibroelastosis is an anomaly observed in Siamese and Burmese cats.[58,117] The disease appears to be heritable in the Burmese but its genetic basis in Siamese is not known.[118,167] Abnormal lymphatic drainage from the heart is thought to cause chronic endocardial edema.[167] The inheritance pattern suggests a dominant trait, though further research on the exact genetic basis is needed.[167] It appears to be almost identical to a similar genetic disease of human infants.[167]

Clinical signs attributable to cardiac failure are seen at 3-16 weeks of age. Sudden death with few preceding signs is the most common presentation. Difficult respiration, open-mouth breathing and cyanosis may be noticed near the time of death in some animals. The left side of the heart, including the atrium and ventricle, are greatly enlarged. Fluid may accumulate in the thoracic cavity as the heart begins to fail. Marked heart enlargement is seen on radiographs and at necropsy. The endocardium is gray to white because of increased amounts of elastic tissue. Similar lesions occur with viral myocarditis, fetal anoxia, nutritional cardiomyopathy (taurine deficiency) and congenital vascular defects of the heart, so a thorough clinical workup is always in order before diagnosing the primary or heritable form of the disease.

Esophageal Achalasia

The muscles of the esophagus normally propel food to the stomach. If the cardiac sphincter fails to relax, food cannot pass easily into the stomach and the esophagus becomes dilated with ingesta. This leads to regurgitation of food. At other times there is unproductive retching. Achalasia has been observed in a group of cats with common ancestry, at the typical ratio for assortment of a recessive gene. Unfortunately, the data are insufficient to firmly establish the mode of inheritance.[21]

Polycystic Kidneys

Polycystic kidney disease (PKD) is manifested as multiple cysts in the renal cortex and/or medulla. Cysts may range from microscopic size to several centimeters in diameter. PKD in man can be acquired, developmental or heritable; this seems to be also true for cats.

A heritable form of PKD has been described in both mixed-breed and purebred cats.[32,170] The Persian breed is particularly affected. The mode of inheritance in people is autosomal recessive or autosomal dominant. Clinical features of PKD in cats resemble those of the autosomal dominant form of PKD in people.[170]

PKD may be asymptomatic for life, or may manifest itself as chronic renal failure. Most clinically affected cats show anorexia, weight loss, depression, vomiting, polyuria and polydipsia at 3-10 years of age. In addition to signs of renal failure, affected cats often have enlarged kidneys, with cystic structures apparent upon ultrasonography.

Pyloric Stenosis

Persistent and sometimes violent vomiting can be a sign of pyloric stenosis.[121] The condition can be relieved by pyloroplasty or pyloromyotomy. Seven of the affected cats described belonged to a related family of Siamese cats, which suggests a genetic propensity. The pedigree data were inadequate to establish the mode of inheritance.[121]

Renal Amyloidosis

This disease is particularly prevalent in Abyssinian cats and the closely related Somali. It has also been recognized in several other breeds. Affected animals are often young adults <6 years of age. A few cats ≥10 years have also died from the disease, however. They display chronic weight loss, dehydration, gingivitis and a rough coat. The kidneys are firm but smaller and paler than normal. There is a slight to severe pitting of the renal capsule and linear banding of fibrosis extending into the minor medulla. The renal lesions are characterized histologically by amyloid deposition, papillary necrosis and interstitial fibrosis. The amyloid deposits may be overlooked because of their weak staining properties. The familial incidence of the disease suggests genetic involvement, but breeding data are too fragmented to define the mode of inheritance. The genetic basis of the defect appears to be complex.

Umbilical Hernia

Umbilical hernia has a low but persistent incidence in kittens and adolescent cats. There is good evidence of a genetic basis for the anomaly.[134] This was first shown in a strain of Abyssinian cats.[67] The incidence among offspring rises sharply when one parent is herniated. The most compelling evidence was obtained from a partially inbred strain of Cornish Rex, in which the incidence approximated monogenic proportions. Unfortunately, breeding data were inadequate for genetic characterization. The most likely explanation is that the defect has a polygenic threshold character.[139]

Urolithiasis

A familial tendency toward urolithiasis has been interpreted as a genetic liability for the disease.[95] Such observations are of interest in alerting a keen observer to the possibility. Details given in reports are inadequate to establish the mode of inheritance, however.

Sex Chromosome Aberrations

Tortoiseshell Males

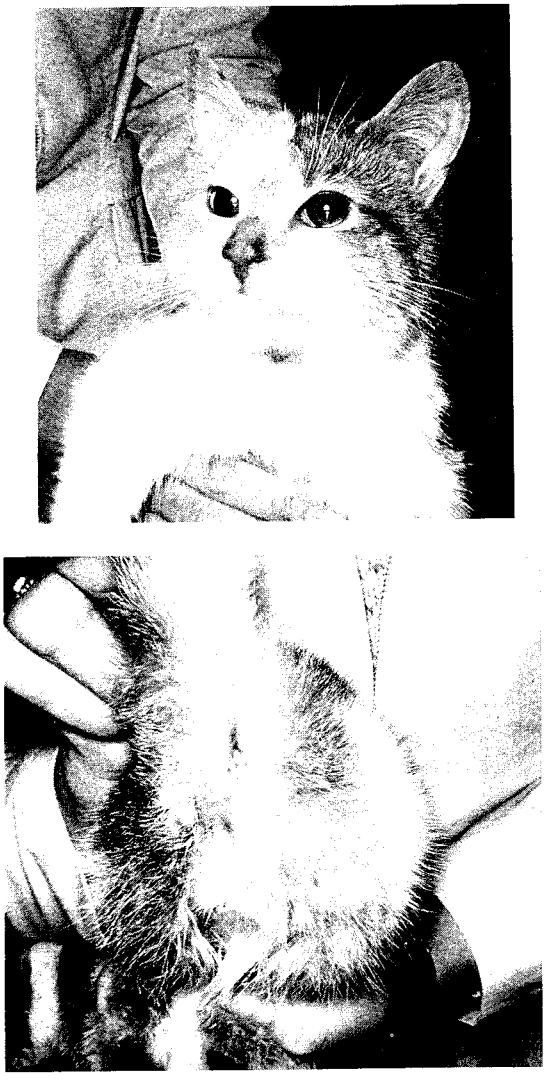
The black and yellow brindle or patchwork pattern of the tortoiseshell should only occur in female cats. Tortoiseshell male cats occur at a low frequency (1 in 3000), however (Fig 19). In most cases, tortoiseshell males have an anomalous chromosome constitution.[16,108,138] Most are sterile. A type of tortoiseshell male is fertile, however.

The O gene is carried by the X chromosome and the tortoiseshell pattern is produced by the heterozygote Oo. In the somatic tissues of the female cat, one of the X chromosomes becomes inactivated or nonfunctional. In fetal development, some somatic cells have one X chromosome inactivated and other cells have the other X chromosome inactivated. Descendants of these 2 different types of cells always have the same X chromosome inactivated as their ancestors. The effect of this differential inactivation would not normally be observed, but it is manifested in the tortoiseshell because of O and o genes on different X chromosomes. Those dermic cells in which the X chromosome carrying the O gene is functional produce red or orange hair, while dermic cells in which the X chromosome carrying the o gene is functional produce black hairs. The mechanics of embryonic cell growth, as well as its vicissitudes, result in the mosaic pattern of the tortoiseshell.

Therefore, the basic requirement for tortoiseshell pattern is the presence of 2 X

chromosomes in somatic tissue, one carrying the Q gene and the other the q; differential inactivation of the X gives rise to the pattern. It is possible to have anomalous sex chromosome constitutions and a male phenotype as a result of nondisjunction of chromosomes, fusion of polar bodies or double fertilization. One fairly common type is the 39,XXY ("Klinefelter"), in which an extra X has been gained.[125] The normal male cat has a 38,XY karyotype. The male-inducing influence of the Y produces a male and the 2 Xs are differentially inactivated. If one of the Xs carries gene Q and the other gene q, the phenotype is a male tortoiseshell.

Figure 19. A male tortoiseshell cat. The cat had the appearance of a female (top), but had typical (though atrophic) male genitalia (bottom).



The more common 39,XXY genotype above does not exhaust the possibilities for tortoiseshell males. These males have also been found with the following combinations of sex chromosomes in their cells: 38,XX/38,XY; 38XY/38,XY; 38,XY/39,XXY; 38,XX/39,XXY; 38,XX/57XXY; 38XY/57,XXY; 38XY/39XXY/40,XXY; 38,XX/38,XY/39XXY/40XXY and other more complex consitutions.[18,20,98,103] Such animals exhibit genetic mosaicism. Some of their cells carry the XX genes, while others have the XY or XXY genes with normal or excessive numbers of somatic chromosomes. These individuals are male but are usually sterile. Their testes are small and flaccid, and spermatogenesis is arrested at an early stage.

Fertile male tortoiseshell cats can sometimes arise from XX, XY mosaicism. If the cells forming the testes are derived from the normal XY karyotype, normal spermatozoa containing the haploid X or Y chromosomes can be formed. The situation would be analogous to the X chromosome mosaicism discussed next. Fertile tortoiseshell males can also be engendered by somatic mutation (occurring after fertilization in the early embryo) of q to Q or Q to q. Some of the cells would contain the X^{o} and others the X^{Q} chromosome; X^{Q}-bearing cells would express the orange color, while X^{q} cells would not. There is *prima facie* evidence for the occurrence of such individuals.[138] Significantly, these tortoiseshell males are fertile because chromosomally they have a "normal" XY karyotype.

The tortoiseshell male is of more than genetic interest in the United States. Like the elusive "pot of gold at the end of the rainbow," rumors have persisted that a tortoiseshell male cat is of great value to the finder. Veterinarians in private practice and in academic institutions are frequently contacted by owners of such cats attempting to "collect their reward." Such people should be gently advised of the rarity of their find but not of its value, which is no greater than for a normal cat.

XO Sterility

The normal female cat has 2 X chromosomes (38,XX). It is possible for one of the

parent cats to lose one of the X chromosomes during development of the gametes. Fertilization of a normal sex cell by an X-deficient gamete would result in an XO genotype. These cats are rare and only a few cases have been reported.[78,116] The XO cat is typically female but may be undersized and sterile. Such animals are likely to come to the attention of veterinarians because of persistent anestrus. Hormone treatment to induce estrus is likely to be unsuccessful. The XO condition can only be determined by examination of the chromosome complement of suspected XO females.

In the normal female cat of constitution XX, one of the X chromosomes becomes inactivated or does not function in the somatic cells shortly after birth. The reason probably resides in the necessity to "equalize" the influence of the X in relation to the autosomes between the sexes. Both the female and male cats have the same number of autosomes but the male has only one X. Hence, to produce the same "balance" between the X chromosome and the autosomes in the female, one of the 2 X chromosomes is inactivated.

An identical result would be achieved if one of the X chromosomes were lost during embryonic development. In other words, the XO female can survive even if the normal growth rate and viability are reduced, as shown by XO females of other species. On the other hand, the XX constitution is essential for maintaining normal ovarian development and function. The ovary of a 3-day-old XO kitten was histologically normal, whereas the ovary of an adult was small and lacked Graafian follicles and primordial germ cells.[78]

X-Chromosome Mosaicism

Two pregnant cats with unilateral ovarian dysgenesis (at ovariohysterectomy) had an X-chromosome mosaicism.[152] Both cats had 3 populations of cells, one containing only 37 chromosomes (missing one X chromosome) (37,X), one containing 38 chromosomes (both X chromosomes present) (38,XX) and one containing 39 chromosomes (3 X chromosomes) (39,XXX). The abnormal ovaries were apparently derived from cells with 37 (X) or 39 (XXX) chromosomes, while the normal ovary was derived from cells with the normal 38 (XX) karyotype. The fetuses had normal sex chromosome complements, apparently because they were derived from ova produced by the normal ovary.

Polyploidy of Autosomal Chromosomes

An obviously stunted and macerated feline fetus removed from a late gestation queen had 39 chromosomes.[7] The extra chromosome was due to trisomy of autosome D_2.

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DEVELOPMENTAL ANOMALIES

Normal Development

Developmental anomalies are caused by abnormalities in maturation of the embryo or any time from the one-cell stage to the full-term fetus. They can have a genetic or nongenetic basis. This section is concerned mainly with developmental anomalies that are either nongenetic in origin or of undetermined etiology.

To understand developmental anomalies, it is important to have basic knowledge of embryogenesis. Embryogenesis in domestic cats begins with the fertilized egg, a single cell about 0.1 mm (4/1000 inch) in diameter and ends 9-10 weeks later with birth of a kitten. After the egg is fertilized in the fallopian tubes, it migrates slowly to the uterus, where it attaches 0-12 days later. The fetus is composed of 250 cells at this point in development and is called a blastocyst. The blastocyst is a hollow ball, with the cells that will form the embryo clustered at one end of the ball. The remaining cells contact the wall of the uterus and form the placenta. The placenta serves both as a source of anchorage and nutrition. Nutrients and oxygen are transported from the maternal blood, across the wall of the uterus, and through the placenta to the developing embryo. Nutrition of the embryo during the early stages is mainly by diffusion, but as the embryo and placenta grow, a network of blood vessels develops both in the placenta and fetus.

Embryogenesis occurs from the 12th through 24th day of gestation. It is during this stage of life that the primitive organs begin to form. Gastrulation is the first event that occurs in embryogenesis. The group of cells that will become the embryo form a structure (gastrula) that resembles a deflated ball collapsed into itself. The wall of the gastrula is made up of 3 concentric layers of cells. The outermost layer is the ectoderm, the middle layer the mesoderm, and the inner layer the entoderm. The ectoderm will become the skin and epidermal tissues (nails, hair, glands of skin), nervous system, organs of sense, and lining membranes of the mouth and anus. The mesoderm eventually forms bone, cartilage, muscles, connective tissues, blood and blood vessels, lymphatic vessels and lymphoid organs (immune system), lining of the thoracic cavity (pleura), heart sac (pericardium), and abdomen (peritoneum), and the epithelial cells of the kidney and sex organs. The entoderm forms the linings of the pharynx, respiratory tract (except for the nose), digestive tract, and urinary bladder and urethra.

The neurula stage follows gastrulation. The neurula resembles a tube that is open along its long axis. The site where the 2 sides of the tube join will become the primitive nervous system and vertebral column. The heart begins to form during this stage, as do blood vessels within the embryo and placenta.

Neurulation is rapidly followed by a period when the primitive organs are formed. The primitive organs are well defined by 24 days of gestation in the cat. The fetus is about 1/2 inch long at this stage and is readily palpable (within its amniotic sac) in the abdomen of the dam.

Fetal growth continues from day 24 of gestation to term at 9-10 weeks. The various organs continue to develop during this period. This development occurs within the framework of the relatively primitive organ anlagen (organ precursors) delineated earlier during neurulation and organogenesis. For example, the renal glomeruli, tubules

and renal pelvis must develop within the anlagen of the kidney. This development must coincide with formation of adjacent blood vessels and lymphatics. The glomeruli must come into a proper relationship with the renal tubules, the renal tubules with the larger urine collecting ducts, and the collecting ducts with the renal pelvis. Various regions of the renal tubules must differentiate from other regions; some for control of electrolyte (salt) excretion and resorption, others for control of water retention and loss, and some for transport of filtered urine out of the kidney. Eventually the renal pelvis must be connected to the bladder by the urethra, and the bladder to the outside of the body by the urethra. Similar types of differentiation occur in all of the organs.

The formation of an individual organ or appendage involves 4 basic steps: growth, morphogenesis, cytodifferentiation and patterning. Growth involves cell replication and a commitment of a group of progeny cells to proceed along a certain course, such as formation of a limb, eye, ear, etc. Morphogenesis is creation of a rudimentary organ or appendage at the proper place within the developing fetus and at the proper time. Cytodifferentiation involves stepwise differentiation of the cells within the organ or appendage primordia. In the case of a developing limb, some groups of cells form bone or muscle, and others, tendons, nerves, skin, etc. Patterning refers to the ultimate end product. If it is a limb, it must mirror the opposite limb in size, position and growth rate. Not only is the limb patterned after its opposite, it is a limb patterned after every cat limb ever formed.

The fetal period ends with birth, but development continues for some time afterward. The fetus must be prepared for birth and an existence physiologically independent of its dam. For this purpose, the cardiovascular, respiratory, digestive and renal systems must become fully functional at the moment of birth or within minutes thereafter. The nervous, immune and reproductive systems, however, are still developing at birth. This development is not complete for weeks or months.

The preceding description of development of a feline fetus does not reflect the complexities of embryogenesis. Embryogenesis involves 2 basic processes: congregation of the cells that will eventually form a particular tissue or organ; and a stepwise differentiation of those cells from a primitive form to a highly specific functional state. Groups of cells are brought together by: evagination (infolding) or exvagination (folding outward) of the primitive blastocyst, gastrula or neurula; in-pouching or out-pouching of groups of cells within the tubular structure of the embryo; and migration of cells or groups of cells from one position in the embryo to another. Cell differentiation occurs through activation and deactivation of various genes and their protein products. These proteins serve as chemical signals. Adjacent cells and tissues interact with each other through chemical signals carried between cells. For instance, one group of cells may be altered in their differentiation when another group of cells contacts them. The interchange of chemical signals between the 2 groups of cells causes old chemical signals to be suppressed and new ones activated. The new concert of chemical signals causes the cells to embark upon new pathways of differentiation.

Given the complexity of embryogenesis, it is understandable that errors occur from time to time. Errors occurring very early in embryogenesis usually lead to fetal death, and abortion or resorption of the embryo. Such errors are seldom witnessed, therefore. Most fetal anomalies resulting in death of the embryo occur during gastrulation. Anomalies observed in full-term fetuses occur later in embryonic development. If the malformations are too great, the fetus cannot make the transition from a dependent to independent existence and dies within minutes or hours of birth. For instance, if the heart is malformed but the effects of the malformation can be circumvented by maternal attachments, the fetus survives in the womb but dies after birth. Malformations that lead to death at or near the time of birth are of limited importance. Malformations that are not immediately life threatening are far more important. Such malformations may be manifested weeks, months or years after birth. At this point, the kitten has established its own identity. Because this identity is often intermeshed with its human benefactor, the malformation is of medical importance. The nature of the malformation must be determined, and

a correction instigated by medical or surgical means, if possible.

Factors that lead to abnormalities in fetal development can be either intrinsic or extrinsic to the fetus. Intrinsic factors are usually of genetic origin; abnormal genes coding for abnormal types or amounts of proteins. If these proteins are important for cell differentiation, genetic defects result. Extrinsic factors usually affect the fetus through the dam. Drugs taken during pregnancy may cross the placenta and reach the fetus. If the drugs disrupt normal fetal development, anomalies may be induced. Such drugs are called teratogens. Radiation can also cause congenital anomalies, usually through chromosomal breakage that leads to gene anomalies. Cats, like all other life forms on earth, are exposed continually to small doses of radiation. Diagnostic radiation (radiographs) should be avoided during pregnancy. Infectious agents, particularly viruses, can also act as teratogens.

The effects of teratogenic drugs are often highly selective, both on the types of embryonic structures they affect and in the period during which they act. For instance, griseofulvin, a common drug used to treat ringworm, causes cleft palates if administered during pregnancy.[119] For such malformations to occur, the drug or its residue must be present in the fetal tissues during the crucial period when the palate is forming. Hydroxyurea, diphenylhydantoin, amaranth and mercury compounds have also been studied as teratogens in cats.[65-67] Their effect is usually seen 24-32 days after conception. Panleukopenia virus can infect the fetus via the placenta. It can cause an almost selective destruction of the Purkinje cell layer of the cerebellum during the last trimester of pregnancy. Affected kittens appear grossly normal at birth but have a peculiar gait (exaggerated or jerking movement of limbs, head, and body) when they begin to walk.

Many developmental anomalies have no demonstrable cause, some have specific causes, and others can be caused by several different factors. For instance, cleft palate can have a genetic basis or can be induced by drugs. Cerebellar hypoplasia in kittens is almost always caused by *in-utero* feline panleukopenia virus infection.[68-70] Several forms of cerebellar hypoplasia in people and other animals, however, are genetic. Though a few developmental anomalies have predictable causes, most occur for no apparent reasons (idiopathic). A few developmental anomalies are linked to certain breed or coat color characteristics. Breeds with greatly foreshortened faces may have a higher incidence of palate and skull anomalies than breeds with normal faces.[94] The foreshortened facial structure of certain cat breeds is influenced by the activities of many genes (polygenic traits). Because of the large numbers of genes involved in some traits, it may be very difficult to determine whether a given anomaly is genetic or nongenetic in origin.

Abnormal Development

About 5% of the patients seen by veterinarians in North America have various congenital defects.[103] The highest incidence was reported in swine and the lowest in cats. Multiple anomalies are seen in 1 in 20 of animals with developmental defects.[103]

Musculoskeletal Anomalies

Musculoskeletal deformities are by far the most common developmental problems in cats and other species. They often occur because of failures in closure of primitive tube-like structures in the embryo.

Schistosoma is a lethal developmental anomaly characterized by fissure of the abdomen and a lack, or rudimentary development, of the posterior extremities. Two kittens with such a defect had severe visceral herniation through an abdominal fissure and malformed posterior extremities.[114] One also had an associated cleft palate.

Failure of proper closure of the primitive neural tube can lead to a number of different defects at any point from the head to the tail. A *meningocele* is herniation of the meninges through a defect in the skull or vertebral column. A kitten with a cerebral meningocele has been described.[42] If it is relatively minor, and no other developmental anomalies are present in the brain, it can be potentially corrected. The one reported case, however, also had agenesis of the corpus callosum, septum pellucidum and hippocampal commissure.

Exencephaly is one of the most common congenital deformities observed among stillborn kittens.[33,138] It is a combination of defects about the face and head, including a dorsal opening of the skull with protruding meninges or brain, bulging eyes, and often a cleft palate. Exencephaly has also been associated with other embryonic tubular defects, such as *craniorachischisis, scoliosis* of the spine and *schistosomia reflexus*.[123,138]

Spinal dysraphism involves failure of closure of the part of the neural tube that forms the vertebral canal. A kitten with thoracolumbar spinal dysraphism was born alive but had no control over its deformed hind limbs.[114] A milder form of abnormal closure of the bony spinal canal, called *spina bifida*, has been described in a large number of kittens (Fig 20).[35,36,59,73,78,91] The disorder is most common in the lumbar spine. The closure defect is sometimes associated with protrusion of the spinal cord or meninges, and/or spinal cord dysplasia. The anomaly is most common in Manx cats, which have a genetic anomaly of the spinal cord. Affected kittens may be clinically normal, or have various degrees of posterior ataxia and gait anomalies. Fecal and urinary incontinence may also be a problem due to dysplasia of the lumbosacral spine.

Vertebral body anomalies are common in cats and usually of no clinical significance.[81] Most are detected on routine radiography. The most common vertebral body anomaly involves the presence of a fourteenth thoracic, or transition, vertebra. Incomplete or fused vertebrae can also be found throughout the spine, but most are concentrated in the thoracic and coccygeal spine. Vertebral anomalies of the coccygeal spine often lead to a *kinked tail*.[19] The kinked tail anomaly may have a genetic basis. A cat with no tail, sacral vertebral anomalies, and spina bifida has been reported.[35]

A 3-year-old cat with multiple skeletal defects of the skull bones, vertebral column and scapula has been described.[136] The cat had foreshortened temporal occipital and parietal bones, fused cervical vertebrae, a malformed thoracolumbar intermediate vertebra, a fused lumbosacral transitional vertebra, and an abnormal scapula.

Anomalies of the limbs are also common in domestic cats. *Amelia* is the complete lack of limbs. This rare defect has been described only once in cats.[19] An anomaly characterized by arrested development of the bones of the forelimbs has been described.[134] These so-called "*kangaroo cats*" have a characteristic appearance (Fig 13). The defect usually appears in females and may be genetic (see section on genetic disorders). *Peromelus ascelus* is an anomaly caused by agenesis of the hind limbs (Fig 21). The one case reported in the cat was nonlethal.[117] *Ectrodactyly*, an improper formation of all or part of a digit, has been described as a possibly heritable defect of the forepaw of the domestic cat.[117] *Syndactyly* is fusion of the digits. The defect is rare but has been reported in a cat.[50] *Polydactyly* is the presence of extra digits, most frequently on the forepaw. It is one of the most common genetic defects of cats (see section on genetic disorders). *Radial hemimelia*, caused by agenesis of the radius, has been described in a cat.[79] *Arthrogryposis* is a congenital fibrous ankylosis (fusion) of the

Figure 21. Peromelus ascelus (lack of hind legs) in a neonatal kitten.[117] (Courtesy of Dr. G. Schneck and Veterinary Medicine Publishing)

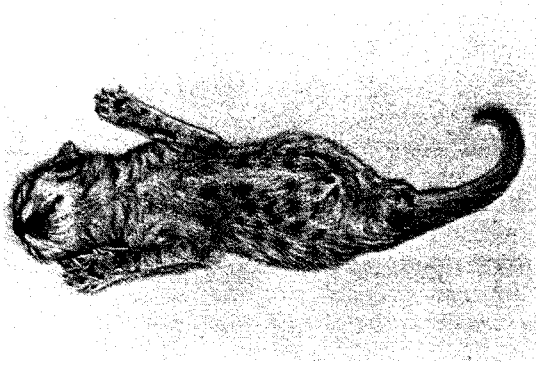
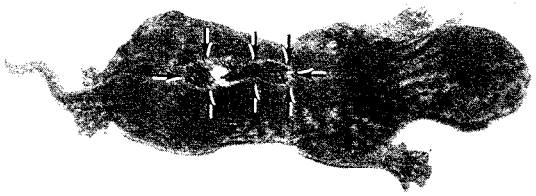


Figure 20. Kitten with spina bifida and rachischisis.[36] The hind legs are contracted. The area of spina bifida is outlined by arrows. (Courtesy of Dr. F. Frye and *Journal of the American Veterinary Medical Association*)



points of the extremities. This condition affected all 4 legs of a 2-month-old kitten.[114]

Harelip results from failed closure of the embryonic tube that forms the midline of the skull, in particular the upper lip. The defect can also involve a cleft between the nasal and oral cavities (involving the upper lip in the process), or a cleft between the upper lip and hard palate.

Cleft palate, sometimes with clefting into the nasal or oral cavity, is one of the most common defects of cats (Fig 14).[19,84,85] The incidence of the disorder increases with inbreeding, suggesting a strong genetic influence. A genetic form of the disease has been described in Siamese.[84,85] Some drugs, such as griseofulvin, have also been incriminated in the disorder.[119] Severely affected kittens have problems nursing, and commonly aspirate milk into the lungs. Surgical correction is difficult in animals this small.

Cleft soft palate is rare in cats. The throat of affected cats has a bird-like or gullet appearance (birds have a naturally cleft soft palate). The problem usually goes unnoticed for the first few months of life. The usual presenting complaint is a chronic nasal infection, due mainly to reflux of food from the oral to nasal cavity. Owners may notice the cat sneezing after eating or drinking. Food may sometimes be observed in the nasal discharge during such bouts.

Pectus excavatum is one of the more common and manageable musculoskeletal anomalies of cats.[8,41,121] Affected kittens are born with a flattened chest and pelvis. Their legs are held to the side rather than beneath the trunk, and they often move by "swimming motions" of their limbs; hence the nickname "swimmer kittens." The developmental basis for swimmer kittens is unknown. It appears to increase in frequency with inbreeding, and some queens may produce several kittens with the disorder. There is other circumstantial evidence, however, that the condition might also result from extrinsic factors, such as drugs or diet. Compression of the heart can be life-threatening in severely affected kittens. Kittens with severe chest compression can be treated with traction sutures and casts, but older cats may need surgical reconstruction.[8,121] Mildly affected kittens often grow out of the condition. As they begin to use their legs more, they learn to adjust and to keep their legs under their trunk. Though they may retain a degree of chest flattening when they are older, they function otherwise in a normal manner.

Excessive *dishing of the face*, referred to as "peke face" because of its similarity to the Pekingese dog, has been described in some long-haired Persian cats.[19] It is probably an exaggerated genetic expression of the polygenes and their modifiers that are normally associated with face structure in the breed. The "Peke face" has been bred into some American Persians and is considered normal.

Aplasia of the ramus of the mandible, associated with an anomalous ossification center, has been described in a cat with micrognathia (undershot lower jaw).[57]

Anomalies of the teeth are common in cats. In addition to developmental anomalies of the jaw that lead to overbite or underbite, several distinct anomalies have been observed. *Malpositioned canine teeth* is one such problem. The lower canines strike against the upper gum as they become full grown. This causes pain on eating and sores in the upper gums where the tips of the canines penetrate the flesh. The canines must be filed down or removed. *Adontia*, the complete absence of teeth, has been reported in one cat.[32] *Enamel hypoplasia*, either partial or complete, has been recognized in a number of cats. The underlying dentine is exposed, resulting in rough, brown, teeth. Dental caries are a problem in such animals. The affected teeth may be covered by reddened inflammatory tissue extending from the gingiva. Enamel hypoplasia does not begin in the fetus because formation of enamel occurs after birth. High fevers, drugs and unknown factors in some way affect formation of enamel in the developing tooth bud.

Some defects are associated with abnormal twinning. *Diprosopus*, the presence of 2 faces, has been described in cats (Fig 22).[2,11,23] The defect is usually lethal within a day or so. *Posterior twinning* due to fusion of the hindquarters of one twin to the body of the other, has been described in cats (Fig 23).[2,98,106,131] A *small extra pair of ears* on each side of the head has been reported in one cat, where it was thought to be a ge-

netic recessive defect. A "*reversed cat*" has been described at necropsy.[135] All internal organs that were normally on the right were on the left, and vice versa. The animal may have been one of a pair of identical twins.

Hernias of soft tissue structures may be either developmental or acquired. *Umbilical hernias* involve a defect in the body wall where the umbilical vessels enter the fetus.[43,51,54] If the defect is large enough, portions of the omentum and omental fat protrude to form a characteristic dome-shaped enlargement beneath the skin surrounding the umbilical vessels. In some cases, herniation may be into a remnant of the allantoic sac. If the defect is larger, viscera may also enter the hernial sac. The condition may have a genetic basis in some animals.[51] It is also a common acquired anomaly. If the queen fails to sever the umbilical cord, the newborn may drag the attached placenta and tear the body wall.[54] The problem is particularly acute when the queen fails to cut the umbilical cords of all of the kittens in a litter. The kittens become intertwined by their umbilical cords. As they become more and more entwined, they end up attached together by the base of their umbilical cords. Herniations of the viscera, strangulation of limbs and umbilical hernias are common in such situations. Though this is an acquired condition, it has been mistakingly described as a developmental *anomaly of the umbilical cord* in at least one report.[88]

Figure 22. Kitten with diprosopus (double face) as a result of abnormal twinning.[11] (Courtesy of Dr. T. Bissonette and *Journal of Heredity*)

Figure 23. Posterior twinning in a feline fetus.[106] (Courtesy of Dr. A. Reese and *Anatomy Record*)

A congenital abdominal fissure with partial evisceration has been described in a kitten.[114] A littermate with the same defect also had a thoracic fissure, schistosomus reflexus and cleft palate.

Inguinal hernias involve weakness in the development of the inguinal canal, through which blood vessels, nerves, lymphatics and the descending testes pass. It has been reported as a developmental anomaly in cats.[49] These hernias are usually quite small and involve mainly serosa, serosal fat and rarely abdominal viscera.

Diaphragmatic hernias are also developmental or acquired. A genetic form involving simple recessive inheritance has been proposed. It has been reported in as many as 1 in 500 births. Acquired diaphragmatic hernias usually involve trauma, though predisposing developmental weakness might exist in many cases.[3,4,17,19,37,58,64,77] Some involve communications between the abdominal and pleural cavities, usually involving the pericardial sac (pericardial-diaphragmatic hernias) (Fig 24).[104] The liver and intestines are often present in the chest or pericardial sac. These cats usually have

problems breathing or may suffer from cardiac tamponade and heart failure or vague gastrointestinal signs. *Hiatal hernias,* involving weakness in the diaphragm where the esophagus enters the stomach, have also been recognized in cats. If the hiatal hernia is large enough, it causes sliding of the gastric cardia into the thoracic cavity. The problem is clinically significant when gastric juices reflux into the esophagus. Reflux of stomach contents leads to esophagitis and persistent vomiting or regurgitation.

Neural and Ocular Anomalies

Congenital defects of the central nervous system and eyes are second in frequency only to those of the musculoskeletal system. *Cerebellar hypoplasia* is probably the most common developmental problem of the central nervous system of cats.[18,26,74,115,118] It is caused in most cases by fetal infection with feline panleukopenia virus.[68-70,75] Queens subclinically infected with the virus during the last trimester of gestation are most apt to produce kittens with this disorder. The virus selectively destroys the Purkinje cell layer of the cerebellum. Affected kittens are born with a small atrophic cerebellum (Fig 25). They appear normal until they begin to walk. Since the cerebellum is important for proprioception (spatial movements), these kittens appear uncoordinated when they begin to walk. They often have a characteristic hypermetria (exaggerated flexion and extension) of the limbs and head while moving. The kittens are otherwise normal, and make good pets. As they get older, they learn to function with their deficiencies but never achieve any degree of normal gait and proprioception.

Hydrocephalus, or "water on the brain," is caused by dilation of the ventricles of the brain with cerebrospinal fluid. The basic defect is inability to transport cerebrospinal fluid from the ventricles to the meningeal spaces and bloodstream. Kittens with hydrocephalus are born with larger-than-normal skulls and open fontanelles (soft spot on the head where the bones of the skull come together). Progressive digitation of the ventricles leads to pressure atrophy of the overlying cerebral cortex. Mildly af-

Figure 24. Lateral radiograph of a cat with a peritoneopericardial diaphragmatic hernia.[3] Barium is seen within intestinal loops in the pericardial sac. (Courtesy of Dr. C. Atkins and *Journal of the American Veterinary Medical Association*)

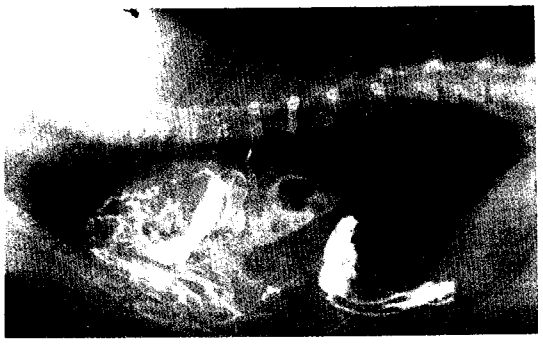
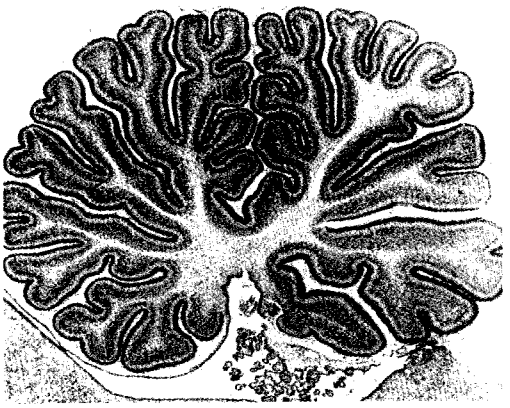
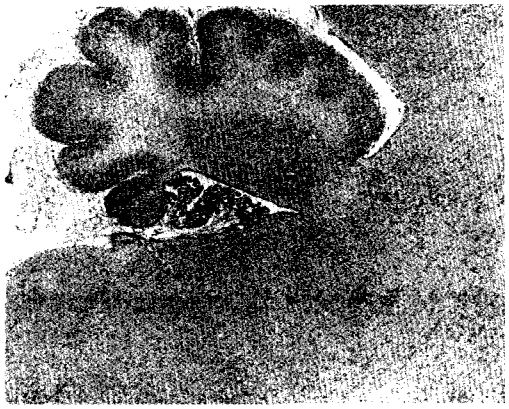


Figure 25. Top: Cross section of the cerebellum of a 14-day-old ferret that was inoculated on the first day of life with inactivated panleukopenia virus.[69] The cerebellum appears grossly and histologically normal. This is in contrast to the cerebellum of a 14-day-old ferret inoculated on the first day of life with virulent feline panleukopenia virus (bottom). The cerebellum of the affected ferret is extremely atrophic, the external germinal layer has been effaced, and the definitive granular layer has not developed. (Courtesy of Dr. L. Killam and *Journal of the American Veterinary Medical Association*))





fected kittens lack normal intelligence, manifested by a decreased response to external stimuli. More often than not, however, the condition is lethal within the first few weeks of life. The condition is possibly heritable in Siamese cats. It has been also associated with other defects, such as cleft palate, harelip, talipes (foot deformity) or generalized edema.[19,58,122]

Aplasia of the corpus callosum, leading to chronic epileptic-type seizures, has been described in a cat.[52]

Cyclopia is associated with midline fusion of developing eyes. Cyclopian kittens, therefore, have one large deformed centrally positioned eye. It is often associated with other defects of the skull and adjacent skin.[29,31] The condition is inevitably fatal.

Microphthalmia is a condition in which the eyes are inordinately small. It has been reported once in a cat but is not an uncommon defect.[19] It is often associated with enophthalmia, cataracts or other ocular anomalies.[99]

Cataracts are opacities of the lens. They are often associated with other ocular anomalies in kittens, such as microphthalmia, persistent pupillary membranes, and persistent hyaloid blood vessels.[99]

Ectopic lenses are rare in kittens.[1,19] They usually result from posterior or anterior luxation of the lens associated with incomplete development of the suspensory ligaments or zonular fibers. They can be associated with *microphakia* (small lens). The luxated lens often becomes cataractous and causes glaucoma if not removed.

Dermoids are vestigial growths of epithelium (containing hair, sebaceous glands and pigment) that are often found on the sclera next to the limbus. They sometimes extend out onto the cornea. If they do not cause corneal irritation and infection, they can be left alone. Excision is necessary when they cause problems.

Glaucoma is an enlargement of the globe due to excessive accumulations of aqueous humor and consequent increased intraocular pressure. It is usually associated with defects in the specialized structures in the base of the iris that drain the aqueous humor produced by the ciliary body. The defect is relatively rare in kittens.[19,102]

Keratoconus refers to a cone-like enlargement of the cornea when viewed from the side. The central cornea is often thin and opaque.[21] *Microcornea* occurs when the anterior cornea is too small. *Megalocornea* is a wide, flattened cornea.[19]

In *lagophthalmia*, the eyelids do not quite meet. This leads to dryness of the central cornea. Since tears are essential for maintenance of corneal hydration and defense against infections, the condition often leads to keratitis and central corneal ulcers that are difficult to treat. The condition is especially common in breeds with foreshortened faces.

Corneal opacities or *dystrophies* are not uncommon in kittens. They often result from bands of persistent pupillary membrane that adhere to the inner surfaces of the cornea, or to stromal edema of unknown etiology.[19,96]

Persistent tearing associated with abnormal nasolacrimal drainage is usually caused by anomalies of the lacrimal lake or nasolacrimal duct between the eye and nose. A defect in the lacrimal lake (pouch formed by the lids, adjacent to the nasolacrimal punctum) is a problem in breeds with foreshortened faces and lagophthalmia. Tears do not normally pool over the nasolacrimal puncta, thus impeding their flow into the nasolacrimal ducts. Rather the tears spill over the lower eyelids. Excessive tearing can also be caused by *atresia of the nasolacrimal puncta* (openings into the nasolacrimal ducts). The puncta are present on the medial surfaces of both the upper and lower lids. In all of these conditions, affected kittens show persistent tearing, discoloration of the hairs around the eyes, and sometimes secondary infectious conjunctivitis.

Colobomas are circular developmental anomalies in the eyelid, iris, choroid or optic nerve. These developmental anomalies often occur together to varying degrees. Colobomatous defects of the eyelids are often associated with iridal anomalies, while choroidal defects are often associated with retinal, scleral and optic nerve anomalies.

Anomalies of the eyelids, though common in puppies, are rare in kittens. Agenesis of the outer half of one or both upper eyelids has been described.[7,111] Most of these cats had strands of persistent pupillary mem-

brane extending from the iris to the posterior surface of the cornea. Notching defects of the iris, enlargement of the optic discs, scleral ectasia and choroidal hypoplasia are colobomatous defects of the posterior aspect of the eye.[7] *Entropion* is abnormal infolding of the upper or lower eyelids, while *ectropion* refers to outfolding. Both of these anomalies are rare in cats, though entropion may be common in some Persians..

Retinal degenerations can be heritable or acquired. The most common degeneration of the latter type is associated with diets low in taurine. Kittens born to taurine-deficient queens have cardiomyopathy and degeneration of the retina. Retinal lesions are characterized ophthalmoscopically by central areas of hyperlucidity and hyperreflexia (increased reflection of light).

Thoracic Organ Anomalies

The heart is formed early in embryogenesis by a complex series of events. It is not surprising, therefore, that there should be a number of developmental anomalies of the cardiovascular system. *Ventricular septal defects* are particulary common in cats.[80,90,120] The resultant hole between the 2 major chambers of the heart is usually quite large and most affected kittens die of heart failure before weaning. *Atrial septal defects* are uncommon in cats.[80,120] If large enough, they also can lead to heart failure early in life.

Neonatal endocardial fibroelastosis is a common anomaly of young purebred kittens.[14,30] Affected animals have cardiac dilation, with endocardial thickening and fibrosis. They usually die of heart failure within the first few weeks or months of life. There is good evidence that the disease is the same as dilative cardiomyopathy in older cats, and that it occurs when queens and kittens are fed a diet deficient in the amino acid taurine.[111]

Patent ductus arteriosus results from failure of the ductus arteriosus to close at birth. The ductus arteriosus is an embryonic communication that shunts blood from the pulmonary artery to the aorta, thus bypassing the uninflated, nonfunctional embryonic lungs. The shunt normally closes at birth when the lungs expand with air. Failure of the ductus arteriosus to close leads to excessive shunting of blood from the high-pressure aortic side to the lower-pressure pulmonary artery side (left-to-right shunt). Cats with patent ductus arteriosus are relatively common. The condition has a possible genetic basis.[24,80,120] Affected animals usually reach adulthood, and some may live long lives. Others, however, eventually develop heart failure.

Aortic stenosis is a relatively common anomaly of cats.[82,120,130] It consists of narrowing of the aortic valve or aortic outflow tract. The stenosis can be either supravalvular or subvalvular. Most affected cats survive to adolescence or into adulthood. If the stenosis is severe, however, heart failure ultimately develops.

Pulmonic stenosis is much less common in cats than aortic stenosis.[120,127,133] It involves narrowing of the pulmonary artery at the level of the pulmonary valve or a subvalvular narrowing. It has also been described in combination with an *aorticopulmonary septal defect.*[133] It may lead to heart failure later in life.

Tricuspid stenosis with an associated atrial septal defect and right ventricular hypoplasia has been described in a young cat.[86] The kitten was in heart failure, and the disorder was confirmed by angiocardiography.

Transposition of the great arteries has been observed in a healthy 4-month-old kitten with a heart murmur.[126] In this condition, the aorta originates dorsal to the right ventricle and the pulmonary artery dorsal to the left ventricle on the opposite side of the ventricular septum. This leads to a patent ductus arteriosus and a ventricular septal defect.

Dextroposition of the aorta (displacement of the aorta to the right) so that it overlies the right ventricle is a rare defect of unknown developmental etiology.[80] The only recorded feline case was detected at necropsy. The animal also had deformities in the ventricular septa and malformed atria. A *common truncus arteriosus* has been described in cats.[16,80] Cats with this anomaly have a common trunk for the aorta, coronary arteries and pulmonary artery that arises from a defect in the ventricular septum. Like dextroposition of the aorta, the condition is rapidly fatal.

A *persistent common atrioventricular canal* has been described in cats.[83] This involves a defect in the atrial and ventricular septa, with anomalous atrioventricular valves. Affected cats die at a relatively young age from heart failure. A multiple anomaly analogous to the *Taussig-Bing complex* in people has been described in a cat.[46] The animal had a ventricular septal defect, dextroposition of the aorta, an overriding pulmonary artery with left displacement, and pulmonic stenosis. The condition was rapidly fatal. A developmental anomaly analogous to the *tetralogy of Fallot* in people has also been described in several cats.[15,17,72] The defect consists of ventricular septal defect, pulmonary stenosis, dextroposition of the aorta, and right ventricular hypertrophy. Affected animals survive for some weeks or months in a state of ill health and ultimately succumb of heart failure. Similar *multiple heart defects* have been described.[27,100] These are basically combinations of the various defects discussed above. Affected kittens are stunted in growth and succumb to heart failure within several weeks or months.

Hypoplasia of the pulmonary trunk has been described.[80] In extreme cases, the animals are dyspneic almost from birth, and die at a young age. Some animals may survive into adolescence or adulthood.

Congenital unilateral *absence of a right pulmonary artery* was observed in a 2-year-old Siamese cat with acute dyspnea and edema of the left lung lobes.[48] At necropsy, the right lung lobes were one-fourth normal size and the right pulmonary artery was absent. Two small anomalous arteries passed from the aorta to the parenchyma of the right caudal lung lobes. The left ventricle was thickened.

Arteriovenous fistulas occur when large arteries connect directly to veins without an intervening capillary bed. If they are large, oxygenated blood is shunted away from the tissues and a larger workload is placed on the heart. A 5-month-old Persian kitten with respiratory difficulty and swelling in the neck had an anomalous internal brachial arteriovenous intercommunication.[92]

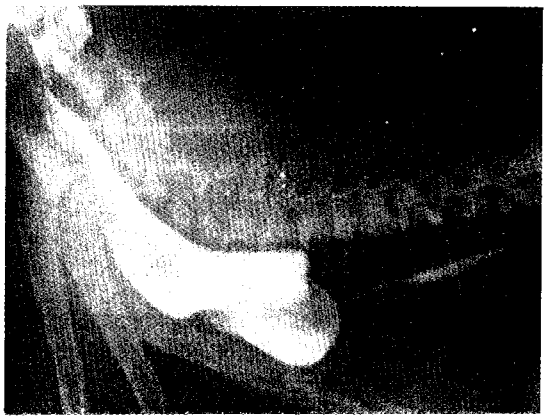
Persistence of the embryonic right aortic arch has been described in cats.[29,47,60,105,110,129] The condition does not involve the circulatory system *per se*. The persistent embryonic right aortic arch encircles the esophagus as it passes over the heart. Clinical signs result from stricture of the esophagus and dilation proximal to the stricture (Fig 26). It usually causes regurgitation of food soon after eating. The defect is visible upon barium administration. The dilated proximal portion of the esophagus often contains a hairball.

Cor triatriatum has been described in a 6-month-old female kitten that died of congestive heart failure.[38] In cor triatriatum, the pulmonary veins enter an accessory left atrium. The true left atrium and the accessory atrium connect through a narrow opening, thus obstructing pulmonary venous return.

Esophageal achalasia or megaesophagus is caused by failure of the esophageal-cardiac sphincter to relax upon presentation of a bolus of food (Fig 27). It is an uncommon defect in cats and thought to have a possible genetic basis.[20-23] The main clinical sign is regurgitation shortly after eating. Numbers of esophageal myenteric ganglia are similar in affected and unaffected cats, suggesting that the defect is different from esophageal achalasia of puppies.[21]

Aneurysm of the septum membranaceum has been recognized in a young cat at necropsy.[80] The aneurysm extended under the cusps of the tricuspid valve.

Figure 26. Persistent right aortic arch in a kitten causes accumulation of barium in the cranial esophagus.[47] Abrupt termination of the enlarged esophagus at the base of the heart is typical of persistent right aortic arch. (Courtesy of Dr. J. Hathaway and *Journal of the American Veterinary Medical Association*)



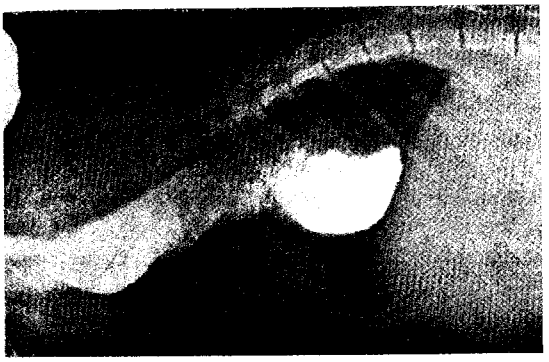
Anomalies of the lung are relatively rare. *Agenesis* of the *right or left lung lobes* has been recognized in cats.[114] The condition is usually asymptomatic and recognized at radiography for other conditions. The heart is characteristically shifted to the side of the missing lung lobes.

Abdominal Organ Anomalies

There are several specific developmental anomalies of the kidneys of cats. The presence of a *single kidney*, usually the left, is a common developmental anomaly in cats, with an incidence at necropsy of 2 in 1000 animals.[12,56,87,89,93,108] The single left kidney is usually larger than normal because of compensatory hypertrophy. The condition is usually asymptomatic and detected upon routine abdominal palpation for other conditions.[87,109] The right kidney is either missing entirely or small and misshapen.[12,87,107] Absence of the uterus and fallopian tube may be seen in female cats with agenic right kidneys.[53,89,108,112]

Renal ectopia is the congenital malposition of one or both kidneys; it is often associated with fusion of the developing kidneys.[56,61,87] The incidence in cats is about 5 in 1000 animals.[62] It occurs more often in male cats than females, and is usually an incidental finding at necropsy or upon clinical workup for renal disease.[87] Kidneys can sometimes be displaced to the pelvic region.[12,62] In one cat, an ectopic kidney was found embedded in the liver.[87] The displaced kidney is often subject to hydronephrosis, pyelonephritis and calculus formation.

Figure 27. Lateral radiograph of a cat with esophageal dilation caused by congenital esophageal achalasia.[23] Unlike the cat in Figure 26, the esophageal dilation extended from the thoracic inlet to the stomach. (Courtesy of Dr. D. Clifford and *JAVMA*)



Fusion of the 2 kidneys, usually at their caudal poles (*horseshoe kidneys*), is commonly recognized in cats.[12,62,87,125] The kidneys are often joined by a thin fibrous cord or a narrow band of renal tissue, giving the kidneys a horseshoe appearance. In some cases, the bridging tissue is much more substantial, forming a *unilateral fused kidney*.[12]

Polycystic kidney anomalies are common in cats.[5,12,25,95] Such kidneys contain a few, or many, small pea-sized cysts. The condition involves malformation of the tubules and can lead to renal failure from progressive fibrosis. The condition may be heritable.[25,87] It has been associated with cystic changes in the liver and pancreas.

Perirenal hygroma, or *perinephric pseudocyst*, is a common developmental anomaly of cats. It is usually clinically silent, and is incidentally detected either through palpation or radiography of the abdomen.[71] In this condition, there is marked accumulation of lymph-like material beneath the renal capsule, leading to renomegaly. The anomaly probably involves intercommunication of abnormal lymphatics with the pericapsular space. Excision of the pseudocapsule has been attempted. This should be avoided if possible, however, because it can lead to ascites in some cases.

Ureteral anomalies of cats resemble those described for people and other animals.[6,10,34,39,87,107,113,124] *Ureteral ectopia* is a condition in which one or both ureters do not enter the urinary bladder at the normal place. Unilateral and bilateral ureteral ectopia occurs at about equal frequency in cats. Females are more commonly affected than males, and most cases are diagnosed before the cats reach 6 months of age.[87] The most common place of termination is into the urethra; vaginal termination is much less frequent. Urinary incontinence, usually evident at 2-6 months of age, is the most frequent presenting complaint.[87] Perineal urine scalding and dermatitis are also prominent. In some cats, urinary incontinence is not the presenting sign. Urine chronically pools in the vagina or urethra

and leads to bacterial cystitis. The major presenting signs in such cats are dysuria, pollakiuria and hematuria. Cats with ectopic ureters and presented only for signs of urinary tract infection tend to be older (6-72 months) at the time of presentation than cats with urinary incontinence.[87] Hydroureter and hydronephrosis are frequent complications of ectopic ureters.[87] Unilateral renal hypoplasia and vulvar anomalies can accompany the ureteral defects in a small proportion of affected animals. Treatment for ectopic ureters is surgical. The abnormal ureters are transposed into the bladder or, in the case of unilateral ectopia, the affected kidney and ureter are removed. Surgical correction usually resolves the incontinence or infection.[87]

Anomalies of the bladder result from abnormal differentiation of the embryonic cloaca, usually resulting in connections between the bladder and colon, bladder and uterus, or *patent urachus*.[63,76,87] Connections between the colon and bladder, or uterus and bladder, usually result in urinary tract infections and associated signs. The urachus, an embryonic connection between the bladder and umbilical vessels, is used by the fetus to eliminate waste. The urachus closes at birth and atrophies. Kittens with a grossly patent urachus drip urine from the umbilical area.[44,116] In less severe cases, the intrabdominal urachus remains open but the umbilical connection closes. This leads to an intra-abdominal *diverticulum* off of the cranioventral pole of the bladder. If the diverticulum is sufficiently large and thin-walled, it can cause urine pooling in the bladder, increased incidence of urinary tract infections, and possibly enhanced incidence of struvite lithiasis.[40,97] Rupture of a diverticulum in a cat led to abdominal urine pooling and peritonitis.[44]

Urethral anomalies are rare in cats. An *ectopic urethra* opening entirely into the rectum has been described in one kitten.[87] The anomaly was also associated with atresia coli. A small *urethrorectal fistula* has been seen in an older cat.[132] The cat had pollakiuria, dysuria and hematuria resulting from a chronic urinary tract infection. *Urethral paralysis or malformation*, leading to urine incontinence, is frequently associated with severe caudal spinal deformities, especially in Manx kittens (see section on Manx defect).[55,87]

Developmental anomalies of the pancreas, liver, gallbladder and common bile ducts are relatively uncommon in cats. *Hepatic cysts* have been recognized in the liver, sometimes associated with polycystic renal disease or persistent urachus.[5] *Pancreatic cysts*, some >1 cm in diameter, have been observed incidentally at necropsy of older cats. It is uncertain whether they are present at birth or develop later. *Biliary atresia* has been recognized in several young cats manifesting poor growth and severe icterus. It involves the smaller intrahepatic biliary system and is usually fatal. *Persistent ductus venosus* is not uncommon.[9] The ductus venosus is a fetal shunt for portomesenteric blood to bypass the hepatic portal system. Failure of this shunt to close diverts venous blood from the intestine directly to the vena cava. This impairs liver development and greatly inhibits the ability to detoxify and process nutrients from the bowel. Affected cats usually have a single shunt between the liver, spleen or small intestine and the caudal vena cava, and manifest signs of periodic dementia, stupor, ataxia, excessive salivation, behavioral changes (hiding, aggression, crying, increased appetite, tail thumping) malaise and lethargy.[9] The shunt can be surgically closed.[9]

Congenital *agenesis of the small and large intestines* is a frequent finding in kittens dying during the first few days of life.[138] *Atresia ani* is a congenital stricture or absence of the anus.[138] Affected kittens may live for days to several weeks, though their growth is impaired and their abdomen is distended with feces-filled viscera.

Acute gastric rupture has been reported as a common cause of death in Abyssinian and Somali kittens. The kittens die within the first week or so of life, after a brief period of weakness and depression. At necropsy, the stomach is ruptured and the abdominal cavity filled with ingesta. The disorder may have a genetic basis.

Pyloric stenosis has been observed in a 6-day-old Persian kitten.[13] The kitten faded over a 4-day period and regurgitated milk from its nose as it nursed. At necropsy, the stomach was greatly dilated with ingesta and the pylorus was stenotic. The condition

may be heritable in some cats (see section on genetic disorders).

Megacolon in the cat is usually acquired (tail-pull injuries, aging) but also may be developmental. Most cats with the developmental form are Manx. Foreshortening of the caudal spine, even though it is not clinically manifested at birth or early adulthood, may be associated with progressive dilation of the colon later in life. This is due to a relative lack of colonic innervation at birth and eventual exhaustion of remaining nerves and plexi. Some non-Manx kittens may be born with *agenesis of the myenteric plexus* of the colon.[28,137] They suffer from malaise, chronic constipation and abdominal distension with hard feces. The condition can be corrected by surgical removal of the colon.

Persistent cloaca is a rare problem in kittens. In this condition, there is a common excretory orifice for both urine and feces. It usually involves atresia ani, with termination of the colon into the urethra. Because of the narrowness of the urethral opening, affected cats are usually severely constipated and clinically resemble cats with megacolon. Kittens with this defect have palpable masses of hard stool in the abdomen and grow more slowly than normal. If the musculature of the anal sphincter is still intact and can be identified, the colon can be transplanted to its normal site.

Reproductive System Anomalies

Cryptorchidism is the retention of one or both testicles at some point along their embryonic and postnatal migration from near the kidneys into the scrotum. Because it is probably genetic in origin, affected animals should not be used as breeders. Most retained testicles can be found in the inguinal canal, and this is the first place that should be surgically explored. If they are not found in this position, the abdominal cavity should be explored. The retained testicle is usually atrophic and does not produce normal sperm. It can produce male hormones, however, and cryptorchid cats can act like intact males. Cryptorchidism can be either genetic or nongenetic in etiology. In some cases, migration of the testicle may be delayed and the testicle will not reach the scrotum until the cat is 4-8 months of age. This can lead to problems between veterinarians and cat owners. If the veterinarian removes only the scrotal testicle, the cat may be presented again several months later for removal of a second testicle. *Monorchidism* refers to failure of one testicle to develop. *Microrchidism* refers to small testicles.

Ovarian hypoplasia is bilaterally small ovaries with incompletely formed follicles.[12] Unilateral ovarian hypoplasia is often associated with X-chromosome abnormalities and mosaicism (see section on genetic disorders). Several anomalies of the uterus of cats have been described. One or both uterine horns may be connected to the uterine body by a small band of connective tissue. The isolated uterine horn often becomes distended.[93] The uterine horns may be fused along part of their course or be unequal in length.[12,19] One uterine horn can be completely absent or present as only a thin fibrous cord, a condition called *uterus unicornis*.[12,19,108] Absence of a uterine horn can be associated with agenesis of the kidney on the same side.[89,108]

Hermaphroditism refers to the presence of both male and female gonadal tissue in the same animal. A cat with an internal ovary/testis and an external testis has been described.[45] *Pseudohermaphrodites* have gonads of one sex but external genitalia that call the actual sex into question. Such disorders are rare in cats.[12]

Developmental anomalies of the mammary glands are relatively uncommon in cats. *Polymastia*, the presence of extra mammary glands that are completely functional, has been described.[12] *Polythelia* refers to more than one teat on a gland; it is often associated with polymastia.[12] Abnormalities of the streak canals and cisterns have been described for cats.[12] These anomalies were associated with sebaceous-gland ducts opening into the streak canal, blind-ending of streak canals near the base of the teat, hairs associated with sebaceous glands that enter the lumen of the streak canal, and a common origin of 2 streak canals.

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BREEDING PROGRAMS

Creating a Breed

The objective of breeding purebred cats is to produce kittens that are vigorous, that consistently reproduce the characteristics of the breed from one generation to another, and that have all of the desirable traits put forward in the breed standard. Most purebred cats are based on combinations of certain coat characteristics, different coat colors and patterns, and various body conformations. These basic features are carefully molded together over many generations.

Many of the basic coat and body traits that constitute a breed started as mutations from the basic domestic cats. Since many of these mutations are rare, the first step in forming a breed usually involves breeding the offspring back to the mutant animal, or by mating the offspring to each other. To avoid concentrating undesirable homozygous alleles, these first breedings should involve as many animals as possible.

For instance, a rare mutation in the type and character of coat (*eg*, Rex) suddenly appears in a male kitten in one area of the world. This mutation is particularly appealing to people and an attempt is made to create a breed of cats based on this anomaly. The mutant male cat would usually be bred to a large number of normal-appearing female cats that are as genetically diverse as possible. If the desired genetic trait is recessive in nature, all of the offspring would carry the desired gene. The offspring would then be bred to each other. A certain percentage (1/4) of the offspring would be homozygous for the recessive gene and have the desired mutant phenotype. These second-generation offspring will breed true if

bred to other homozygous recessive animals. If there is a large pool of homozygotes to choose from, further inbreeding can be kept to a minimum. If the initial pool of homozygotes is small, and if continuous backcrossing to the original mutant is carried out, the number of different alleles at gene loci other than the mutant loci will be very small. Breeds started from a narrow genetic base may be inbred from the beginning and subsequent genetic manipulations will be extremely difficult. This difficulty arises from the limited assortment of alleles at all gene loci from which the breeder selects.

Assuming that the initial gene pool is as heterozygous as possible for all genes other than the ones required to give the breed its identity, the next step in breed evolution is creation of bloodlines. Bloodlines seldom arise from a joint consensus among all of the foundation breeders. If all of the breeders were in complete agreement as to how the breed should develop, the result would be one bloodline rather than many. Differences in perspective allow for many different bloodlines. Different perspectives are more apt to occur when various breeders are geographically or ethnically separated. A comparison between the same breed of cats in various countries of Europe, or between Europe and North America, yields more differences than a comparison of cats from the eastern and western United States. One breeder may favor a certain body conformation over another, while a second breeder might be more interested in certain coat characteristics or patterns. Bloodlines should evolve from the initial group of animals as early in breed creation as possible. The more phenotypic differences that eventually develop between bloodlines, the more genetic differences there will be between them. These phenotypic and genotypic differences allow for a tremendous amount of latitude in future breedings. Crosses between distantly related bloodlines will be more apt to result in offspring with extra vigor.

The success of a breed is determined by genetic manipulations done at its inception. Purebreds should begin from as wide a genetic base as possible. Diversity of opinions as to what the breed should look like are healthy and should be encouraged rather that suppressed. Show judges should also be allowed to develop some degree of differing opinions on what is an acceptable interpretation of written breed standards. A consensus among judges usually results in one thing; breeders select their stock for the same characteristics, resulting in extensive inbreeding and the discarding of phenotypically distinct bloodlines.

Breeding Practices

Four major breeding practices are used to develop and refine a pure breed of cats: close inbreeding, moderate inbreeding or linebreeding, linecrossing and crossbreeding.

Close Inbreeding

Close inbreeding involves mating individuals that are closely related to each other, such as matings of first cousin, mother to son, father to daughter, brother to sister, and offspring to grandparents.

Inbreeding is common, especially in the initial stages of breed development. Such inbreeding fixes the desired trait and increases the number of individuals that are phenotypically desirable. Inbreeding, however, leads to homozygosity. If inbreeding is done improperly, the resultant homozygosity also brings out deleterious traits, as well as desirable traits. To avoid buildup of deleterious genes, breeders must start with the widest possible genetic base and moderately inbreed as much as possible.

Linebreeding or Moderate Inbreeding

Linebreeding is breeding individuals within the same bloodline. A bloodline is a genetically and sometimes phenotypically distinct group of cats within a breed. Individuals within a bloodline differ from each other in most generations; common ancestors are only found far back in the early stages of the breed's formation.

Moderate inbreeding entails matings to more distant relatives than sons, daughters, mothers, fathers, cousins or grandparents.

The pedigree of a linebred kitten oftens show the same outstanding individuals on both maternal and paternal sides. Therefore, the percentage of kittens with allelic genes from those outstanding parents is high. If the bloodline is large and genetically diverse, this degree of inbreeding usually is

not deleterious. If the line is genetically close, however, linebreeding is equivalent to close inbreeding. That is to say, if the third cousins and great grandparents are as genetically homogenous as the individual's parents and first cousins, then it is somewhat presumptuous to believe that close inbreeding and linebreeding are any different. As it happens, linebreeding is popular among breeders of purebred cats. When linebred animals begin to lose vigor and reproductive capacity, the genetic diversity of the line has been essentially lost.

Linecrossing or Outcrossing Within a Breed

Linecrossing involves mating good breed examples of one bloodline with good breed examples from other more distantly related lines. It is the basis for creation of new bloodlines and should be the most widely conducted breeding practice. Ideal linecrossing involves selection of bloodlines that each have different strengths and weaknesses. The greater the phenotypic differences, the more genetically diverse are the blood lines. By mating individuals of 2 different bloodlines with complementing traits, a small proportion of their offspring have the good characteristics of each of the 2 lines without any of the bad. For instance, animals of one bloodline are known for their beautiful eyes, but have poor coats. Cats of another bloodline have good coat characteristics but poor eyes. When cats of the bloodlines are crossed, a small percentage of the offspring will have the desirable traits of both. Such individuals have a minimal genetic homozygosity for traits other than the ones being selected.

Good linecrossing requires thought and planning. It is also time consuming. Many breeders are unwilling or incapable of conducting sound programs that emphasize linecrossing. It is much easier, quicker, and ultimately cheaper to use inbreeding and linebreeding to obtain cats with the desired traits. Unfortunately, deleterious as well as desired genes are concentrated in the offspring, and the bloodline loses vigor.

Crossbreeding or Outcrossing To Another Breed

Crossbreeding is mating individuals from different breeds. Crossbreeding can be the basis of new breeds and is allowed in several established breeds. Animals with one or more desired traits are mated with animals having other desired traits. Crossbred animals are often more robust than either parent, a phenomenon known as hybrid vigor. The more phenotypically different the 2 breeds are, the more genotypically different they will be, and the more likely that hybrid vigor will be obtained. If the parental breeds are similar in many ways, as in conformation, head shape and coat color, both breeds are more genotypically similar and hybrid vigor in their offspring will be less noticeable.

Outcrossing To Nonpedigreed Cats

Outcrossing is sometimes used to increase the vigor of a breed. Nonpedigreed Japanese Bobtail cats have been imported to interbreed with pedigreed Japanese Bobtails in the United States. The British outcross their Cornish rex cats to domestic cats every third generation. This practice has assured the vigor of the breed.

Loss of Vigor

Intensive inbreeding within genetically homogenous blood lines ultimately leads to loss of vigor. This loss of vigor is usually manifested by decreased size at maturity, slowed growth, increased severity and duration of common infectious diseases, smaller litter sizes, increased neonatal deaths, and more developmental anomalies. The increased incidence of disease and lowered fecundity then impacts negatively on the breed's or bloodline's popularity.

Loss of genetic vigor within a breed or bloodline is often caused when breeders try to accentuate normal breed characteristics to the extremes of the breed standard. As an example, the face structure of some cats is abnormally flattened. Further attempts to shorten or widen the face beyond the current norms may increase developmental anomalies of the face, increase susceptibility to eye infections and decrease size. Some of these side effects occur because of anatomic factors (lagophthalmos, impaired tear drainage). Others arise from accumulation of associated deleterious modifier genes. Some flattening of the face can be brought about by minor genetic changes. Moderate

flattening of the face requires substantially more inbreeding, while severe flattening requires the activity of numerous genes. Accumulating enough modifying genes to bring about severe facial shortening requires a great amount of selection. If animals are selected and inbred to achieve one characteristic, it is almost certain that genetic diversity will be limited for other traits as well.

Genetic Anomalies

Progressive inbreeding could lead to a gradual decline in breed vigor. Before there is a total loss of vigor, however, the incidence of genetic anomalies may be a problem. Purebreeding, by its very nature, limits the number of possible alleles at each gene loci. The more homogenous the genetics of a bloodline or breed, the likelier it is to mate 2 individuals with similar deleterious genes. Genetic anomalies are generally of 4 types: simple autosomal recessive, simple autosomal dominant, polygenic, or sex-linked recessive. Examples of genetic defects that fit each of these categories have already been given.

Genetic anomalies are usually well established in a bloodline or breed by the time they are noticed. The mobility of people and their cats, and the notion that everyone must breed cats with the currently popular look, assures that the defects will be far flung. Genetic defects are more likely to be spread by males than females. Stud cats can sire hundreds of kittens within a year or less, while females can only produce a handful. It is not surprising, therefore, that many genetic defects can be traced ultimately to a male that was a great show winner several years before the appearance of the defect in the breed.

Eliminating Genetic Defects

What can a breeder do once a defect appears? The first, and most difficult step, is to get other breeders to recognize the existence of the defect and to work cooperatively to eliminate it. Second, the nature of the defect must be determined. Is it genetic, environmental or both? For example, cardiomyopathy occurs in both dietary and genetic forms. Before the importance of adequate levels of dietary taurine was understood, many catteries had tremendous losses from this disease. It was almost impossible, however, to get breeders to recognize the severity of the problem and to help in its elimination. Fortunately, the true cause of most cases of cardiomyopathy was discovered. The discovery did not come from any effort on the part of breeders, but rather from a serendipitous observation made by a cardiologist who noticed a relationship between cardiomyopathy and retinal lesions of the type previously described for cats fed taurine-deficient diets.

Nutritionally induced cardiomyopathy is not just a nutritional problem, however. Genetics may also play a role; most cats fed older taurine-deficient diets do not develop cardiomyopathy. This suggests that some cats differ in their dietary taurine requirements, or in the effects that low taurine levels have on the heart. It is not surprising, therefore, that cardiomyopathy was believed at one time to be largely a genetic disorder. Some breeds and bloodlines of cats develop feline infectious peritonitis (FIP) at a higher rate than others. Does this mean that FIP is a genetic disorder? No, FIP is caused by a virus. Genetic resistance factors play an important role in the disease, however. It is not always easy to determine whether any particular disorder is genetic or environmental.

Once a disorder is found to be of genetic origin, an effort must be mounted to eliminate it from the breed. The approach taken depends on what type of genetics are involved, that is, simple recessive, dominant, polygenic or sex-linked.

Theoretically, genetic defects caused by dominant genes should be the easiest to eliminate. Only affected individuals carry the genes, and these should be easy to recognize and remove from breeding. This is seldom the case, however. Most dominant genetic anomalies are caused by genes that are greatly influenced by modifier genes. Individuals with the abnormal gene are normal as long as certain modifier genes are not present. An example of such a situation is seen in the Burmese breed.[3] Massive lethal facial anomalies are thought to be caused by an autosomal dominant gene that is modified by a number of other genes. These modifying genes may be the same genes that were concentrated in the breed when the face structure was changed.[3]

Dominant traits of this type must be treated more as recessives.

Genetic anomalies associated with autosomal recessive genes will not be eliminated from a bloodline or breed merely by not breeding affected individuals. For every affected (homozygous recessive) individual, there are 2 heterozygous recessive cats. Because affected animals are usually not bred, the source of most affected cats is breedings between apparently healthy cats that carry one of the abnormal genes. Outbreeding also does not eliminate the problem. When a heterozygous carrier cat is bred to a distantly related animal (almost certainly a homozygous normal), half of their kittens will be carriers. This will not be the same carrier incidence obtained upon breeding 2 heterozygous affected animals, but the basic problem will not be resolved. Outbreeding yields no affected animals in the first generation, but thereafter the incidence is the same as before outbreeding.

There are only 2 proven means to eliminate a recessive gene from a breed or bloodline of cats. The first is to find a way to identify the apparently healthy carrier cats and eliminate them from breeding, and the second is test breeding. Rigorous selection of breeding cats is in some cases a more practical alternative and may gradually eliminate a genetic defect.

Identify Carriers: Identification of carriers is obviously the quickest, most effective and ultimately the cheapest means. Healthy heterozygous carrier cats, regardless of the trait, usually have some biologic abnormality. Female cats carrying the hemophilia gene have levels of factor VIII protein in their blood that are intermediate between those of homozygous normal and homozygous affected animals. The same is true for cats with the various storage diseases (mucopolysaccharidosis, lipid storage diseases). However, there are many recessive traits for which the genetic heterozygotic defect is unknown. If the precise defect is not known, there is currenty no way to devise tests for the detection of heterozygous carriers. Scientists have started to use DNA diagnostic technology to identify inherited diseases in cats. In the future this may allow screening of breeding cats with a blood test before mating.

Test Matings: Test matings involve breeding individuals with unknown genotypes with individuals of known genotype. The true genotype of the unknown individual is reflected by the phenotypes of the offspring. The fastest way to prove an animal is to breed it to an individual that is homozygous for the deleterious trait. If the healthy individual of the pair has one abnormal gene, half of their offspring are phenotypically abnormal. It does not take many kittens to determine whether an individual is free of the deleterious gene with such breedings. Unfortunately, homozygous affected individuals are often not healthy enough to breed. Most test matings involve, therefore, breeding healthy animals of unknown genotype to apparently healthy animals known to be heterozygous carriers of the deleterious gene in question.

Test matings are usually directed toward exonerating stud cats rather than queens. The reason for this is obvious. First, a stud cat is far more valuable and has a greater cumulative effect on good or bad traits in the breed or bloodline than a female. This is because the male can produce many more offspring. Second, it is easier and faster to prove a male because he can produce many more offspring in a brief time. Finally, if all affected animals are not bred and all stud cats are free of the abnormal gene, all kittens will be phenotypically normal regardless of the phenotype of the queens. For instance, given an anomaly of the normal X gene (x), all males will be XX and some females will be Xx and some XX. Regardless of which female the XX male is bred to, all of the kittens will be phenotypically normal (XX or Xx). None will be xx. Theoretically, a simple recessive genetic anomaly can be phenotypically eliminated from the breed by just making sure that all male cats are homozygous normal.

How many normal kittens must a male cat produce before it can be certified free of a simple recessive genetic defect? The answer depends on what type of female he is bred to and what degree of confidence (probability of error) is desired. It is preferable to breed the male to females known to carry the abnormal gene (homozygous or heterozygous). When such animals cannot be identified, the accepted practice is to breed the male to his daughters or siblings.

The daughters do not need to be from the same mothers. It is implicit that the male not be repeatedly bred to the same female. The progeny must be from as many different females as possible. The accepted level of confidence is 95%, that is, enough kittens are produced to lower the probability of the male's being a carrier to 5% or less. The minimum numbers of consecutively normal progeny required to certify a male free at the 5% level, using different types of matings, are listed in Table 1.

Some geneticists do not believe that a 5% possibility of error is acceptable, and advocate an error rate as low as 1%. To reduce the error to such a level, the number of consecutive normal kittens in an unknown male x heterozygous female mating would be 17 rather than 11.

The same type of test mating program must be carried out for sex-linked traits. Because most sex-linked traits are carried by the female, apparently normal females must be bred to apparently normal males. Apparently normal males are always homozygous normal in the case of sex-linked characteristics. Using the hemophilia gene (h) as an example, an X^HY male is bred to a carrier female X^HX^h. Half of the female offspring are homozygous normal and half are heterozygous carriers. Half of the males are normal and half are hemophiliacs. In such a breeding, the chances that the first male will be hemophiliac are 1 in 2 (1/2 or 50%) the chances that the next male will also be a hemophiliac are 1/2 x 1/2 (1/4 or 25%), the chances that the third male also will be hemophiliac are 1/2 x 1/2 x 1/2 = 1/8 (13%), the fourth 1/2 x 1/2 x 1/2 x 1/2 = 1/16 (6%), and the fifth 1/2 x 1/2 x 1/2 x 1/2 x 1/2 = 1/32 (3%). The chances that 5 consecutive males will be normal are, therefore, less than 5%.

Table 1. The number of consecutive normal offspring that must be produced by a normal-appearing male cat to certify him free of a given recessive genetic trait varies greatly with the genetic makeup of the females to which he was bred.

Matings	Number of Consecutively Normal Offspring
Male x homozygous affected female	5
Male x known heterozygous female	11
Male x apparently normal daughters	23
Male x full siblings (if one parent heterozygous)	23
Male x full siblings (if both parents heterozygous)	17
Male x full siblings (only if a common ancestor is heterozygous)	23

Test mating requires production of many kittens, most of which will be affected or carry the deleterious trait. It is necessary for breeders who undertake this method to ensure that all kittens produced are placed as pets to be altered. Moderate selection (eliminating affected cats from breeding) is rarely effective in ridding a breed of a genetic defect. However, rigorous selection (eliminating affected cats and the sire and dam) will in time be successful. In this case the gene pool of a breed may be seriously diminished, and expansion will be necessary through some type of outcrossing.

Elimination of polygenic traits is the most difficult. Test matings are impossible in such a situation due to the large number of genes involved and the infinite number of variables. A vigorous program of testing and elimination of affected individuals is the only course of action. Only the most severely affected are eliminated from breeding at the start. The phenotypic expression of the abnormality will become less severe and less frequent with time. If further reduction in the incidence of the anomaly is required, the emphasis of culling should be progressively changed to include fewer and fewer affected animals. The process of eliminating polygenic abnormalities can take many years or even decades. The trait will disappear from the breed or bloodline as slowly as it appeared.

The most difficult situation is eliminating polygenic anomalies that have a threshold effect. There are few gradations of the phenotypes; the offspring are normal or abnormal. In this situation, many of the apparently normal animals also carry the abnormal genes, and matings between normals may produce almost as many abnormal animals as matings between affected individuals. The only way to handle such a

situation is to vigorously cull all cats that have ever produced abnormal individuals.

Some genetic anomalies persist even in the face of control measures. The most common reason is relaxation of culling by breeders. This may be especially true when the incidence of certain anomalies begins to decrease and the problem is no longer perceived as serious. Emergence of a new champion male carrying the abnormal gene can trigger a new epidemic of mutants.

A second possible explanation for persistence of a defect is genetic linkage. The defect may be genetically linked to some breed characteristic, or paradoxically, some trait that is beneficial to health. The best examples of the former are found within such breeds as the Manx and Scottish Fold. Genes for these traits are lethal or sublethal but also are responsible for the desired phenotypic traits of taillessness and folded ears. Other deleterious genetic traits have been linked to coat color or skull conformation. Examples of the latter usually involve highly inbred lines of cats. Inbreeding usually leads to loss of vigor. In such a situation, the more homozygous (less vigorous) animals are culled and the heterozygous (more vigorous) animals are saved for breeding. Without doing anything about eliminating heterozygous animals that carry the deleterious genes, nothing much can be accomplished by culling. Offspring of heterozygous individuals tend to be healthy or sickly; the sickly ones are continuously culled and the healthy ones bred. This becomes a never-ending cycle.

Recommended Breeding Practices

A few general rules brought out in this discussion must be reemphasized:

Close inbreeding should only be reserved for creation of new breeds and fixing of certain genetic traits.

Linecrossing should be the basis of most matings. Linebreeding should only be done when the desired bloodline is large and genetically diverse. Optimal linecrossing or linebreeding should involve careful planning. This can usually be accomplished by selecting individuals with complementing weaknesses and strengths. A few offspring will have the complementary traits of both parents; these should be selected for show. If the mating involves individuals with all of the same phenotypic strengths, the likelihood that the parents are genotypically homogenous is high.

Breeders should become aware of what constitutes a different bloodline. Many breeders have no concept of what makes a bloodline. They believe that because Mrs. Jones has been breeding cats in California for many years, her cats are a different bloodline from Mrs. Smith's cats that have been bred for many years in New York. If 2 bloodlines are phenotypically similar, and have many of the same individuals in their pedigrees, they are not different bloodlines. Breeding Mrs. Smith's cats with Mrs. Jones' cats under this circumstance is not linecrossing, it is moderate inbreeding. If the lines are genetically very close, it can even be close inbreeding.

Breeders should work carefully to prevent emergence of genetic traits. Animals should be bred along correct genetic principles. Defects should be rapidly identified and eliminated. This may require a concerted effort among breeders. Overbreeding of certain toms should be discouraged. Toms that become very popular on the show circuit can be responsible for hundreds of kittens in a very short time. Given the fecundity of cats, thousands of cats directly related to certain toms can be produced within several years.

Do not breed for extremes in show standards. Fixing of extreme traits requires a great deal of inbreeding. Phenotypic selection of this magnitude can seldom be achieved without inbreeding at other genetic loci.

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